STUDIES IN PERINATAL PAEDIATRICS

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PREFACE

This thesis comprises five studies in perinatal paediatrics associated with foetal and infant mortality and morbidity. It is well known that perinatal mortality rates have declined over most of the world in this century. There remain peristent problems which have not been resolved as rapidly as might have been hoped or expected. In addition as a result of more efficient and efficacious paediatric care defective and damaged infants tend to survive now where formerly they would have died. It is evident that the saving of infant life is only of value if these babies can become independent and capable human beings. It follows that in many instances the root of the problem lies further back than in the paediatric care of the newborn infant.

The problem of perinatal loss and of the danger of physical and mental disability from perinatal causes presented itself to me with force in 1959, whilst acting as locum Senior Registrar to the Paediatric Unit at Stobhill Hospital, Glasgow. At that time I was concerned with the daily management of the infants of the Premature and Sick Nurseries of the Maternity Unit. We had no knowledge of the welfare of these babies after discharge from hospital. I therefore organized an Out-patient Clinic for all low birth-weight babies, so that they could be seen during the first year of life. Their physical and mental status were assessed, and the findings related to maternal and neonatal conditions.

It was apparent that a considerable number of low birth-weight babies was of greater maturity than the birth weight would suggest. A

separate study was therefore undertaken for the examination of the perinatal factors concerning these small, mature babies in comparison with the small, immature infants.

These low birth-weight babies accounted for two-thirds of the total perinatal mortality in the Unit. It was a reasonable extension therefore to survey the remaining one third of infants who were still-born or who died neonatally, thus giving an over-all picture of the features of perinatal loss in the Stobhill Maternity Unit.

Amongst the low birth-weight babies was a number of twins. These infants have been dealt with as a separate group. Their maternal and neonatal characteristics have been considered.

Renal-tract infection in pregnancy has been of much interest in the past decade and in my study of perinatal mortality overt infection was noted retrospectively to occur more frequently amongst mothers with perinatal loss than amongst mothers with healthy infants. Further, during recent years there have been contradictory reports as to whether or not such infection is an aetiological factor in the birth of "premature" infants. In 1961 therefore I undertook a prospective study of maternal renal-tract infection, screening the mothers attending the Stobhill Antenatal Clinic by the use of fresh drop-preparations of urine stained with Gram's stain. In 1962 my interest was stimulated to extend the series further by the introduction of a chemical method of detecting significant numbers of bacteria in the urine, which I was able to carry out personally. Coincidentally with this the Bacteriology Department at Stobhill Hospital agreed to carry out bacterial counts by

the fluid-dilution technique on such specimens as I submitted to them. This step led to the identification of the organism and its drug sensitivity, so that at this point, and with the permission of the obstetricians, I was able to treat these patients before they developed symptoms. Ultimately bacteriological examination of the urine by the quantitated-loop technique became and remains routine practice for all pregnant women at their first visit to the Antenatal Clinic. It was thus possible to survey a large number of patients, to appraise the maternal factors associated with renal-tract infection, and to assess its effect on the foetus and infant. This work forms the basis of three papers which have been published already*.

These five subjects form the matrix of this thesis, viz., a survey of the causes of perinatal mortality; a study of the perinatal characteristics of low birth-weight babies with special reference to their physical and mental development in the first year of life; an examination of the characteristics of small, mature infants; an outline of the perinatal characteristics of twins associated with low birth-weight and finally the section on maternal renal-tract infection and its effect on the foetus and infant. Much has been learnt from these studies but many more problems have been raised which would form starting points for further work.

The thesis is set out in two volumes. The first volume contains the text, comprising short introductions, materials and methods, results,

*Patrick, Marguerite J. (1966) J. Obst. & Gynaec. Brit. Comm., 73, 973
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discussions and summaries. The second volume comprises the tables and figures for ease of relating them to the text, followed by the appendices and the references.

I wish to thank Dr. I.D. Riley for his support throughout the preparation of this thesis. My thanks are also due to Dr. D. McK. Hart for access to obstetrical patients and to Dr. J. Stevenson for the bacterial counts. Many of the photographs were taken by Mr. W. Waldie. Finally I have to thank Mrs. M. Scoullar for her care and patience in the typing of this thesis.

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PERINATAL INFLUENCES RESULTING IN THE DEATH OF THE SINGLETON FOETUS OR INFANT

INTRODUCTION

It was not until the middle of the 18th century that interest began to awaken in neonatal mortality and morbidity. In 1749 the death rate in infants at the London Lying-in Hospital was one in 15. The causes were varied. They included Jaundice and Apnoeic Attacks (Burton*, 1742), Neonatal Tetanus or "Nine-Day Fits" (Clarke*, 1789), and "Malignant Familial Jaundice" (Underwood*, 1784). Much loss of life and morbidity was undoubtedly due to sheer neglect, ignorance, or both.

