Pathways in the study of perinatal disease

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For about fifty years I have actively studied the nature and cause of disease. I would like to explore a few aspects of our understanding over that period of disease as it affects the fetus in utero and the newborn baby. This is a period of life of special interest in that it often concerns the interplay of conditions which can arise in two separate individuals. It includes the study of developmental biology, the modifications imposed on the fetus by multiple disturbances in the maternal and fetal relationships and the many challenges the baby meets as it must rapidly adapt to an entirely new environment at birth.

To the clinician a disease may present as a complex of signs and symptoms. Often to the pathologist it is only the structural changes revealed by the naked eye or by the microscope. To appreciate in detail the structural framework of disease is of great value for its understanding. Often it imposes a useful discipline limiting useless speculation. Morphological descriptions alone tell us little of how diseases evolve, and, increasingly, for any real understanding we must think of both health and disease as a study in biology, and hope to understand them both by using and selecting relevant studies in all the life sciences. Pathology must be a dynamic study rather than descriptive and static, and must also relate to all studies on the living patient.

If for convenience we think of a disease as an entity, we can think of our understanding of it evolving and advancing along many different directions or pathways. Some of these may define its origin and behaviour more clearly and others may show its affinity with other biological events both normal and abnormal. Especially when pathways of investigation link up with others in allied disciplines, this may allow a rapid advance and widening of our understanding. Indeed, today almost all advances are made when pathways in apparently unrelated disciplines thus converge and unite. It must be accepted that many pathways that open with promise end in blind alleys, or at best make only a minimal contribution. However, today's cul-de-sac may be tomorrow's avenue of advance.

Before reviewing some examples of how researches have opened up pathways leading to a wider understanding, it is essential to know from where we started and where we are now. Access to the consensus of existing knowledge has advanced in the last three or four decades. Descriptions, for example, of congenital abnormalities, once only available by searching through dusty and poorly illustrated journals, are now well presented and often beautifully illustrated. We must rejoice that facts once in the possession of the few are now so generally available. With this information explosion a new problem arises. This is the

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multiplication of journals and monographs and their increasing cost, and the declining resources available to libraries for their purchase. The problem is not access to photostats of a few papers on a specific problem. It is the inability to read and to assess continually and critically all relevant studies and especially those necessary to prepare or revise a really comprehensive text, monograph or review. I believe this is now becoming nearly impossible with the resources available in many medical schools.

**CONGENITAL ANOMALIES**

Throughout history, man has been interested in congenital abnormalities and especially in the more bizarre malformations. Descriptions of the form and morphology of gross malformations have advanced relatively little in the last forty or fifty years. Sophisticated techniques have with increasing accuracy unravelled anomalies, such as cardiac malformations, during life rather than in the post-mortem room. X-rays are often essential even at post-mortem for precise diagnosis. Inborn errors of metabolism continue to operate throughout life and differ from the once and for all disruption of normal structural development responsible for a malformation. Some, such as cystic fibrosis, may show at post-mortem marked and progressive structural changes even in the perinatal period, others only such subtle structural changes as those of galactosaemia. Many inborn errors of metabolism can be identified only by chemical screening tests in selected population groups.

Important recent developments have been not in anatomical but in epidemiological studies. These have shown the widely different incidence of specific anomalies, but strangely not the total number of anomalies, in different racial groups. They have emphasised that affected individuals often show multiple and apparently independent anomalies. Recent studies of artificially aborted embryos have shown a higher incidence of abnormalities than at normal birth. It would seem that many early and spontaneously aborted embryos must be abnormal. Often the malformations, such as hare lip and polydactyly, recognisable in these artificially aborted early embryos, are no more severe than those in fetuses surviving to term. This would suggest that abnormalities often represent a more complex and lethal disorganisation of development than is structurally apparent. Related to this is the increasing recognition that aborted conceptuses often show a disorganised and sometimes bizarre arrangement of their chromosomes.

