FOETAL PHYSIOLOGY AND CHILD HEALTH*

BY

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It is my duty and pleasure to offer to the British Paediatric Association my thanks for the honour conferred on me by their invitation to deliver this lecture, the more so as it is the occasion of a joint meeting with the Society of Medical Officers of Health, whose Child Welfare Group has done such notable work in translating into administrative medicine the findings of the clinician and the laboratory workers. I hope what I have to say will be worthy, not only of the occasion, but of the great clinician in whose name this lecture has been founded.

George Frederick Still, whose memory it is my privilege to honour to-day, was physician in charge of the Department of Paediatrics at King's College Hospital, and physician to the Hospital for Sick Children, Great Ormond Street. He was the outstanding paediatrician of his time. He was small of stature, quiet, without bombast, but nevertheless replete with personality; a great clinician whose powers of observation, examination, and deduction at the bedside enabled him to advance his subject in a manner given to few of us. He was not an experimental physician in the modern style, far from it, nevertheless he did not disdain the aid to be obtained from the clinical laboratories. His influence on the medicine of his time was outstanding, and we may well pay testimony to-day to the fact that he was a power for health in the child of his generation, and in the child and adult of this and future generations.

The Problem

My task this afternoon is to show some ways in which the study of the physiology of the foetus can guide us in the preservation of the best health in the child and in after life. While the tag *mens sana in corpore sano* is true and the roots of mental disorder may strike back to intra-uterine life and earlier, I will restrict myself to the pre-natal development of the *corpus sanum*.

Methods of Study

In this lecture I am frankly stating the point of view of the laboratory worker. I can only give pointers to the clinician on possible ways of solving his problem. It is important to remember always that the clinician and the specialist in the preservation of child health—whether he be paediatrician, medical officer of health, or social worker—provides the problem in the vast majority of cases, though the first class scientist can, as in all branches of science, see his own problem. The physician is a biologist providing the spark which ignites the physiologist. The physiologist is often a dissatisfied clinician seeking new methods of approach to the problems before him.

There are two lines of approach, observational and experimental, and both are applicable to man as well as to animals. In each type the essence is the application of the principle of scientific method. An experiment may, of course, be one provided by nature, whether by famine, war, or other cataclysm. Many such have occurred in Europe and Asia during the war; they become experiments when observed methodically and scientifically.

It is worth while here to point out that experiments on man are of two types: the therapeutic, where some procedure is initiated and designed to benefit the individual patient, a reasoned and hopeful step; and the investigational one, in which the objective is primarily for the benefit of mankind and not necessarily for the patient. Of the most finished of these are the investigations of McCance, in which comparisons are made of the body fluids of the adult and the newborn infant (McCance, 1946; Jones and McCance, 1949). In fact, in many cases one must resort to observations and experiments on animals. For animal experiments to yield results applicable to man and to avoid fallacies, three criteria must be satisfied. (1) There must be such similarity of species that there is structural, biochemical, and functional resemblance to man. (2) There must be similar reactions in animals and man to the same changes in environment and the same experimental

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procedures. (3) It being still a question of probability and not certainty, there must be available the experience of the human application before results are finally accepted.

Techniques and Procedures

Apart from observations, there are two major types of experimental approach in animals and man

conditions are almost (with the substitution of saline for amniotic fluid) identical with those *in utero*.

Observations can be made not only with the eye, but also by any suitable recording apparatus, whatever method of experimental procedure is adopted. Quite understandably, accurate precision biophysical techniques are used more and more as they become available. Here it is fundamental to

bear in mind that the mere use of expensive and highly accurate and modern apparatus does not in itself alone ensure accuracy of work. Three other things are required in a biologist using accurate physical apparatus, such as photo-electric recorders, electronic amplifying valves, and Geiger-Müller counters for radioactive isotopes. These are skill, experience, and the biological training to interpret and assess the results and controls at their true value. In this case the word 'biological' does not mean clinical; it means functional biology in the old-fashioned sense of the word, namely, the fusion of physiology, zoology, and botany. In addition to

this, it cannot be over-emphasized that most important of all is the sound biological training needed to plan and design the right experiment to give results and answers of value.