Little was known of maternal conditions leading to foetal loss. It was not until 1901 that William Ballantyne, in Edinburgh's Simpson Memorial Hospital, was allocated one "Pre-maternity" bed for the care of the unwell pregnant woman, and not until 1915 that the idea of an ante-natal unit as we now know it was first put into practice. It was only five years ago, in 1963, that the First Report of the 1958 British Perinatal Mortality Survey (Butler and Bonham) was published. Thus, it is evident that while the concept of Neonatal Paediatrics may be 200 years old that of Perinatal Paediatrics is only some 50 years of age. In this time progress has been considerable, some notable advances have been made, but there remains much to be done, and several of the original problems are as yet unsolved.

* Quoted from Craig (1946)

Definition of Perinatal Mortality

For the purpose of this study the term perinatal mortality is defined as the loss of any foetus or infant between the 28th week of gestation and the 28th day of life. In the recent study on Perinatal Mortality (Butler and Bonham, 1963) the seventh day of life is taken as the upper limit. This difference is of little importance in the present series, reducing the perinatal mortality rate from 4.9 per cent. to 4.7 per cent..

The Purpose of Analyzing the Causes of Perinatal Mortality

The purpose of analyzing the causes of perinatal mortality is at least threefold. The rate should be known in any one Maternity Unit so that comparison can be made with other Units, and improvements brought about where facilities or capabilities are lacking. Secondly, such a review should enable one to recognize the sudden short-term deviations from average within the Unit, thus enabling the cause to be recognized early and dealt with expeditiously. With the coming of the computer this should become a practical proposition. Thirdly, a continuing analysis of perinatal mortality will show on a long term basis those areas of obstetrics and paediatrics in which research is most urgently required.

Part I of this thesis is based on births which took place six years ago in the Maternity Unit at Stobhill Hospital. It indicates the progress which has been made in that time and illustrates fairly well the three points already mentioned, which make constant review of perinatal mortality an essential for the best results for mother and child. This

review assesses the size of problem, recognizes some of the short-term variations, and in particular re-emphasizes some of the older problems related to perinatal mortality which are not yet solved.

Little reference is made to autopsy results as the information available on this aspect of perinatal death was incomplete, post-mortem examination having been carried out on rather less than half of the total number of infants lost. It was thought of interest rather to examine the causes of mortality as they developed from the pre-natal period in that this is the main way in which such deaths will be prevented.

MATERIALS AND METHODS

The study took place over a 17-month period from January 1st, 1959, to May 31st, 1960. An analysis was made of all singleton stillbirths and neonatal deaths. During this period 3,093 singleton babies were delivered in the Maternity Unit, Stobhill Hospital, at over 28 weeks gestation. One hundred and fifty-three (4.9 per cent.) were lost between that time and the 28th day of life. Eighty-seven (57 per cent.) were stillborn and 66 (43 per cent.) died during the neonatal period. The information available was transferred to punch cards for analysis.

Initially all 153 infants dying perinatally were analysed for duration of gestation, range of birth weights and for the distribution of stillbirths and neonatal deaths according to maturity and birth weight. Thereafter, it seemed reasonable to divide the infants into two groups referred to as Group I and Group II.

Group I comprises 70 infants who were stillborn or died from congenital defects, accidents of labour, haemolytic disease of the newborn, placenta praevia and intrapartum sepsis. These babies accounted for 45.8 per cent. of the total perinatal mortality in the Unit during the period under survey. There were 37 stillbirths and 33 neonatal deaths.

Group II babies are most easily described as those babies who showed none of the above conditions. The disturbance was apparently one of environment, usually the result of maternal illness, or a malrelationship in physiology between mother, placenta and foetus. There

was no gross structural abnormality of the foetus, no apparent mechanical difficulty in delivery sufficient in itself to account for foetal loss, no iso-immunization and no sepsis. Eighty-three infants died perinatally in this group, accounting for 54.2 per cent. of the total perinatal mortality in the Unit. There were 50 stillbirths and 33 neonatal deaths.

For certain comparisons it was necessary to form a control group. This group comprises 100 mothers and babies selected on the basis that after delivery the baby required no special nursery care but was fit to accompany the mother to her beside direct from the labour room.

RESULTS

All Perinatal Deaths

The Duration of Gestation

Table I shows the duration of gestation in these 153 pregnancies. Seventy-eight infants (50.9 per cent.) were of at least 37 weeks maturity, whilst the remaining half were of under 37 weeks maturity. It is noteworthy that 51 infants (33.3 per cent.) were between 37 and 40 weeks maturity.

Range of Birth Weights

Table II shows the birth weights of these 153 infants who were stillborn or died neonatally. There is no marked peak incidence in perinatal mortality in any one birth weight group although birth weight 1,501 g. to 2,000 g. makes the largest percentage contribution.

