It appears that propatyl nitrate is a potent drug for the relief of acute attacks of angina pectoris but is of little or no value in prophylaxis. In our opinion there is as yet no drug which can be relied upon to abolish or diminish the frequency of attacks of angina pectoris.

Conclusion

In the doses used sublingually propatyl nitrate and PETN did not differ significantly from a placebo in abolishing or diminishing the frequency of attacks of angina pectoris.

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FATTY CHANGE IN THE MYOCARDIUM OF THE NEWBORN

BY

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Recent perinatal mortality surveys have shown that in many babies dying either during or soon after delivery no cause for death apart from asphyxia can be found. Our own figures for the Glasgow Royal Maternity Hospital reveal that at least 33% of perinatal deaths have to be classified as such. Yet the term is a loose one, and the findings at necropsy vary greatly. In many, however, appearances suggestive of cardiac failure are seen. In these cases there is distension of the right heart, especially the atrium, together with congestion of the great veins. Enlargement of the liver is not generally noted, but on section blood pours from the cut surface. One other feature suggesting venous congestion is the marked distension of the umbilical vein in the ligamentum teres. This appearance was seen in babies dying shortly after delivery and was even more marked in other cases showing hyaline membrane formation. This conception of cardiac failure as a factor in death of the newborn has been suggested by many clinical observers (Rowe and James, 1957; Burnard, 1959; Brown, 1959), and Lendrum (1955) was of the opinion that it was primarily due to a left heart failure.

Obviously this failure is functional in nature, but it is the purpose of the pathologist to find, if possible, some morphological counterpart for the clinical and post-mortem appearances. It was therefore decided to examine the myocardium in these cases to determine whether the failure was accompanied by histological change or not.

Material and Methods

Altogether 72 cases were studied, 15 being stillbirths and 57 neonatal deaths. These were unselected and included infants of all degrees of maturity. Macerated stillbirths were excluded from the survey. It is the custom in this hospital to place the bodies of all babies in a refrigerator within one hour of death. Necropsies were carried out within 24 hours. Longitudinal blocks through atrium and ventricle were taken from both sides of the heart, the left block longer than the right in order to identify the side of origin. Material was fixed in buffered formalin (pH 7) and also in picric alcohol. Frozen sections were stained for fat with Sudan IV and paraffin blocks with haematoxylin and eosin and lead

tetra-acetate Schiff (L.T.A.S.). Material fixed in picric alcohol was examined for glycogen, using Best's carmine stain. Later in the survey, however, this was discontinued, as it was found that L.T.A.S. gave a relatively good estimate of the amount of glycogen present. The grading of both fat and glycogen was made on a 0, +, ++, +++ basis and was carried out in advance of the routine post-mortem histology without reference to the individual records (Fig. 1). In this there was less chance of the grading being influenced.

Results

On analysing the findings it soon became apparent that the amount of glycogen present varied greatly from case to case, but fatty change followed a much more definite pattern. In no instance did the left heart ever show more fat than the right, nor the atrium more than the ventricle. Indeed, in 50% of the cases the right ventricle showed most change, while in the remainder both ventricles were equal. Apart from the fact that the average duration of life was shorter—namely, 28 hours

Fig. 1.—Fatty change in the myocardium, grade + + +. (Frozen section stained with Sudan black.)

—when fatty change predominated in the right heart and increased to 40 hours when both ventricles were equal, no difference could be seen in these two groups. Thus it seems that fatty change appears earlier in the right heart.

As already mentioned, there were 57 unselected neonatal deaths in the series; the results of their analysis are shown in Table I. Also included are six stillbirths, which are discussed later. All cases were graded according to the amount of fat present in the right ventricle.

TABLE I.—Cause of Death and Incidence of Fatty Change in the Right Ventricle in 57 Neonatal Deaths and 6 Stillbirths

Cause of Death	No. of Cases	No. of Cases Positive	No. of Cases Strongly Positive
Hyaline membrane disease	21	17	11
Asphyxia	7	5	3
Haemorrhages	15	7	2
Rhesus incompatibility (4 stillbirths)	8	6	3
Unavoidable foetal blood loss <i>in utero</i> (1 stillbirth)	3	3	2
Placental insufficiency	2	2	1
Congenital heart disease	3	3	3
Pulmonary hypoplasia (1 stillbirth)	4	2	0

Hyaline Membrane Cases

The largest group consisted of 21 cases with hyaline membrane disease. All were premature and showed post-mortem changes of cardiac failure, with the exception of two, where it was presumed that large terminal intraventricular haemorrhages had relieved the venous pressure. Apart from four cases, which are discussed later, fatty change was present in all the hearts. Thus 17 (81%) were positive—11 of them (52%) strongly positive.