Basic Material

Theory of Pattern and Gradient in Development. D'Arcy Thompson (1916) in his classic 'Growth and Form' shows that growth is an orderly and progressive change, subject to definite laws, but varying in rate and degree along definite 'gradients' of growth. The variation in rate in different directions determined the 'form' of the organism. C. M. Child (1941), the American zoologist, showed that these gradients, whether spreading outwards or arranged along an axis with poles (polarity) at each end, were present not only in the organism as a whole, but in portions and even in cells. Further, the gradient was shown by all functional components: oxygen consumption, metabolic rate, enzyme activity, and protein deposition, to mention a few. These gradients are controlled by intrinsic factors, genetic and species, and by extrinsic factors,

FIG. 1.—The size, shape, and proportions of the human foetus from the 7 mm. stage to full term, showing different parts growing at different rates in succeeding stages, the head preceding the trunk, the fore limbs rather faster than the hind limbs (Fig. 225, *Kollmann's Handatlas des Entwicklungsgeschichte*, 1907).

in the field we are discussing. These are the use of the whole animal and of caesarean section under anaesthesia. The latter approach was first used by Cohnstein and Zuntz in 1884, and was revived in 1923 at St. Thomas's Hospital Medical School, London. It rapidly spread after the publication of the first results in 1927 (Huggett, 1927). In the hands of Eastman and Kellogg in the United States, and of Barcroft and Barron at Cambridge, it has spread over the whole field. By this procedure it has been possible to treat the unborn foetus as an entity and to study it at any foetal age at leisure. It has been of particular service in the study of the placental mechanisms, since retraction of the placenta does not occur. It is, however, particularly suitable for foetal investigations, since, by using large animals such as sheep, the foetus is of a convenient size unobtainable in most laboratory animals. The anaesthetized mother is delivered by section in a bath of saline at body temperature and the foetus kept submerged in the saline outside the abdomen and attached to the unretracted placenta by the pulsating umbilical cord: in other words,

diet and environment. We see this theory exemplified when we look at growth from conception to adulthood and the rates of growth of different embryonic organs.

Theory of Partition of Nutrients. Hammond (1944) has put forward this theory based on the

FIG. 2.—The changing proportion of the human body during prenatal and postnatal growth (Fig. 112, 'Developmental Anatomy,' Arey, 1934).

work of Thompson and Child. It is unproven, but it is a good working hypothesis based on the facts as known, and has withstood the criticism of Barcroft (1946).

The foetus and placenta have a high metabolic rate, especially in early intra-uterine life. Therefore they can successfully compete with maternal organs for nutrients in the blood stream. If in food shortage there is a depletion, then the placenta, with its high basal metabolic rate successfully obtains its requirements, whereas adipose tissue at the other extreme not only fails to obtain its limited requirements but, owing to the low control of the blood stream, loses weight. This would happen by a reversal of the normal chemical equation of synthesis in accordance with the Law of Mass Action. This hypothesis will explain why in iron shortage, protein shortage, salt or vitamin deficiency in pregnancy dietaries, when there is competition between the mother and child, there is born a healthy child without anaemia, of full weight, and of good calcification, from a mother who is anaemic, poor in weight, with defective teeth, or osteomalacia acquired during pregnancy. Dietary supplementation is therefore indicated. Further, in moderate deficiencies the child will be short of stored material and will run out of stores before lactation is ended, especially of iron, and so have a lowered resistance to infection. In this connexion one can refer to the long series of publications from the school of Parsons in Birmingham, the work of McKay and Goodfellow (1931), and of Strauss (1933); all are now of classical importance. Iron supplementation of the diet is essential for the

mother on a normal diet, and becomes essential for the foetus also if rations are grossly depleted.