The Contribution made by Short Gestation and Low Birth Weight to Perinatal Mortality

By comparing tables I and II it is seen that both immaturity and low birth weight make appreciable contributions to perinatal mortality, but that many babies also die who, by the duration of gestation or birth weight might be expected to survive. Low birth-weight babies prepond-erate over immature babies, indicating a tendency for these babies to show retardation of intrauterine growth.

Distribution of Stillbirths and Neonatal Deaths According to the Duration of Gestation and the Birth Weight

From table I it is seen that stillbirth was more common than

neonatal death in those infants of over 37 weeks maturity, the ratio being 52 to 26, compared with 35 to 40 in those infants of under 37 weeks maturity (p 0.01). Similarly in Table I it is seen that in those infants weighing over 2500 g. at birth the ratio of stillbirths to deaths was 36 to 17, compared with a ratio of 51 to 49 in the infants weighing 2500 g. and less at birth (p 0.01). Thus stillbirth is a feature of the mature infant approximating normal birth weight, rather than of the immature, low birth-weight infant.

Time of Neonatal Death

Table III shows the time of death in the 66 infants dying neonatally. Fifty-seven (86.4 per cent.) died in the first week of life, whilst only nine (13.6 per cent.) died between the end of the first week and the 28th day of life.

PERINATAL DEATHS: GROUP I INFANTS

(Congenital Defect - Accidents of Labour - Haemolytic Disease of the Newborn - Placenta Praevia - Intra-partum Sepsis)

Seventy of the total of 153 infants (45.8 per cent.) dying perinatally belonged to this group. Table IV shows the number of infants lost by stillbirth or death from these five well-recognized causes.

Congenital Defect

Table V shows the types of congenital defect present in forty infants whose loss was primarily attributed to this cause. Defects of dorsal mid-line fusion were commonest, accounting for 50 per cent. of all lethal congenital abnormalities and 13.1 per cent. of the total perinatal mortality in the Unit. Genetic defects comprised 20 per cent. of the abnormalities and a group of miscellaneous defects the remaining 30 per cent. Details of these cases are given in Appendix A.

Accidents of Labour

Thirteen major accidents of labour accounted for 8.5 per cent. of the total perinatal mortality in the Unit. Eleven infants were stillborn and two died neonatally. Table VI shows the type of accidents which occurred. The numbers are too small to indicate any broad features. Appendix B shows the details of these cases.

Haemolytic Disease of the Newborn

Haemolytic disease of the newborn due to Rhesus incompatibility

accounted for eight perinatal deaths (six stillbirths and two neonatal deaths), 5.2 per cent. of the total perinatal mortality in the Unit. Details of these cases are shown in Appendix C.

Placenta Praevia

Placenta praevia accounted for six losses, 4.0 per cent. of the perinatal mortality for the Unit, comprising two stillbirths and four deaths. Details of these cases are shown in Appendix D.

Intra-Partum Sepsis

Intra-partum sepsis accounted for the loss of three infants, 2.0 per cent. of the total perinatal mortality of the Unit, one being stillborn and two dying neonatally. Details of these cases are shown in Appendix E.

PERINATAL DEATHS: GROUP II INFANTS

Eighty-three of 153 infants (54.2 per cent.) dying perinatally belonged to this group. They comprised infants in whom no readily apparent gross abnormality was seen. Abnormalities of environment, or in the foeto-placental-maternal relationship was probably present. Thus maternal factors are of considerable importance and are examined in some detail in the ensuing section.

The Duration of Gestation

Table VII shows the duration of gestation in 83 infants of Group II dying perinatally. It shows that immaturity made the largest contribution to perinatal loss, but that 21 per cent. of losses nevertheless occurred between the 37th and 40th week of gestation. The table shows that stillbirths outnumbered neonatal deaths by 50 to 33 in these infants dying of "environmental" causes.

Range of Birth Weights

Table VIII shows the birth weights of these 83 infants dying perinatally and the distribution of stillbirths and neonatal deaths in each weight group. It is seen that over one third of the infants weighed 1500 g. or less, and that 77.1 per cent. of the perinatal mortality in Group II babies was accounted for by infants weighing 2500 g. or less at birth. In the low birth-weight babies 54.7 per cent. were lost by still birth and 45.3 per cent. by neonatal death, whereas in the bigger babies

78.9 per cent. were lost by stillbirth and 21.1 per cent. by neonatal death.

Intra-uterine Growth Retardation

By comparing tables VII and VIII it is seen that this group of babies tended to show dysmaturity in the form of intra-uterine growth retardation, 66 per cent. being of less than 37 weeks maturity but 77 per cent. being 2500 g. or less in weight at birth.