When the cases were divided into three groups according to the amount of fat present in the right ventricle, each presented a distinct clinical picture (Table II). The first group of five cases with marked fatty change were typical examples of the so-called "hyaline membrane syndrome." Initially all the babies were in good condition, but after a few hours they developed respiratory distress and deteriorated, dying approximately 43 hours after delivery. Hyaline membrane formation was marked in each of these babies.

In the second group of six cases showing moderate amounts of fat the condition of the child at birth was variable. Occasionally slight improvement occurred, but deterioration eventually set in and the babies died some 30 hours after delivery, the hyaline membrane being if anything less prominent, but variations were wide.

In the third group of six cases with only slight fatty change the condition of the babies was never good and

TABLE II.—21 Cases of Hyaline Membrane Disease

Amount of Fat	No. of Cases	Average Maturity (weeks)	Average Weight of Baby (g.)	Average Condition of Baby	Average Amount of H.M.	Average Duration of Life (hours)
+++	5	31.5	1,558	Good—slow deterioration	+++	43
++	6	31	1,363	Variable—slow deterioration	++	30
+	6	30.5	1,567	Poor	++	9
		?	2,040	Oedema ++. Serum proteins 4.9 g.%	++	29
		30	1,420	Poor. ?Foetal blood loss	+	5
0	4	31	1,240	Poor. Alveolitis placentitis	++	9½
		32	1,050	Poor. Neuroblastoma—one adrenal	+	3

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all died within a few hours of delivery. The hyaline membrane was patchy and areas of primary atelectasis were frequent. One felt that the latter was more important than the membrane itself in causing the baby's death.

It was remarkable how easily each of the above groups could be identified and how they showed this direct relationship between the degree of fatty change, the duration of life, and to a less extent the amount of membrane formation.

Asphyxial Deaths

There were seven neonatal deaths in which the post-mortem findings showed appearances suggestive of asphyxia. Five of the babies were premature. All had signs of cardiac failure, and fatty change was present in the myocardium in five (71%); it was marked in three (43%). In the remaining two cases, which were negative, intrapulmonary haemorrhage had occurred. The number in this group is too small for further analysis, but I had the impression that the fatty change could once again be related to the duration of anoxia.

Haemorrhage

The 15 cases in this group presented a very varied picture at necropsy. In four babies with cerebral birth injury cardiac failure was not a feature, and even in the remainder, where the haemorrhages were asphyxial in origin, as in intraventricular haemorrhage, signs of venous congestion and cardiac failure were not usually found. Neither was fatty change in the myocardium prominent. In only two cases was it marked, and in both these babies the haemorrhages were slowly cumulative and asphyxial in origin.

Rhesus Incompatibility

Eight cases were included in this group, four stillbirths and four neonatal deaths. Unlike the majority of stillbirths examined, the stillborn hydropic babies in this group showed evidence of fatty change in the myocardium. In all four the myocardium was pale and there was evidence of hypertrophy. In two of the neonatal deaths the infants showed hyaline membrane formation and they also had marked fatty change in the heart. The remaining two were negative for fat, and, though no valid explanation can be given, it is interesting to note that both babies were delivered by caesarean section. They lived for seven and nine hours respectively.

Gross Oxygen Lack in Utero

Two conditions likely to cause gross foetal anoxia are considered here. In the first group, three babies died of anaemic anoxia due to unavoidable foetal blood loss. All were extremely pale and the great vessels and heart were empty at necropsy. Fatty change was seen in the myocardium and in two of the three cases it was marked. One of these was a stillbirth. The others survived only a few hours.

In the other group of two cases the anoxia was thought to be due to placental insufficiency. This condition is always difficult to assess, but in addition to the placental changes, which were obvious, the babies were long, thin, and wizened. They lived only 12 and 45 hours respectively. Though both showed evidence of fatty change in the myocardium, more was found in the baby which died the sooner.

Congenital Heart Disease

All three babies with congenital heart disease showed marked fatty change in the myocardium. Deaths in this group occurred between the first and third days, and only one baby was premature.