In the early part of the century, speculation as to the basis of abnormalities was along pathways now largely abandoned, and often seemed to point to familial inheritance. The simplest examples were recognised but the many different genetic and environmental influences contributing to and necessary for the expression of all but the simplest examples of genetic inheritance were not appreciated. Eugenists, overimpressed by selective breeding in animals, even raised false hopes of the elimination of many imperfectly defined defects.

Early in this century, experimental embryology was emphasising the effect of noxious chemical and physical influences on free-swimming embryos. In the forties, studies on mammalian reproduction and human pregnancies increasingly suggested at a low level of probability that environmental conditions might influence the incidence of malformations. These environmental influences became an acceptable basis for human malformations only with the recognition of the influence of rubella and of the embryopathic drug thalidomide. The emphasis on environmental influences was valuable, but numerous attempts to
identify other teratogenic agents, chemical or infective, operating alone in any significant number of anomalies have been unrewarding. Studies, such as those showing the effect of nutritional deficiencies on the proper closure of the neural canal may suggest that, at most, environmental influences modify the expression of other, presumably multifactorial genetic factors.

A specified defect can only occur if a teratogenic agent operates at a relevant period of development, and for most defects this is long before the sixth to eighth week of menstrual age. If drugs are to do harm they must have been taken early, and, for severe defects, before many women are sure they are pregnant. The evidence does not support the present widespread concern, nor the judgements of American courts of law, that almost all drugs are potential teratogenic agents.

After the recognition of the basis of Down's syndrome in 1959, many useful paths to understanding abnormalities have come from the study of chromosomes, of groups of genes and even of individual genes. Abnormal chromosomal patterns and enzyme defects in cells taken from the early embryo may increasingly allow parents the choice of eliminating affected products. Attempts at genetic engineering will occasion even greater practical and ethical problems. There is also the increasing problem so common in medicine today of limited resources but ever increasing demand. It is undesirable to seek publicity and research funds by raising expectations of any early, general or widespread application of methods of genetic control which cannot hope to be fulfilled.

BIRTH TRAUMA

Physical birth trauma is now rare and, indeed, it was always rare in Belfast obstetrical practice. Statistics have always been unreliable. For long it was incorrectly thought by many that subarachnoid and intraventricular haemorrhage was traumatic. It is the result of anoxia operating in the actively developing subependymal area of the immature brain. Again, pathologists, poorly trained in the technique of the perinatal post-mortem, can all too readily tear engorged intracranial sinuses and bridging veins and be deceived by blood escaping at the post-mortem. Small amounts of blood in the anterior and middle fossae may not be the cause of death. One may find blood pigment in relation to dural surfaces or in the tentorium long after birth and unrelated to illness or death. Haemorrhages into the scalp and even into skeletal muscles are rarely important. Gross injuries, such as subcapsular tears of the liver with resultant intra-peritoneal haemorrhage are exceptional. However, for a short period in the mid-sixties, extensive traumatic pulmonary interstitial emphysema with unrecognised pneumothorax was encountered here in a cluster of infant deaths. It was apparently due to imperfect control of apparatus used for artificial respiration. To hold the benefits of advances along any pathway demands perpetual vigilance.

PERINATAL INFECTIONS

Infections acquired in intra-uterine life and from the new environment during and after birth make a fascinating study. Some infections reach the fetus across the chorionic villi from the maternal blood, others spread from the amniotic sac before, or more often after, its rupture, and yet others are acquired in the birth canal or from the external environment.