The Distribution of the Sexes in Group II Infants

There was a preponderance of males in Group II infants dying perinatally. In Table IX the sex distribution in these infants is compared with that of the control group of healthy infants. The difference is statistically significant at p value 0.02 and 0.01. It is of interest to modify table IX by adding the sexes of infants of Group I, in order to find the over-all distribution of the sexes in these infants dying perinatally, and to compare it with the normal sex ratio for total births as given by Butler and Bonham (1963). Table X shows the result. The over-all sex ratio in this series, of 55.5 per cent. male to 44.5 per cent. female, is very similar to the over-all ratio of 51.7 per cent. and 48.3 per cent. shown by Butler and Bonham. Amongst Group I infants there is a preponderance of females over males amounting to a difference of 15 per cent. which is due to those infants with defects of midline fusion, mainly anencephaly. Amongst Group II infants, however, the preponderance of males over females amounts to 35 per cent.

All factors for which I have information were worked through statistically according to the sex of the foetus. There was nothing significant in the relation of the sex of the infant to duration of gestation, birth weight, maternal age, parity, previous obstetrical history, mode of delivery or duration of membrane rupture prior to delivery. The consideration of maternal illness however was of interest. Since the ratio of males to females in this series is approximately 2 : 1 (56 : 27) any illness occurring alone or in combination with other illness at a ratio greater than 2 : 1, when compared according to the sex of the infant, may be related to the fact that the foetus was male. Pre-eclamptic toxaemia when combined with ante-partum haemorrhage showed a ratio of seven males to one female, ante-partum haemorrhage alone a ratio of 8 : 5, pre-eclamptic toxaemia alone 1 : 1, antepartum haemorrhage with anaemia 11 : 3 and anaemia alone 2 : 0.

Thus pre-eclamptic toxaemia with antepartum haemorrhage is related to the male sex of the infant. Ante-partum haemorrhage with iron-deficiency anaemia is found slightly more often with a male than a female foetus.

Maternal Factors in Group II Babies

Age. Table XI shows the ages of 83 mothers of infants dying perinatally and of 100 mothers of healthy infants. The mother over 30 years of age had a significantly increased risk of foetal loss ($p < 0.05 > 0.02$).

The distribution of stillbirths and deaths is also shown in this table. Neither stillbirth nor neonatal death was a particular feature

of either age group and in both age groups stillbirth was the more common mode of loss.

Parity. Table XII shows the parity of 83 mothers of infants dying perinatally and that of 100 mothers of healthy infants. Significantly more mothers of infants dying perinatally were pregnant for the fourth time or more ($p < 0.01$). There was no significant difference in the distribution of stillbirths and deaths in relation to parity. The primigravid mothers did not have an increased perinatal mortality rate in this series.

Height. Height, when considered for mothers of 150 cms. (5 feet) and less, and over 150 cms. had no bearing on perinatal mortality, nor on the distribution of stillbirths and neonatal deaths.

Previous Obstetrical History. Table XIII shows the incidence of miscarriages, stillbirths, previous premature live-births and of maternal illness in previous pregnancies in 57 mothers of infants dying perinatally, and 56 mothers of healthy infants. The birth of a low-weight baby (2500 g. or less) previously is the only factor which is significantly more frequent in the mothers with perinatal loss in their current pregnancy. The distribution of stillbirths and deaths showed no pattern in relation to previous obstetrical history. The numbers were small.

Maternal Illness in Current Pregnancy. Table XIV shows the number of illnesses in each of these 83 mothers of infants dying perinatally and in 100 mothers of healthy infants. The former group of mothers individually showed more numerous illnesses than the latter group ($p < 0.01$).

Table XV shows the type and incidence of illness in these 83 mothers and amongst the 100 mothers of healthy infants. Antepartum

haemorrhage and pre-eclamptic toxaemia were significantly related to foetal and infant loss ($p < 0.01$ in both instances) as was overt urinary-tract infection ($p < 0.05 > 0.02$). Iron-deficiency anaemia was more common in the group of mothers with healthy infants than with infants dying perinatally ($p < 0.05 > 0.02$). The duration of gestation at the time of antepartum haemorrhage was not related to the fatal outcome ($p < 0.20 > 0.10$) but pre-eclamptic toxaemia occurring at under 34 weeks gestation was significantly more frequent in the mothers with perinatal loss than in the mothers of healthy infants ($p < 0.01$).

Appendix F shows the miscellaneous illnesses which were present in these two groups of mothers. Intestinal obstruction with laparotomy was common to both groups as was rheumatic heart disease. Table XVI shows the percentage contribution of each illness towards total morbidity (125 illnesses) in these 67 mothers. Over all, antepartum haemorrhage made the biggest contribution to maternal morbidity, accounting for one third of the total number of illnesses in these mothers. Pre-eclamptic toxaemia accounted for 22.4 per cent. of illness. Anaemia and urinary tract infection made lesser contributions of 14.4 per cent. and 12.8 per cent. respectively. The remainder (the miscellaneous groups of illnesses, hypertension and hydramnios) made small contributions to maternal morbidity.