Pulmonary Hypoplasia

Two cases of anencephaly and two with renal abnormalities are included in this group. All showed pulmonary hypoplasia (Potter, 1952). The renal abnormalities were bilateral polycystic kidneys and renal agenesis, and there was also some evidence of cardiac hypertrophy.

One of the anencephalics lived one and a half hours. Despite this short interval, some fatty change was present in the right heart, while none was seen in the left. The other anencephalic was stillborn and showed no evidence of fatty change.

Both babies with renal abnormalities were liveborn. The infant with renal agenesis lived half an hour and showed slight fatty change in the right heart, but not in the left. No fatty change occurred in the case of polycystic disease of the kidney, and this baby lived for one hour. However, here the pulmonary hypoplasia was less marked, the lungs weighing twice as much again as those in the cases of renal agenesis.

Stillborn Babies

Nine fresh stillbirths, two of them premature, were also examined, and the hearts of all these babies showed no evidence of fatty change.

Glycogen

So far the amount of glycogen found has not been considered. This varied greatly throughout the heart. Highest concentrations were noted in the papillary muscles and in the atria. Slightly less was found in that part of the ventricle immediately beneath the endocardium, and this decreased towards the pericardial surface. The actual amounts varied widely in left and right heart, and no one side was consistently the higher. This made assessment difficult.

Some of the variability in results may in part be due to post-mortem glycolysis, although, in view of the refrigeration, this ought to have been minimal. However, taking this into consideration it is interesting to note that those cases showing the most marked fatty change apparently also had an extreme degree of glycogen depletion. This is shown graphically in Fig. 2. Here it can be seen that as the fatty change increased so the incidence of complete glycogen depletion rose in each group and when fatty change was marked 73% of cases showed no stainable glycogen.

Discussion

One of the features of this analysis of fatty change in the heart of newborn babies is the similarity shown by the deaths due to asphyxia and hyaline membrane. Evidence of cardiac failure is seen in both and is associated with an atelectasis which may be primary or secondary, depending on the type of case. In each, fatty change in the heart is marked and increases with the duration of life. Glycogen depletion is also a prominent finding in both. Broadly speaking, though the initial processes may be different in these two conditions, it is possible that, terminally at least, the same factors may be present. Bound *et al.* (1956) compared the effects of oedema and

haemorrhage seen in asphyxial lungs with those of hyaline membrane formation and found they were all remarkably similar. These authors actually stated that the one term "pulmonary syndrome" should cover all three conditions. Indeed, there is no clear line of demarcation between each group, and this is evident in the present survey.

In the six hyaline membrane cases with +fat it is doubtful if the very patchy membrane formation is of any significance at all. These babies are really dying of a primary atelectasis and ought to be included in the asphyxial deaths. Ranström (1953) was probably the first to draw attention to this group. He described in detail the histological appearance of the lungs, but did not analyse his findings further, though he felt the membrane was less important as a cause of death. Thus combinations of the two conditions occur, and, even in asphyxial deaths, hyaline masses, which have similar staining properties to that of the membrane, may be seen lying in partially collapsed alveoli.

Since there is this close association and lack of clear demarcation between the asphyxial and hyaline membrane deaths, I wonder if some common factor may not be present in each. The post-mortem appearances in both groups indicate a right heart failure, and underlying this there is the occurrence of atelectasis, sometimes primary, sometimes secondary, frequently mixed. This atelectasis is likely to have a double effect. There will be varying degrees of anoxia with consequent effects on metabolism, and intrapulmonary pressure will almost certainly be high (Rowe and James, 1957; Adams and Lind, 1957). In pulmonary hypoplasia similar conditions probably also exist, but here the inability of the lungs to expand, and not atelectasis, is responsible for the raised intrapulmonary pressure and possible increased load on the right heart.

This being so, it is interesting to note that fatty change was also found in all three cases of congenital heart disease. From the above it seems reasonable to suggest that an excessive load was placed on these hearts, thus increasing their metabolic demands, but owing to their inadequately maintained circulation and consequent anoxia their metabolism was probably deranged.

FIG. 2.—Incidence of glycogen depletion in relation to fatty change.