We can chart hard-won knowledge of these infections in different ways. We can emphasise that some — rubella, toxoplasmosis, inclusion body disease and

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Syphilis — may infect from early in pregnancy and from the maternal blood. They may be manifest in a premature or term stillbirth, at the birth of a live-born infant, in the early days of life, in infancy, in childhood or even only in adult life. A great load of infection occurs around the time of delivery, and nearly all of this is bacterial and runs its course in the first three days of extra-uterine life. In others a wider spectrum of lesions is involved. Often the lesions are not specific for the disease, and for the recognition of many of these infections in their less overt form, and, to determine the agent responsible for many, we have to use new pathways made available by advances in microbiology. A few virus infections of interest, but mostly uncommon, occur just before, during or after delivery, and usually, but not always, from the mother. Considerable uncertainty exists for some, and there are difficult problems as to the route and time of infection and other problems such as those relating to vertical transmission of hepatitis B virus through many generations in some ethnic groups.

If the wall of chorion and amnion are examined after birth, a reaction by polymorphs may be found spreading in and around the blood vessels of the chorion and even into the wall of the umbilical vessels. It becomes increasingly frequent as labour is prolonged after the membranes rupture. About 10 per cent of placentas show the reaction. Bacterial cultures from the amniotic surfaces are of limited value and many normal placentas are contaminated. Many with reaction yield no organisms on conventional bacteriological study. For long, many maintained that this amnio-chorionitis was not an infection. Only a small proportion of the infants thus involved develop an inflammatory reaction in the lung in their first three days of life. However, a pneumonic reaction has been recorded in up to 15 per cent of all intra-partum stillbirths. Again organisms may or may not be recovered from the lungs.

Increasingly over the years, and with more adequate bacteriological techniques, organisms, including Mycoplasma and anaerobic and micro-aerobic bacteria, have been implicated in the reaction in the chorion and amnion and shown to invade the lungs and the blood streams. It has become increasingly certain that this inflammatory reaction is always infective. Occasionally the fetal membranes and even the lungs may be similarly infected by organisms entering across intact but devitalised membranes. Again, organisms, including sometimes virulent Group B streptococci, may be aspirated from the birth canal and cause pneumonia and fulminant septicaemia without this amnio-chorionitis. It should be emphasised that the reaction, involving as it does the large and relatively few vessels of the chorion, gives little opportunity for blood stream dissemination of organisms of low virulence or for absorption of toxins. It is different when the air spaces of the lungs, filled with amniotic fluid and with their numerous thin-walled capillary plexuses, are involved. There the organisms may proliferate as in a culture medium, cause an inflammatory reaction and allow toxic absorption and often a blood stream invasion. Of itself, amnio-chorionitis is probably rarely significant.

An association between perinatologists, pathologists, bacteriologists, virologists and immunologists has in recent years opened up many important pathways in the understanding of perinatal infections. Studies of immune tolerance to rubella in early embryos and of congenital immune defects in early life have contributed in turn to advances in immunology.

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OXYGEN DEFICIENCY AND PERINATAL DEATH

All recognisable disease conditions — congenital, traumatic, infective and such miscellaneous conditions as blood and metabolic disorders — can explain only a proportion of perinatal deaths. About 40 per cent of deaths, and predominantly the deaths of premature infants, remain unexplained. These babies show changes sometimes minimal and difficult to evaluate. These are regarded as secondary to anoxia, or more correctly hypoxia. This anoxia might damage the parenchymatous cells of the brain or perhaps the heart and other organs, or could involve the interstitial tissues. Cellular damage may cause death in those who fail to establish respiration. In those who breathe for a period, the cellular changes sometimes found, especially in the brain, do not involve respiratory centres or areas concerned immediately with survival.

Changes in blood vessels and support tissues are often prominent, and especially in premature infants. Thin-walled and poorly supported blood vessels rupture in the rapidly developing sub-ependymal matrix around the brain ventricles, and, less importantly, in the subserosal tissues over viscera, and sometimes into the lung substance. More important is the accumulation of oedema fluid interfering with oxygen transfer in the body and lungs, and in the septa of the lungs perhaps splinting the tissues and impeding respiratory movement. This fluid crosses the placenta readily from the relatively large maternal blood volume, and its escape into fetal tissues is therefore not opposed by fetal haemoconcentration. In anoxia of some duration this is serious and comparable to overhydration by an intravenous drip in later life. There must be concern about the influence of overhydration on absorption of amniotic fluid from the distal air spaces.