An assessment was made of the severity of illness in the mothers with perinatal loss and those with healthy infants. Four types of illness, antepartum haemorrhage, pre-eclamptic toxaemia and hypertension, anaemia and clinical urinary tract infection, were assessed as severe,

moderate or mild. In addition it was felt reasonable to classify some of the miscellaneous illnesses as making the mother severely ill. The criteria used for this classification are shown in Appendix G. Table XVII shows the results. It indicates that the severity of maternal illness has a significant bearing on perinatal mortality as judged by this series ($p < 0.01$).

Three Further Considerations

It was felt that three other factors were of interest in relation to the severity of illness in these mothers of infants dying perinatally; namely maternal age, parity and maturity.

The Relation of Maternal Age to the Severity of Illness. Table XVIII shows that maternal age had no bearing on severity of illness in these mothers of infants dying perinatally as considered in this series.

The Relation of Parity to the Severity of Illness. Table XIX shows the relationship of parity to the severity of maternal illness in these pregnancies with perinatal loss. It illustrates the high incidence of severe and moderately severe illness in primigravidae and again in mothers who are pregnant for the fourth time or more. The second and third pregnancies are characterized by illness of less severe degree.

The Relation of the Severity of Maternal Illness to Maturity. Table XX shows that between 28 and 41 weeks the degree of severity of maternal illness was similar when the 28 to 33 week period was compared with the 39 to 41 week period ($p < 0.10 > 0.05$). However, after 42 weeks gestation only mothers with mild illness or none were seen, indicating that post-

maturity itself is a hazard to the foetus.

Mode of Delivery in 83 Infants Dying Perinatally

In table XXI the mode of delivery in the 83 infants dying perinatally is compared with that of 100 healthy infants. There is no significant difference in the numbers delivered either by spontaneous vertex or by Caesarian section. Abnormal vaginal deliveries are more common amongst the infants dying perinatally than amongst the healthy infants.

Delivery by breech occurred in eight of the 11 abnormal vaginal deliveries of infants dying perinatally. Only one of these was at full-term, and the remaining seven were between the 28th and 34th week of gestation. None of the healthy infants was born by breech delivery.

Table XXII shows the duration of gestation in eight infants dying perinatally and of 10 healthy infants born by Caesarian section. Six of eight babies lost perinatally were of under 37 weeks gestation, whilst all 10 in the control group were of over 37 weeks gestation.

Thus it is seen that immaturity makes a contribution to perinatal mortality where the mode of delivery is abnormal.

Administration of Analgesia and Anaesthesia

The numbers of mothers of group II infants dying perinatally and of healthy infants receiving analgesia or anaesthesia within 12 hours of delivery were compared. There was no significant difference.

Duration of Membrane Rupture Prior to Delivery

No significant difference was found in the duration of membrane rupture prior to the delivery of 71 infants dying perinatally and 89 healthy surviving infants. The reduced numbers under consideration here are due to omission of Caesarian section births and those labours in which the interval was not recorded.

Other Factors Associated with Perinatal Death in 16 Mothers with no Apparent Illness and 26 Mothers with Mild Illness

Appendix H summarizes the histories of 42 mothers of infants dying perinatally in whom there was either no recognized illness (16), or evidence of only mild illness (26), insufficient in itself to account for foetal or infant loss. These histories were examined for any special features of duration of gestation, birth weight, percentage of expected weight for gestation, previous obstetrical history, maternal age and parity. Over-all there was little difference to be seen between the details of these pregnancies and those of the remainder of the group II infants.

Other directions of consideration were then pursued with the following results:-

i. Intra-uterine Deaths, Clinical Findings Subsiding. (Case numbers 53, 55, 56, 60 and 62). In five mothers classified as having mild illness the foetus had died in utero by the time the patient was admitted to hospital, and it seems probable that the findings were subsiding by this time. In two there was evidence to suggest that there had been a fairly

severe pre-eclamptic toxaemia, and in three there was hypertension.

ii. Duration of Gestation over 42 Weeks. (Case numbers 67, 68, 69, 70, 71 and 72). In six patients the duration of gestation was over 42 weeks. In one patient the duration of gestation was as long as 46 weeks, and in another 47 weeks according to the date of the last menstrual period. This prolongation of gestation could account for the loss of the foetus.

iii. Bad Obstetrical History. (Case numbers 35, 36, 38, 43, 51 and 66). It is apparent from Appendix H that six mothers had a history of more than one unsuccessful pregnancy (miscarriage, stillbirth or low birth-weight baby). These six mothers produced only six normal babies in a total of 27 pregnancies. Or, unloading the numbers by removing one for the pregnancy by which this case has been selected, it would mean that six mothers had produced six normal babies in 21 pregnancies. In the group of control mothers with healthy infants, matched as closely as possible for age and parity, six mothers produced 21 normal babies in 25 pregnancies. Taking into consideration six mothers with severe or moderately severe illness similarly matched, 18 normal babies were derived from 26 pregnancies. There is, therefore, a group of mothers, or parents, whose reproductive capability appears to be inherently subnormal.