PREMATURITY AND IMMATURITY. Wallace (1948), working with Hammond, showed that in pregnant sheep (full term 150 days) at 91 days diet had little influence on different organs or on the foetus as a whole, but after that date until full term a high protein and vitamin diet resulted in well-formed lambs and vice-versa. His results are shown in Table 1 and in Fig. 4. After four weeks on a maintenance diet, six pregnant ewes were put on a low diet giving loss of maternal weight, and six on a high diet giving ample supplies and gain of weight. At the fourteenth week three of each group exchanged dietaries until full term. At term it was clear that the diet in the first 13 weeks had little effect on the lamb, but the diet in the last eight weeks was the determining factor. Further, it increased the milk yield immensely. The high diet yielded a high birth weight, high milk yield, good lamb growth, and zero neonatal mortality. Further, the low dietary lambs had a retarded physiological development of the

TABLE 1
INFLUENCE OF HIGH AND LOW PLANE DIETS IN LAST EIGHT WEEKS OF PREGNANCY ON BIRTH WEIGHT AND POST-NATAL GROWTH (WALLACE, 1944 AND 1946)

Diet	High Plane	Low Plane
Effect on ewe weight (lb.) ..	44 gain	11 loss
Birth weight (lb.) ..	10.4	6.8
Milk yield in third week (lb.) ..	50	30
Milk yield over 16 weeks (lb.) ..	443	292
Lamb weight at 16 weeks (lb.) ..	72	56
Temperature control at birth ..	Present	Absent
Neonatal mortality ..	Nil	High

FIG. 3.—Diagram of priority of partition of nutrients according to metabolic rates. The demand for nutrients by an organ varies as the number of arrows shows. Shortage in the blood stream means that those tissues with the lower demand fail to compete with those with higher demand and stop growing or may even lose weight (Hammond, 1944).

FIG. 4.—Level of nutrition of ewe during pregnancy upon size of lambs at birth (Wallace, 1948). Two series of ewes fed on low rations and high rations to 91st day of pregnancy respectively. Each series was then divided, half being put on high and half on low plane of diet or rations.

temperature control mechanism at birth, and this would contribute to a high neonatal mortality.

These facts explain the points brought out by Illingworth, Harvey, and Gin (1949), that poor birth weight is effective for many years after birth in contributing to retarded development, despite the views of Hess and Chamberlain (1927).

The crucial thing is that each organ has its specific date of optimum growth according to the pattern of development. At that date, whether prenatal or postnatal, it needs ample supplies of foodstuffs. If each organ does not obtain them at that time, it is a poor substitute to give them later, since they cannot be usefully used by an already formed organ, but are utilized by other organs whose specific date of optimum growth coincides with the accretion of foodstuffs. A child who was fed on poor food supplied in early life has a light skeleton and a poor musculature, and does not restore these by 'feeding up' in those years after the dates for building skeleton and muscle. What is good for the child is also true for the foetus.

Mechanism of Action

There are three major factors of intra-uterine origin influencing the health of the child: the genetic, the placental, and the foetal. The first will not be now considered, but the other two groups repay attention.

Placental Factors

Placental Morphology. It was shown by Grosser (1925) and by Mossman (1937) that histologically the placentas of mammals can be grouped in four classes according to the number of layers intervening between the maternal and foetal bloods at full term. All begin with six layers: the maternal endothelium, the uterine connective tissue ('syndesmium'), the maternal uterine epithelium (endometrium), the foetal chorionic epithelium and syncytium, the foetal villous connective tissue and the foetal endothelium of the villous blood vessels. As the placenta grows in different types it loses varying numbers of the intervening layers, so that in the human placenta we have a haemo-chorial placenta at term; that is, maternal blood is in direct contact with the chorion of the villi. In the rabbit, some of the chorion goes and we get a haemo-endothelial placenta; in the dog there is an endothelio-chorial; in the ungulata, a syndesmo-chorial; and in the pig, an epithelio-chorial placenta, in which no tissue at all disappears.

FIG. 5.—Diagram illustrating the Grosser-Mossman classification of placentas. The black spots represent foetal corpuscles and the rings the maternal corpuscles, each enclosed in their vascular endothelia. The progressive approximation of the blood streams in the last stages of the four main types of placenta is shown.

Placental Diffusion. The view is that the placental diffusibility bears an approximate relation to the number of intervening layers. This is, it appears, true for inorganic crystalloids as shown in the beautiful work of Flexner and his colleagues (1942) with isotopes on the permeability of different types of placentas to water and sodium chloride in which

FIG. 6.—The permeability of the rabbit's placenta to Na^{23} at different foetal ages correlated with the villous structure (Flexner and Gellhorn, 1942).