All babies, whatever their cause of death, may show in some degree these changes since tissue anoxia is a universal terminal event. Those dying during or after birth from anoxia arising from causes outside their own body, and which I have designated as extrinsic or environmental anoxia, can and should be so recognised only when a most meticulous study excludes all other known causes of death. When an infant dies from extrinsic, as opposed to intrinsic or secondary, anoxia we must expect to find the cause in unfortunate conditions in its environment operating before or during delivery. These are essentially the concern of the obstetric side of the perinatal team. They may be briefly reviewed.

Oxygen levels to the fetus may be impaired by a few maternal extra-placental influences, such as maternal circulatory collapse, haemorrhage or severe anaemia. These and prolapse of the cord and other obstetrical complications may erode or destroy the capacity of even a healthy placenta to sustain an adequate oxygen level to the fetus. Close co-operation and frank discussion between the obstetrician and the pathologist is always essential in perinatal studies and here clinical data are often more important than any anatomical findings.

In the search for other causes of extrinsic anoxia we are concerned with the utero-placental unit. As in every organ there is here a reserve of function. There are efficient and less efficient placentas. The reserve varies from patient to patient. As pregnancy advances it tends to decline relative to the increasing fetal demands. It may decline differently for different functions. Biochemical measures of various metabolic functions do not necessarily measure oxygen transfer. However, their decline and any failure of the fetus to grow must be in some degree disturbing. Some infants may start with better placentas than others and should survive more degenerative change. The recognition by histological study that a grossly normal
placenta had a lowered reserve at birth is more difficult than many will admit. Morphometric studies of the total area of the villi and of the capillary networks where transfer occurs are tedious and only a few are available. They have revealed something of the attrition of the smaller ‘breathing’ villi towards term and of its acceleration in toxaemia. Attempts to assess that this has occurred in a normal or toxaemic pregnancy by transmitted light or phase contrast microscopy and by detecting an increase in the stroma of the villi, thickening of the basement membranes, or an increase deposit of fibrinoid material in and on the smaller villi are all without any quantitative basis and are all subjective. Dramatic gross lesions, such as a retro-placental haemorrhage aborting the villous placenta, are rare but probably not all are recognised. Multiple infarcts may be impressive, but often more significant are diffuse degenerative changes which may or may not co-exist. Admittedly a large red infarct occurring very shortly before birth may sometimes escape recognition.

It now seems increasingly probable that the various conditions, known and unknown, producing a low reserve placenta operate through changes in the decidual vessels and those of the uterine wall and with resultant disturbances of the intervillous circulation. The inescapable difficulty is that these vessels are left in the uterine wall as the placenta tears away through the maternal decidua and are not available for study. Changes may be seen in the shed placenta, but it is still uncertain what changes are most significant as an index of functional impairment. It is against this background that we must welcome progress in monitoring at intervals during late pregnancy the pattern of fetal blood flow through the umbilical cord.

FACTORS IN THE INFANT MODIFYING INTRINSIC ANOXIA

We have still many unanswered questions as to how anoxia or an anoxic episode, however induced, threatens the life of the newborn. Does it operate alone or are other factors sometimes or often concerned? Indeed, we may be overlooking something else of importance. Some anoxic lesions, such as sub-ependymal haemorrhages, are lethal. Oedema of tissues and especially of the lungs progressively impairs oxygen transfer. In the forties we were too content simply to echo Drinker’s dictum ‘Anoxia begats anoxia’, but in essence it is true. Hydrogen ion and electrolyte disturbances occur and progress if uncorrected, but are now usually controlled.