iv. Late Pregnancy After Long Interval. (Case numbers 60 and 62). Two mothers, both aged 38 years, both obese and hypertensive, had intrauterine deaths and were delivered at 40 weeks. The first patient's previous pregnancies had been at the age of 22 and 24 years. The second patient's previous pregnancy was at the age of 20 years. The latter patient also had a urinary tract infection. In both mothers the foetus

was dead at the time of admission to hospital. It seems probable that hypertension was subsiding by the time the patients were delivered and therefore these patients are also included in paragraph i, "Clinical Findings Subsiding".

v. Late Abortions. (Case numbers 31 to 48 inclusive). Eighteen mothers were delivered before the 32nd week of gestation, nine with a history of bleeding as the only abnormality. Two of these had started bleeding at a time when they would have been classified as abortions had they delivered immediately. Two of these mothers are also included in the group of mothers with bad obstetrical histories.

vi. Eleven Remaining Cases. (Case numbers 49, 50, 52, 54, 57, 58, 59, 61, 63, 64 and 65). Nine of these deaths were due to a combination of causes, none of which in itself would necessarily prove fatal, nor indeed does the combination invariably prove fatal, whilst in two (cases 63 and 65) no abnormality was made out to account for the loss.

DISCUSSION

All Perinatal Deaths

One hundred and fifty-three singleton infants were lost by stillbirth or neonatal death during the 17-month period under survey in the Stobhill Maternity Unit. The loss amounts to 4.9 per cent. of 3,093 deliveries. Only nine infants were lost between the end of the first week and the 28th day of life making the stillbirth and early neonatal death rate 4.7 per cent.. This is a higher figure than that of the First Report of the 1958 British Perinatal Mortality Survey (Butler and Bonham, 1963), in which 617 stillbirths and early neonatal deaths occurred in a total of 16,994 deliveries, a perinatal loss of 3.6 per cent.. Richards and Lowe (1966) show a perinatal mortality rate of 3.0 per cent. in England and Wales in 1963. The extent of mortality in the present series probably reflects only the high number of maternal, foetal and labour abnormalities which are dealt with in hospital practice. Stillbirths outnumbered early neonatal deaths in all three studies, accounting for close to 60 per cent. of losses.

The duration of gestation in one third of infants dying perinatally was between 37 and 40 weeks, a time when one would reasonably expect a successful outcome to pregnancy. Fifty per cent. of infants were of less than 37 weeks gestation, and one third of the total were of under 34 weeks gestation. The remaining 17 per cent. were of over 40 weeks maturity, which in itself adds to the risk of perinatal loss. Whilst

the margin of immaturity compatible with survival is increasing due to improved paediatric care, the margin of postmaturity compatible with survival is probably smaller, since we know of no sure way of restoring placental function once it has begun to deteriorate. Forty weeks is the optimal time for delivery of the human foetus under physiological circumstances and there is a tendency for those born before or after this time to die out.

The birth weight of 65 per cent. of infants dying perinatally was 2500 g. or less indicating either immaturity or intra-uterine growth retardation, or both. Since the 37th week of gestation is the time at which the foetus, under physiological conditions, reaches 2500 g. (Scammon and Calkins, and Streeter, quoted from Potter, 1961) it is apparent there is an element of dysmaturity amongst these babies dying perinatally and that the tendency is towards undergrowth. Acceleration of growth in utero is seen in some foetuses particularly those of mothers with diabetes mellitus. In the present series one case illustrates this well; the child was delivered at 31 weeks because of placenta praevia and was 158 per cent. of her expected weight. Ten more babies dying perinatally were over 125 per cent. of their expected weight thus raising the question as to whether or not their mothers might be pre-diabetic or suffer from another as yet unrecognized condition. The subject of intra-uterine growth is discussed further in Part II.

The excess of stillbirths over neonatal deaths has already been

mentioned. It is only amongst those infants of over 37 weeks gestation and over 2500 g. at birth that this prepoderance is seen. This appears to be due to infants born at full term who suffer from lethal congenital defects, accidents of labour, haemolytic disease of the newborn and intra-partum sepsis as well as to some of the infants of Group II.

Perinatal Deaths, Group I

Congenital Defects

Amongst the infants of Group I congenital abnormality was the commonest cause of mortality. These defects have been classified in three main groups: defects of dorsal mid-line fusion, genetic defects, and a miscellaneous group of defects of organogenesis.

Potter (1964) states:-

> "Pathology may consist of localized abnormalities in the form of certain parts of the body, of abnormality of an entire type of tissue wherever present in the body, of disturbances in various parts of the body occurring in recognized combination, or in seemingly random association. Such defects may be a primary manifestation of certain genes, noxious agents, or they may be secondary to a change produced in another tissue which was the primary target of the responsible agent. Also included as

> congenital defects may be conditions whose fundamental pathology consists of chromosomal or chemical abnormalities in which abnormality of form may not exist."