On the other hand, in the cases of rhesus incompatibility, placental insufficiency, and foetal blood loss *in utero* a high degree of anoxia must have existed even before birth, and it is possible that here the heart is already damaged and unable to maintain ordinary pressures. In the cases of rhesus incompatibility the infants were also extremely oedematous, and the obviously increased blood volume would add to the cardiac difficulties.

In contrast to cases of foetal blood loss *in utero* are those babies who die of haemorrhage in the neonatal period. Here the picture is not generally one of persistent or progressive anoxia, nor is there usually any evidence of cardiac failure at necropsy. It is not surprising that fatty change in the myocardium was infrequent and of mild degree.

It is more difficult to explain why certain cases of hyaline membrane disease do not conform to the general pattern. It will be remembered that there were four such cases in which no evidence of cardiac failure or of fatty change in the myocardium was seen. No real explanation for these cases can be offered, but it may be that the mechanism of formation of the membrane differed in these babies. Papers by Gitlin and Craig (1956), Van Breemen *et al.* (1957), and Carone and Spector (1960) have suggested that the membrane has an endogenous vascular origin, and this idea is now generally accepted. This being so, it is quite conceivable that general factors giving rise to pulmonary oedema, as well as local conditions peculiar to the pulmonary circulation, may play a part in membrane formation. Table II shows that in all four babies complicating factors were present and that each of these might well have influenced the development of pulmonary oedema. In these circumstances there might well be little obstruction to the pulmonary circulation and no increase in cardiac work.

Before concluding, it should be pointed out that it has not been the purpose of this paper to consider fat metabolism or fatty change in the neonate in any great detail. On the other hand, it does seem that in many cases some derangement of cardiac metabolism occurs before death in the newborn and that this can at least in part be related to anoxia and increased cardiac effort. It is independent of the maturity or nutritional state of the child and is not present in stillbirths, apart from a few expected exceptions. Experimental work on cardiac metabolism indicates that the heart does not use glucose directly—at least not to any great extent (McGinty and Miller, 1932). Under normal conditions lactic acid is the final product which is utilized, but it seems likely that another source of energy is fat (Cruickshank, 1936).

Whatever the intimate details of the metabolic process, it seems obvious that, in the circumstances prevailing, fat is transported to the myocardium under the stimulus of energy demands. Possibly, owing to anoxia, catabolism does not keep pace with the supply, thus leading to the deposition of fat in a stainable form. This is in line with modern thought on so-called "fatty degeneration" of the myocardium (Dible and Gerrard, 1938). Only in conditions of great stress is glycogen called upon as an emergency fuel (Fletcher and Waters, 1938). If this is so, it may explain why extreme glycogen depletion was a late feature in some of our cases where fatty change was marked. Of course it is realized that the histological assessment of glycogen is

fraught with difficulty, and no definite claims can really be made in this respect at present, but it is interesting to note that the distribution pattern throughout the heart corresponds to that of chemical analysis (Cruickshank and Shrivastava, 1930; Blume, 1934).

Summary

Fatty change in the myocardium is a fairly constant feature in neonates showing evidence of cardiac failure at necropsy.

It was seen in babies dying of asphyxia, hyaline membrane disease, haemolytic disease of the newborn, unavoidable foetal blood loss *in utero*, placental insufficiency, congenital heart disease, and pulmonary hypoplasia.

It was not a prominent feature in deaths due to haemorrhage in the neonatal period, and with few exceptions was not found in stillbirths.

When present, fatty change tended to occur earlier and was more pronounced in the right heart. It is suggested that this may be related to raised pressure on the right side and increased cardiac effort resulting from atelectasis, together with the effects of anoxia itself. The extent to which each factor contributes will vary from case to case, as illustrated by the findings in congenital heart disease and haemolytic disease of the newborn. On the other hand, anoxia without cardiac stress, as seems to occur in cases of haemorrhage in the neonatal period, does not result in fatty change in the myocardium.

Possibly the fat is transported to the heart, but, owing to the extenuating circumstances, is not adequately metabolized and so becomes unmasked.

In hyaline membrane disease an interesting correlation existed between the amount of fatty change, the duration of life, and to a less extent the amount of membrane itself. There were four exceptions to this general rule, and it is possible that other factors, not necessarily cardio-respiratory in origin, may occasionally be responsible for membrane formation.

In almost a third of hyaline membrane cases the membrane is patchy and the babies live only a few hours. Death is really due to a primary atelectasis. It is very doubtful if these cases should be classified as hyaline membrane deaths.

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