FIG. 7.—The permeability of placentae of different Grosserlossman groups to Na^{23} . The increase in permeability in te pregnancy occurring with approximation of the blood reams in the rodents on the one hand, and uniformity of permeability through pregnancy in the sow at the extreme is shown (Flexner and Gellhorn, 1942).

he used heavy water or sodium chloride with Na^{23} as the isotope. We see well how the passage increases in the late months. It is also in some degree shown for some colloids, e.g. antibodies, as we see in Rodolfo's work (1934) on the passage of antibodies across the placenta of the rabbit.

Water may pass by diffusion but there are

problems which cannot usefully be discussed here. However, sodium chloride, oxygen and carbon dioxide appear to diffuse across under pressure in all types and to be reversible if the gradient is reversed. Asphyxiation of the pregnant ewe under caesarean section results in carbon dioxide going back to the foetus (Huggett, 1927). This reversibility rules out active placental gaseous secretion. Roughly speaking, molecules under 350 molecular weight appear to diffuse (Anselmino, 1929). There are, however, important exceptions, both in placental types and in individual substances, so important

FIG. 8.—Permeability of the rabbit's placenta to antibodies at different times during prenatal life (Rodolfo, 1934).

that we must consider the possibility of active placental intervention, secretion or vital activity as a factor in transfusion.

Active Placental Intervention. The evidence for this is profuse. It rests on the staining of the placenta in man and other animals. Perhaps the best description is that given by Wislocki and his colleagues at Harvard, who have shown, to take three instances, that the human placenta contains considerable amounts of stainable enzymes, notably phosphatases (Dempsey and Wislocki, 1947), which we know to be active in the metabolism of fats and carbohydrates: it also has two types of stainable iron, that interpreted as being in association with oxidative enzymes (which often contain iron), and that identified as transport iron (Dempsey and Wislocki, 1944). Finally, it is possible to identify histologically materials in association with the staining reactions of steroid hormones (Wislocki and Bennett, 1943) such as oestrone and progesterone which are known to be secreted by the placenta into the mother. In other words, the placenta, unlike the capsular membrane of the kidney or the lung epithelium, has materials which would probably be

redundant if simple diffusion were the sole transport mechanism. It is possible to illustrate this fact by a consideration of certain specific materials.

LIPIDS. Popják (1947) gave potassium phosphate labelled with radioactive phosphorus, P^{32} , to pregnant rabbits and later extracted the phospholipids from the maternal blood, the placenta, the foetal blood, and the foetal liver. He then estimated the amounts of P^{32} in the four purified phospholipids. He showed that there was more in the placental fraction than in either of the two blood fractions. Therefore there must have been a fresh synthesis of lipids in the placenta, otherwise, if mere storage had occurred, there would have been identical amounts of P^{32} in each fraction. Also, since the foetal blood lipid had a third and lower content of P^{32} it could not have been formed by mere diffusion, but must have been made by an active chemical katabolic process in the placenta. That is, active secretion and not diffusion was the mechanism. Similar reasoning showed that lipid concentration in the foetal liver was active and not passive.

CARBOHYDRATES. Again, if glucose be injected into the maternal or foetal blood of the sheep, it appears on the other side very rapidly (Huggett,

Warren, and Winterton, 1949). But at the same time there is a slow, long-continuing rise in the blood of a second sugar normally present in sheep foetuses, namely fructose. The total concentrations will exceed in the foetus the maternal glucose. In a case of viable twins, we found that if one was separated immediately after birth, but the cord of the second left intact with its umbilical circulation, there was a distinct difference. Though both twins had been injected with the same amount of glucose, the second only formed fructose, showing that it is made by the placenta and not by the foetus itself from glucose. Further, fructose normally disappears from the lamb within 24 hours of birth (Cole and Hitchcock, 1947).

T.R.S.=maternal blood reducing substance (99% glucose). F.=foetal blood fructose.

FIG. 9.—Chart of the passage of glucose across the placenta of the sheep and formation of fructose.

FIG. 10.—Chart of the production of fructose by the placenta but not by the foetus. Glucose infused into twin foetuses during caesarian section. One umbilical cord then cut and foetus detached, other left attached. Fructose only found in second case but steadily disappeared in detached foetus.

It is clear, therefore, that the placenta passes sugar across by two mechanisms, one probably by simple diffusion and the other by an active transmutation into fructose.

