RECENT ADVANCES IN PÆDIATRICS

EDITED BY

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PREFACE

THIS edition follows on similar lines to those of its predecessor, but the chapters being somewhat fewer, each author has been free to cover his subject in rather greater detail. One chapter, that on Tuberculosis, bears the same title as in the first edition, but its content, like that of all the remaining chapters, is entirely fresh.

The subjects chosen are intended, as before, to display the growing edge of pædiatrics today, the theoretical interest as well as the practical importance of a subject entering into the choice. For example, though cases of hypothyroidism with goitre are not common, their study throws so important a light on thyroid physiology that a full discussion of these cases is merited.

In the preface to the last edition, written in 1954, reference was made to signs of a slackening in the pace of major new advances in the field of clinical pædiatrics. This trend has become more conspicuous in the intervening four years, and it seems likely that we have entered an era when pædiatric research (apart perhaps from the psychological field) must turn increasingly for fresh inspiration to the fundamental biological sciences upon which pædiatrics itself rests—to embryology, genetics, physiology and biochemistry, and also to comparative and veterinary medicine. Here this view finds expression in the fact that an animal physiologist is the author of the opening chapter.

The standard set by these authors who contributed to the first edition has made it a grateful task to assemble the team of contributors to its successor. I cannot sufficiently thank the friends and colleagues on both sides of the Atlantic for the good-humoured resignation with which they have suffered the cajolings, criticisms and textual excisions received at the hands of an editor, himself often sorely pressed by exigencies of time and space.

I am indebted to my colleague Dr. Janet Roscoe who again, by taking over some of my work, has freed me to undertake this. The experience and skill of Mr. J. Rivers and Mr. J. A. Rivers of J. & A. Churchill, Ltd., have smoothed my way at every turn. Lastly, my wife by her willing acceptance of my preoccupation with this book over the past year has contributed to it in no small measure.

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A NUMBER of illustrations in this volume have been taken from previously published works, and a list of these is given below. The Editor gratefully acknowledges the kindness of publishers and of editors of journals who have given their consent to the reproduction of these pictures.

Cold Spring Harbor Symposia on Quantitative Biology, Figs. 1, 6, and 11 in Chapter 1.

Josiah Macy Foundation, First Conference on the Physiology of Prematurity, 1956, Fig. 1.12.

Proceedings of the 5th International Congress of Otorhinolaryngology, Fig. 12.5.

Archives of Disease in Childhood, Figs. 2.1, 6.2, 10.3–5.

British Medical Journal, Figs. 2, 3, 4 and 10 in Chapter 3.

Journal of Laryngology and Otology, Fig. 12.1.

Journal of Physiology, Figs. 3–5, 7–10, 13 and 15 in Chapter 1.

The Medical Press, Figs. 1–9 in Chapter 7.

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CHAPTER 1

CHANGES IN THE CIRCULATION AT BIRTH AND THE EFFECTS OF ASPHYXIA

GEOFFREY DAWES

DURING the past thirty years the changes in the heart and lungs at birth have been studied much more intensively, yet even now textbooks of physiology devote little more than a page to the subject, and fail to mention at all the special physiological problems concerned with fœtal and neonatal life. This is surprising, for the changes which take place at birth are probably the most dramatic in the whole of our lives, and it may seem miraculous that the infant should survive them at all. Some investigators have therefore been led to suggest that these changes take place slowly, that, for instance, blood flow through the lungs increases over the last month or two of gestation and during early neonatal life. We now know that this is not so, the transition is abrupt but all the changes are not completed at once. For several days after birth, various adjustments are taking place, which in the human infant are not finished for 1–2 weeks. The idea is therefore taking shape of an intermediate condition of the circulation, intermediate between that of the fœtus and the adult (Fig. 11, p. 25; Born *et al.* 1954), which is of particular interest to those concerned in resuscitating the newborn baby and in nursing him through the first few days of life.