In any failure to achieve and maintain extra-uterine respiration, lung function is concerned, and some deficiency must occur here especially in those children in whom respiration is readily established but becomes progressively less satisfactory. There is a wide variation in the intra-uterine age of the premature infants thus affected, but lung development may not always reflect fetal age. It did seem from a study of the Harvard material by the limited histological techniques available in 1946–47 that neither fetal age, birth weight nor infant length consistently measured structural maturity. However, any structural differences in lung development on any definition of maturity seemed entirely insufficient to be related to the outcome. Later, neoprene injection studies and micro-dissection of the more terminal air spaces showed better detail in three-dimensional studies and especially the scarcity of the elastin support structures in the lungs of premature infants. Some knowledge of lung structure was gained, and it is still just possible that the elastin support of terminal air spaces develops in response to intra-uterine breathing movements and at any given fetal age may show
meaningful individual variations. However, no anatomical basis, apart from that of gross immaturity, was found sufficient to explain why some infants die from respiratory distress. This was not to open a pathway for significant advance. Personal research moved into other areas, and in perinatal pathology to the study of the placenta.

About this time interest generally moved to Gruenwald’s work on surface tension at the aqueous-air interface in the air spaces and its control by a surfactant substance so that air spaces would neither over-expand on inspiration nor collapse fully during expiration. Surfactant production is dependent on the maturity of lung cells secreting it. Measured by assay in the liquor amnii, is is only in part related to fetal age. It is not useful to return to old fatalistic concepts that some infants die simply because they are premature even in the sense that their enzyme mechanisms for synthesis of surfactant are relatively immature. Other factors, including anoxia, may contribute to surfactant deficiency at birth and in the first few days. With increasingly successful therapy the deficiency is now often transient and there is rapid maturation of synthesis after birth. Problems still remain of the significance of an episode of anoxia and of surfactant and perhaps other factors in any failure to adapt to extra-uterine respiration.

Often on critical analysis we cannot properly ascribe a perinatal death to one single cause. Anoxic conditions leading to oedematous lungs and tissues predispose to infection, and bacterial infections spreading in these oedematous tissues may produce deceptively little reaction. The venous congestion of anoxia may enhance any bleeding from torn venous sinuses in the skull. Again too often we are all inclined to accept death as due to some congenital anomaly of very doubtful relevance.

Progress has been made and the pattern of advancing, ramifying and sometimes divergent paths has changed and is almost unrecognisable from that forty years ago. Endless highways and byways beckon and must be explored. I wish all of you success and adventure and as much pleasure and excitement as we have had over the last half-century.

REFERENCES
The developing literature was extensively reviewed in successive editions of the texts by Morison and by Potter. In the two volumes edited by Aladjem and colleagues, contributions from many relevant disciplines were presented by different workers and the pathology was discussed by Morison. Recent publications tend to deal with more limited aspects and to be monographs. The present discussion on infection is based on the author’s 1979 paper.

Aladjem S, Brown AK, Sureau C, eds. Clinical perinatology. 2nd ed. St Louis: Mosby, 1980.
Aladjem S, Vidyasagar D, eds. Atlas of perinatology. Philadelphia: Saunders, 1982.
Fox H. Pathology of the placenta. London: Saunders, 1978.
Hanshaw JB, Dudgeon JD. Viral diseases of the fetus and newborn. Philadelphia: Saunders, 1978.
Larroche J-C. Developmental pathology of the neonate. Amsterdam: Excerpta Medica Foundation, 1977.
Morison JE. Foetal and neonatal pathology. 1st, 2nd, 3rd eds. London: Butterworth, 1952, 1963, 1970. Also translated as Patologia fetale e neonatale. Rome: Abruzzini, 1954; and Patologica fetal y neonatal. Barcelona: Editorial Pediatricia, 1972.
Morison JE. Perinatal infection. In: Wynn RM, ed. Obstetrics and gynecology annual, vol 8. New York: Appleton-Century Crofts, 1979: 147-78.
Potter EL. Pathology of the fetus and the infant. 1st, 2nd, 3rd eds. Chicago: Year Book Medical Publishers, 1951, 1961, 1976.

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