Of practical importance to this question and to those interested in human physiology, is the relation of the mechanism of fructose production to fructosuria in man. Here it is important to note two things: first that this is a rare condition, and secondly, that neither we nor Karvonen (1949) have been able with the best modern techniques to confirm the presence of fructose in human foetal blood as described by Orr in 1922. It is present only in certain species of mammalian embryos. Also, concerning the passage of sugars we know that human and rodent placentae contain considerable amounts of glycogen which is very stable and

independent of the maternal blood stream. The function of glycogen is unknown: in fact, at the moment, the more we know about it the less certain we are of its interpretation (Huggett, 1929; Davey and Huggett, 1932; Dempsey and Wislocki, 1944; Wislocki, Deane, and Dempsey, 1946). The occasional presence of fructose in adults is a clinical problem remaining to be solved, but one which, we feel, is being opened up, particularly by the work of Mann and his colleagues at Cambridge, who have shown that it is present in seminal fluid, secreted by the seminal vesicles under androgenic control, and utilized aerobically by spermatozoa (Mann, 1946; Davies and Mann, 1947; Mann and Parsons, 1947). It is of interest to note that fructose is always found associated with the foetus or the reproductive tract.

PROTEINS. There is evidence that nutritional quantities of proteins probably pass by amino acid diffusion under appropriate pressure gradients. But the whole problem of the Rh factor has led to our recasting our ideas about protein passage, and, further, the disorders of childhood for which it is apparently responsible, are multiplying annually.

It is now clear that, while antigens pass across hardly at all, antibodies pass with relative ease. But only about 50% of human placentas are permeable to the passage of the Rh antibody from a Rh-negative mother back to the Rh-positive foetus (Hughes, 1949). This differential permeability has been predicted by Haldane (1942), and there appears some evidence of a biological variation in the permeability of the placenta (Dienst, 1905). On the other hand, while antibodies in the maternal blood normally pass the placenta, Hartley (1949) has shown that there is a peculiar selectivity present in this organ. A woman with diphtheria at the end of her pregnancy received purified antitoxin. It was assumed that the twins she carried would be immunized. Nevertheless, they developed diphtheria after birth and one died. It was found that crude antiserum and precipitated globulin passed the placenta, but purified detoxicated antiserum did not traverse. The placenta, therefore, has a selective action, since larger molecules passed across but smaller ones were excluded. It is important here to refer to the work of Brambell and his colleagues in north Wales. They have shown that in the wild rabbit (whose placenta is histologically a shade more permeable than the human) maternal proteins enter the foetus and kill a percentage of a litter by fibrin formation (Brambell and Mill, 1947).

There is no point in referring here to the rôle of the placenta as a ductless gland controlling maternal metabolism in pregnancy. The theme has been beautifully developed by Professor William Newton

of Edinburgh in some of the most finished examples of scientific method in this generation of scientists.

Our new problem therefore is, To what extent are the functions and development of the placenta under our control? There is, I am glad to say, some hopeful evidence, since it is possible to alter its morphology (Huggett and Pritchard, 1945; Pritchard and Huggett, 1947; Popják, 1946).

Foetal Factors

Foetal antenatal functions can be divided into those which continue into post-natal life with no abrupt change, and those which have such a change. Taking the second group first, we can list them as: (1) Closure of the umbilical circulation, the ductus venosus, and the hypogastric arteries; (2) closure of the foramen ovale and the ductus arteriosus, with opening of the pulmonary circulation, this occurring first; (3) the volume of circulatory blood; (4) cessation of placental transmission and the onset of alimentary and full renal function; (5) fall of external temperature, and therefore the task of constant temperature control (successful in the plantigrade newborn, such as lamb and foal, but inadequate in human newborn); (6) sensory stimulation of the skin on a new scale and distribution; (7) a changed pattern of growth with different rates for different organs.

Among the functions which, so far as we know, undergo no abrupt change, we can include motor function and control by the brain and cord, apart from responses to new stimuli. Further, there is the growth of the metabolic functions which are accompanied by a steady fall in the metabolic rate. In addition, there is the growth with the total neuromuscular mechanism of the control of temperature which, however, does not reach full function until some months after birth. The newborn infant is, like the amphibian, a cold-blooded animal.