The Fœtal Circulation

The course of the fœtal circulation has been the subject of intermittent controversy for many centuries. Harvey unquestionably understood the functional significance of the two great fœtal passages, the *ductus arteriosus* and the *foramen ovale*, which permit the two ventricles to work in parallel, pumping the blood from the great veins to the arteries. But the era of anatomising which followed was characterised more by a multiplicity of theories than by experimental verification of the way in which the blood circulated in the fœtus. Indeed experimental studies of any kind depended on the development of the necessary techniques. In 1888 Cohnstein and Zuntz made a few observations on fœtal lambs, but it was not

until Huggett in 1927 had demonstrated that it was possible to deliver a fœtus, still attached to the mother, with the umbilical cord intact and in reasonably good physiological condition, that the new era of experimental fœtal physiology began.

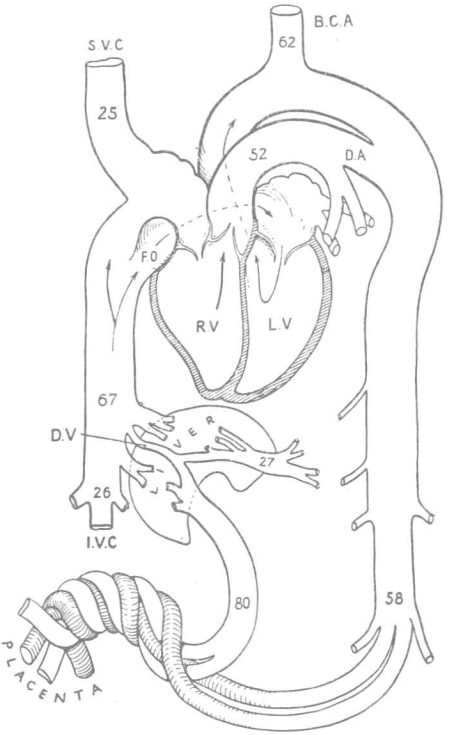

FIG. 1.1. The circulation in the fœtal lamb. The figures indicate the percentage O_2 saturation of blood withdrawn simultaneously from various vessels, and are averages from 6 lambs. I.V.C., inferior vena cava; S.V.C., superior vena cava; D.V., ductus venosus; F.O., foramen ovale; D.A., ductus arteriosus; B.C.A., brachiocephalic artery.

One of the first problems which had to be tackled was one of the oldest. Long ago it had been suggested, by Sabatier in the eighteenth century, that the best oxygenated blood in the body (that coming from the placenta by the umbilical vein and the ductus venosus, Fig. 1) might pass through the heart without mixing, to supply the head and the heart. The blood containing the least oxygen was thought to pass through the ductus arteriosus into the descending

aorta, and thence to the placenta. The great difficulty in accepting this hypothesis was in understanding how two streams of blood could pass each other in the right atrium, without mixing.

In fact it had already been demonstrated (by Wolff, also in the eighteenth century) that no such supposition was necessary, the difficulty did not exist, for the foramen ovale does not lie between

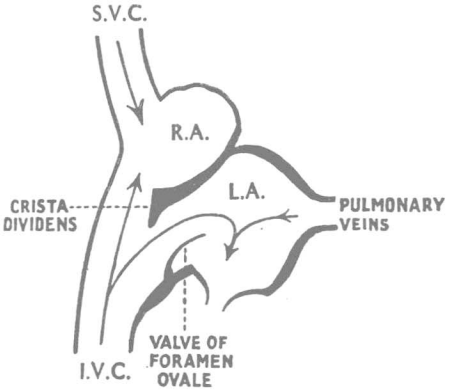

FIG. 1.2. Diagram of the great veins, to show that in the fœtus the inferior venal caval blood splits into two streams, one of which enters the right atrium, while the other passes through the foramen ovale into the left atrium.