In practice it is not always possible as yet to identify closely the cause or nature of the defect. Most investigators are impressed by the multiplicity of agents capable of producing a range of abnormalities, depending on the maturity of the foetus at the time of action, the amount or dosage of the damaging agent, and also on the genetic make-up of the foetus.

Many agents, naturally-occurring and experimental, are now known to be teratogenic. Haring and Lewis (1961) give a comprehensive list. It seems probable that in natural circumstances, at any one time, many fewer agents will be responsible for human abnormality. Nevertheless, it is only be experimental work, perhaps sparked off by clinical observations, that progress can ultimately be made regarding teratogenic agents. This aspect was emphasized by the thalidomide episode, and since then a considerable number of drugs has been comdemned for use in the pregnant woman. McDonald (1961), writing on maternal health in early pregnancy and congenital malformations, found a higher incidence of major defects (anencephaly, hydrocephaly, cardiac defect and hypospadias) in laundry workers, which she attributed to the heavy type of work performed. However, this is not the heaviest type of work undertaken by women, and there may be some specific chemical agent used in laundries which is teratogenic. This is the kind of lead which might

be taken up with the hope of discovery of new toxic agents in every-day use.

The time at which the assault on the foetus is made is of importance in determining the system involved and the extent of involvement. This implies a fairly minute knowledge of embryological development, the kind of information which is to be found in the work of Millen (1963) on "The Timing of Human Congenital Malformations, with a Time-table of Human Development". Rubella is the disease of which we know most with regard to the time of infection and its effect on the foetus. Table XXIII indicates the high risk of the first four weeks. Whitehouse (1963) described a deformed foetus in which the mother suffered from rubella during the month before her last menstrual period, and considered this to be the cause of the defect. This case would seem to indicate that the ovum had been damaged, or that the virus had persisted and damaged the conceptus. The first three months, and particularly the first four weeks are the times at which the foetus is most susceptible to damage, when there is rapid multiplication of relatively undifferentiated cells. Similarly the dose of X-radiation is of importance, the repeated exposures necessary for pyelography for example being contraindicated. The effect of the dose is also dependent on the period of gestation during which the agent is acting and it is recommended that no X-ray should be carried out on a young married woman after the first two weeks from the beginning of the last menstrual period (Apgar, 1961), nor, if newly-pregnant for the first trimester. It is noteworthy that agents damaging to the foetus

may produce no upset in maternal well-being.

The mode of action of all agents damaging to the foetus is by interference with some aspect of cell metabolism. Those agents causing malformation also cause a rise in embryonic mortality (Wilson, 1959). Thiede and Salm (1964) noted some 60 per cent. of spontaneous aborted foetuses to be chromosomally abnormal and stated that

> "all available evidence indicates that the incidence and severity of congenital malformations are inversely proportional to the gestational age of the conceptus".

The abnormality may involve damage to the sperm or ovum, or directly to the developing foetus. Potter (1961) states that the ageing ovum is more likely to be abnormal than the ageing spermatozoon. The result of damage may be resorption of the foetus, or death of cells, resulting in deformity and overgrowth of surrounding tissues, or merely retardation of cell metabolism with undergrowth. Where there is an infectious agent the nature and end of the process will depend on the persistence or eradication of the invading organism.

Roentgen-ray irradiation can produce congenital abnormality either by inducing chromosomal abnormality or by direct cellular damage to the foetal tissue. Puck (quoted from Apgar, 1961), using human chromosomes in tissue culture "regularly reproduced fractionation of the chromatids, abnormal division, translocations and the like" by radiation. Brent and McLaughlin (1960) produced abnormality in rats by direct damage to the foetal tissue, and not through placental irradiation injury or changes

in the maternal metabolism. In Hiroshima microcephaly due to direct ionizing radiation was seen in the infants of mothers who were between the 7th and 15th week of pregnancy at the time of the explosion of the atomic bomb (Miller, 1956) and this finding has been confirmed in a 20-year follow-up study by Wood, Johnson and Omori (1967), whilst an increased incidence of leukaemia was also found. Brill and Forgotson (1964) state that X-ray pelvimetry may be leukemogenic to the foetus. In addition to the danger of radiation injury to the individual in connection with investigations, therapy or occupation, there is the danger of increasing levels of world ionizing-radiation. The National Academy of Sciences (U.S.A.) has recommended a maximum cumulative dose of not more than 10 roentgens per individual from conception to 30 years of age in the population at large, and of a maximum cumulative dose of 50 roentgens for the individual. It is thought that radiation changes within somatic cells are incompletely additive throughout life.

Experimentally, anoxia and hypoxia have been found to produce congenital defects in mice, (Ingalls, Curley and Prindle, 1952). This might appear to be a very basic requirement for normal human development. Apgar (1961), however, states that there is "no good evidence in human being that there is such an association", and deplores "the temptation to transfer findings in lower animals to man".