Quite clearly the more premature an infant or the more immature it may be, due to malnutrition of the mother, the more it will lack development of these functions. It is therefore of the utmost urgency to maintain the maternal nutrition in pregnancy optimal in quantity and quality. It is pertinent here, however, to refer to the beautiful and finished research of two united teams of workers in this branch of physiology. Oxford and Cambridge, at the instigation of the late Sir Joseph Barcroft, joined forces in the personalities of Barcroft, the late Alfred Barclay and Kenneth Franklin, now at St. Bartholomew's, ably assisted by many colleagues, especially from the United States. They brought light into intra-uterine and neonatal darkness, often the short wave light of x-rays, but they clarified the situation and elucidated

FIG. 11.—The palates of two rats, A and B, at birth. Rat B was born with a cleft palate from a mother kept on a riboflavin-free diet during pregnancy. Rat A was a normal control (Warkany, Nelson, and Schraffenberger, 1943).

the physiology of a region which Blalock has transmitted into practical surgery for the infant.

Concerning the functions which undergo the abrupt change, I would speak of three. You are all aware of the finished and lucid work on the kidney of the newborn by Professor R. A. McCance and his colleagues. He has told you of it. It must be confessed that we know little of renal function before birth, but it is quite clear from his results and from the histology of the glomerulus, that it is adequate but imperfect, has little concentrating power, and possesses a salt intolerance, if one may use the term.

My former colleague, David Greenfield, now professor of physiology at Belfast, and Keith Cooper, now with the Royal Air Force, turned from studying the blood flow in the brain when subjected to big gravitational forces, to the blood flow in the umbilical cord. By enclosing the sheep foetus in a saline-filled box (a plethysmograph) without injuring or disturbing the umbilical cord, they were able to apply sudden pressures sufficient to stop the venous flow back to the foetus but not to stop the arterial flow out. Thus the foetus shrank as the outward blood flow to the placenta continued unchanged. As a result the rate of flow through the placenta was measured (Cooper and Greenfield, 1949; Greenfield, 1949; Cooper, Greenfield, and Huggett, 1949). This measurement by Greenfield and Cooper has laid the

foundation of an accurate knowledge of the cardiac output and of the foetal metabolism. Correlated with oxygen and nutrient contents we are enabled to obtain clearer pictures of foetal metabolism than ever before (Cooper, Greenfield, and Huggett, 1949).

We have discussed a pattern of growth, the role of the placenta in transmitting nutrition, and the power put into our hands by Greenfield to measure total metabolism. In 1921, Zilva, Golding, Drummond, and Coward showed that absence of vitamin A in the diet of pregnant animals caused congenital cataract. This was forgotten until the last war when simultaneously Gregg in Australia (1941) and Warkany in the U.S.A. described congenital defects. Gregg's discovery, as is well known, was in infants born of mothers who in pregnancy between the restricted period of the fifth and eighth weeks were ill with German measles. Warkany and Nelson (1941), in a series of papers beginning in 1941, showed that pregnant rats on a riboflavin-deficient diet delivered themselves of litters with bone and thyroid defects, provided that the diet deficiency was before the thirteenth day. It would appear that the rubella virus (if we may so call the active agent) can attack enzyme systems actively engaged in optic lens formation and heart formation. When these tissues are formed other enzyme systems are not so attacked; similarly, vitamin A and riboflavin are essential as catalyst

FIG. 12.—Three figures illustrating the progressive loss of bones and digits in rats at full term when delivered from mothers maintained on diets of varying shortage of riboflavin. The absence of digits in the paw is shown and also the fusion of small bones or complete absence of ossification in bony centres (Warkany and Nelson, 1941).

for lens or bone-forming enzyme systems, but not for enzyme functioning in the formation of other organs.

Finally, I would close by referring to the work of Dr. Kenneth Cross which, like Greenfield's, exemplifies the value of accurate work allied to modern precision methods. He has addressed himself to the basic physiology underlying respiration and foetal apnoea. Haldane in 1904 showed us the rôle of gases in controlling the respiratory centre. Cross (1949) has attempted this evaluation in the infant and finds that the physiology is not the same as in the adult: that is, it may be possible that once again we are dealing with an imperfectly formed function which must, like all others, be assessed for the infant and child by standards different from the adult if we are to make good progress in treating our children.

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