the two atria, but between the inferior vena cava and the left atrium (Figs. 1 and 2). The anatomical evidence for this is well summarised by Barclay, Franklin and Prichard (1944). Nevertheless current medical thought ignored this evidence, and as late as 1930 Kellogg appears unaware of it; misled by experiments on fœtal puppies which, as Barcroft (1946) points out, must have been in unphysiological condition (their blood contained almost no oxygen) he concluded that the two bloodstreams mixed completely in the fœtal heart. It was not until Barclay, Barcroft, Barron and Franklin united their efforts and, in 1938–9, applied the new technique of cineangiography to the fœtal lamb, that convincing physiological evidence was obtained to support the long forgotten anatomical findings. Here for the first time were pictures of the fœtal circulation in life. They showed that the stream of blood flowing up the inferior vena cava divided into two portions on the *crista dividens* as it reached the heart. The larger portion passed directly from the inferior vena cava through the foramen ovale into the left atrium, while the smaller continued onwards to join the superior vena caval

stream in the right atrium. *All* the superior vena caval blood entered the right atrium, and none passed down into the inferior vena cava to enter the foramen ovale. This anatomical arrangement is not peculiar to the lamb. Thus both Barcroft (1936) using fœtal guinea-pigs and Windle and Becker (1940) using kittens and guinea-pigs, commented on the fact that right atrial blood was darker than left atrial. And more recently Lind and Wegelius (1954) and Handler (1956) have shown by cineradiographic observations, in the fœtal baby and puppy respectively, that the foramen ovale lies between the inferior vena cava and the left atrium, functionally. There is not, therefore, any necessity to suppose that two streams of blood, of widely differing oxygen content, cross in the right atrium without mixing.

Although the anatomical basis for Sabatier's hypothesis (as it is sometimes called) of the fœtal circulation is now well established, the postulated functional consequences do not necessarily follow. Thus it has been widely suggested that the fœtus derives an advantage from the anatomy of its circulation, in that the head and heart are supplied with blood containing substantially more oxygen than that which goes to the placenta. Huggett (1927) showed that there was such a difference in goats and Barcroft's observations on the fœtal lamb confirmed this finding. The latter found a carotid O_2 saturation of 40–50% (*ca.* 25 mm. Hg tension) and an umbilical arterial O_2 saturation of about 30% (18 mm. Hg). On the other hand these observations were few in number and the blood samples were not withdrawn simultaneously. When samples were taken simultaneously the difference between the carotid and umbilical arterial O_2 saturation (23 observations on 17 lambs) was only 6%, corresponding to a difference in tension of only 3–4 mm. Hg (Dawes, Mott, Widdicombe and Wyatt 1953, Dawes, Mott and Widdicombe 1954). This can hardly be regarded as a very substantial advantage, for in these experiments the average carotid O_2 saturation was about 62% (30 mm. Hg tension). There are no published observations on other species in good physiological condition, so we have at the moment to rely entirely on these findings on the fœtal lamb. As the mean O_2 saturation of the umbilical venous blood was 80%, and that in the portal vein, abdominal inferior vena cava and superior vena cava about 25%, there was evidently very thorough mixing of the different blood streams in the heart and great vessels, even though the foramen ovale does not lie between the two atria (Fig. 1).

Cineradiographic observations in the fœtal lamb also indicated that the pulmonary circulation time was prolonged, and the impression was formed that the volume of blood flow through the lungs

was small, particularly when compared with that through the placenta (Barclay, Franklin and Prichard 1944, Barcroft 1946). Observations on fœtal babies and puppies have led to the same conclusions (Lind and Wegelius 1954, Handler 1956). These views are supported by measurements of the pressures within the great

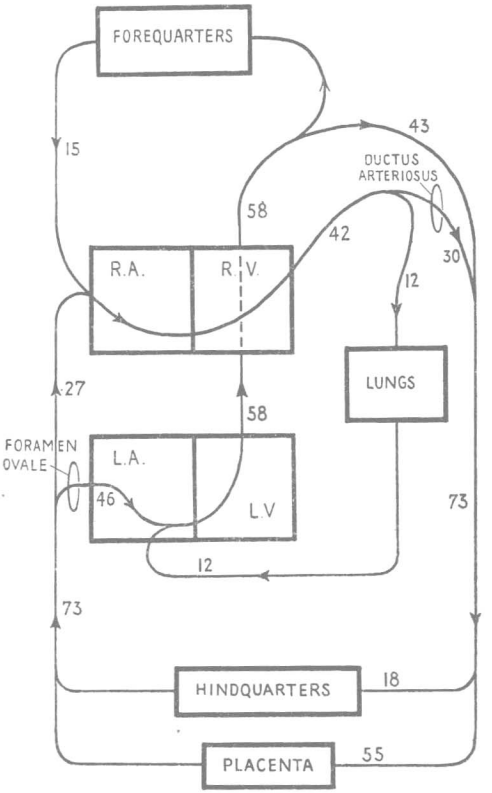

FIG. 1.3. Diagram to show the relative distribution of blood flow in the mature fœtal lamb.

vessels, but neither these, nor cineangiographic observations, are capable of giving accurate estimates of the relative proportion of blood flow through the great vessels. Further information has been obtained both indirectly and directly.

At various points in the fœtal circulation two streams, of differing oxygen content, mix. Thus in the right atrium, a stream containing

say 67% O_2 from the I.V.C. mixes with one containing about 25% O_2 from the S.V.C. and coronary sinus (Fig. 1). The oxygen content of the mixture ejected from the right ventricle into the pulmonary trunk contains 58% O_2. It is thus possible to calculate the proportion of each of the two confluent streams. By an extension of this argument and by making various assumptions it is possible to arrive at an approximate estimate of the relative volume of blood flow through each of the main vessels (Dawes, Mott and Widdicombe 1954). The principal results of these calculations are illustrated in Fig. 3, a schematic diagram of the fœtal circulation, which shows that 55% of the combined output of both ventricles goes to the placenta, which can be regarded as a low resistance circuit placed in parallel with the fœtal tissues, both systemic and pulmonary. Of the total cardiac output only about 12% passes through the lungs, which therefore offer a high resistance to blood flow. The foramen ovale and ductus arteriosus carry 46% and 30% respectively. As both ventricles work in parallel to drive blood from the great veins to the aorta, there is no need for their output to be exactly equal, and indeed the evidence suggests that the output of the left ventricle may be greater than that of the right.

Direct measurements of umbilical blood flow have also been carried out, either by the use of a fœtal plethysmograph (Cooper, Greenfield and Huggett 1949, Acheson, Dawes and Mott 1957) or by inserting a flowmeter into the umbilical vein within the abdomen (Dawes, Mott and Rennick 1956). The volume of blood flow so measured in mature lambs varied from about 100–180 ml./kg./min. Comparable measurements for total pulmonary blood flow are not available, but flow through the left lung amounts to only about 5–10 ml./kg./min. This is just about what might be expected from the indirect calculations outlined above.

These measurements also provide information on another point. Patten and Toulmin (1930) have suggested, on the basis of measurement of the cross-sectional areas of the great vessels at various gestational ages, that pulmonary flow may gradually increase towards term and that the transition from the fœtal to the neonatal condition may, therefore, be more gradual than abrupt. It cannot be too strongly emphasised that these calculations are most misleading. The main resistance to blood flow is in the *small* pulmonary blood vessels and not in the large ones, and in any event it is impossible to guess at the rate of flow through a main blood vessel without knowing the pressure drop along it, and whether flow is laminar or turbulent, as well as its cross-sectional area. In point of fact,

measurements of pulmonary blood flow in fœtal lambs show that flow is at least as great, or even greater, per kg. body weight, in those of less than 120 days gestation age as compared with those of more than 140 days (term is about 147 days).

The Oxygen Environment of the Fœtus

Not only does the course of the circulation change abruptly at birth, but also the oxygen environment of the fœtus. Although the oxygen saturation of the umbilical venous blood is about 80% in the mature fœtal lamb, the oxygen saturation in the arteries which actually supply the fœtal tissues is much lower, varying from 62% in the carotids and 58% in the descending aorta down to 52% in the pulmonary arteries (Fig. 1). Consequently the oxygen tension of *arterial* blood supplying the fœtus is less than 30 mm. Hg, compared with nearly 100 mm. Hg in the adult.

In babies the oxygen saturation of umbilical arterial blood at birth is even lower than that of the fœtal lamb, ranging from a mean of 10–33% according to numerous authors (Smith 1951, Acheson, Dawes and Mott 1957, for references), with an O_2 tension of only 8–16 mm. Hg. As the lowest arterial oxygen tension recorded in man at extreme altitude is 29 mm. Hg it is evident that many babies are very short of oxygen indeed on delivery. This, however, should not be taken to indicate that the normal infant *in utero* during the last few days of gestation is necessarily in the same condition (indeed it is very hard to believe that this could be so). It is inevitable that delivery, either vaginal or cæsarean, should interfere with the placenta and umbilical flow in the human infant, whereas in an acute experiment on a sheep it is possible to make a very wide exposure and thus avoid compressing the placenta and cord. Nor, in the latter, is there any danger of placental separation. It is therefore probably best to keep an open mind, for the moment, as to the normal level of oxygenation of the fœtal baby. Rooth and Sjöstedt (1957), for instance, suggest that the umbilical arterial O_2 saturation may normally be about 40%.

Barcroft (1946) concluded that there was a progressive fall in the carotid oxygen saturation of the fœtal lamb towards the end of gestation. We have not been able to confirm this conclusion, which was based on rather few observations (Born, Dawes and Mott 1955, Dawes 1955–6). Walker and Turnbull (1953) and Walker (1954) have described a fall in the venous and arterial O_2 content of cord blood at the end of gestation in newborn infants. But whether this fall is really representative of conditions *in utero* before labour

begins, or whether it is a reflection of the greater difficulties experienced by older infants during delivery, is a matter for speculation. While Walker and Turnbull's observations have been confirmed by some workers, others have failed to do so (for references, Walker 1955–6, Rooth and Sjöstedt 1957). Yet it is undoubtedly true that infant mortality is lowest at term, and thereafter increases. It is tempting to suggest that this is attributable to a fall in the O_2 supply to the fœtus after the end of term; it is equally probable that both the increase in mortality and any fall in arterial O_2 saturation are due to the greater size of the infant during labour. Turnbull and Baird (1957) have also found that, in primigravidæ, increasing maternal age is associated with an even greater fall in umbilical *venous* O_2 saturation at the end of term; in this series the length of labour and fœtal weight had no influence on the O_2 saturation. This very interesting observation illustrates the importance of maternal factors on the O_2 supply to the fœtus at delivery.

There is one other physiological detail. In the fœtal lamb, anoxia can cause an immediate increase in the oxygen-carrying capacity of the blood, within a few minutes (Born, Dawes and Mott 1956). It is not necessary to attribute the rise of hæmoglobin content of human cord blood in anoxia (Walker 1955–6) solely to a process of acclimatisation acting over the past few days or weeks. It *could* be a rapid process taking place during labour as a result of interference with the placental circulation. We are therefore no nearer to a solution of the problem of what the normal oxygen environment of the human fœtus is *in utero*, *before* the onset of labour. As yet, there is no direct evidence of a progressive reduction in the supply of oxygen to the "post-mature" human fœtus under normal physiological conditions.

Tying the Cord and the First Breath

The low umbilical arterial O_2 saturation of the newly delivered baby has been referred to above. The average newborn baby is already asphyxiated. In order to study the effect of an acute interruption of umbilical blood flow in an uncomplicated form it is therefore necessary to use animals. The fœtal lamb may be delivered under local anæsthesia and placed alongside the mother, where it lies quietly without breathing so long as the placental circulation is adequate. Tying the cord causes an immediate small rise of blood pressure, because it stops the large flow of blood through the placenta, and thus more than doubles systemic arterial resistance. After an interval of perhaps half a minute the lamb becomes partly