It is evident that the genetic make-up of a foetus determines the presence of some defects absolutely. This is especially so when the parents are consanguinous. Gene penetrancy may enhance or modify defects, the factors determining this being uncertain. The manifestation of an

abnormal gene may be the result of environmental circumstances during the pregnancy or long before. Roberts (1962), states that each normal person carries between three and eight seriously harmful recessive genes, but that this is no cause for concern unless marriage takes place between blood relations. The risk for several quite common and other more obscure conditions is given by Roberts, and is based on the fact that some 40 per cent. of parents seeking advice at the Genetic Counselling Clinic at Great Ormond Street already have one defective child. Such a service is now of importance with the recognition of an increasing number of genetic and chromosomal defects. Some of the chromosomal defects are now recognizable prior to delivery by culture of foetal cells from specimens of amniotic fluid obtained by amniocentesis (Steele and Breg, 1966). Such a diagnosis would lead to the avoidance of risks to the mother which might be justifiable to ensure the safe delivery of a normal child, or might even lead to the early artificial termination of pregnancy.

Under some circumstances therapeutic abortion should be strongly recommended. These include maternal rubella in the first four weeks of pregnancy and possibly in the second four-week period. Similarly a potential risk of foetal abnormality due to a dominant gene might be considered an indication for the termination of pregnancy.

The pregnant woman exposed to rubella should be protected with gamma-globulin. The diagnosis is not difficult in epidemic times, but contact with a sporadic case may pass undetected. With improving laboratory methods there should be time to establish the diagnosis firmly before considering therapeutic abortion. The delay is 10 days for

primary isolation of the virus, and three to four weeks for the demonstration of a rising antibody titre (Plotkin, 1964).

Death from congenital malformation can be prevented in some instances by early diagnosis and specialised care. Malformations of the gastrointestinal tract are particularly amenable to treatment (Wallace and Saunders, 1959). These include oesophageal atresia, pyloric stenosis, imperforate anus and malrotation of the gut. Genito-urinary obstruction and choanal atresia can also be relieved by surgery. The surgical treatment of meningococles is still disappointing and the survival of such infants with progressive hydrocephalus has added greatly to the numbers of physically and mentally defective children requiring special care. In a series of 100 cases Merril, Isom and Anslow (1962) found that two children were within normal limits, 51 died, and of the remainder 17 were "hopeless", 17 were "non-competitive" with a mean I.Q. of 65, and 15 were "competitive" with a mean I.Q. of 95. Thus it is seen that the aim should be prevention of the defect rather than repair of the defective child.

Defects of Dorsal Mid-Line Fusion. These defects, including anencephaly, hydrocephaly, encephalocoele and meningocoele, constituted 50 per cent. of the total perinatal mortality in the Unit. The rate per 1,000 total births was 6.5. This high incidence in the Stobhill Unit is by no means exceptional. Butler and Bonham (1963) found that defects of dorsal mid-line fusion amounted to 5.8 per 1,000 deliveries in England and Wales

in 1958. Anencephaly is the lesion seen most frequently, followed closely by meningocoele alone or with hydrocephaly. All combinations of the lesions and variations in anatomical extent are seen. Table XXIV shows the incidence in this and other studies. Infants with anencephaly produce no problem of infant morbidity since all are stillborn or die within a few hours of birth. The size of their contribution to perinatal loss, however, has made them the subject of much consideration.

The aetiology of mid-line fusion defects is uncertain but genetic factors may exist. Anencephaly and meningocoele are both known to occur more frequently in the mother who has already had a child with such a deformity. In the present series three mothers of anencephalic infants had other similarly deformed babies, two anencephalic, and one with a meningocoele and hydrocephalus. Three out of nine is a high incidence compared with the experience of others, for example Murphy (1936), Record and McKeown (1950), Doran and Gutkelch (1961) and Milham (1962). Marcus and Brandt (1960) found the incidence amongst neonates with a previously affected sibling to be nine times as great as in the general community. Roberts (1962), states that for parents of two offspring with major central nervous system defects there is a 1 in 7 risk of a third. This lends considerable weight to the belief that these defects are genetic in origin. On the other hand the continued occurrence of such defects despite their early lethal nature suggests that other factors are involved. Kalter (1963) after analysis of twins and siblings considered anencephaly and spina bifida to be of environmental rather than genetic origin, although hydrocephalus is sometimes sex-linked.

There is evidence to suggest that hypoxia may be a cause of these defects. In 1924 Talbot noted frequent foetal malformation in the presence of placental damage, possibly the result of localised hypoxia. Ingalls, Curley and Prindle (1952) considered that low tissue oxygen in the mother and foetus would produce local stress on rapidly differentiating tissues, and demonstrated that low atmospheric oxygen could produce anencephaly in mice. Further Vogel (1961) has described the cerebral circulatory abnormalities in human anencephalics and has found areas of haematopoiesis amongst the disorganized tissues, the presence of which he regards as evidence of anoxia.

It seems probable however that some noxious agent, especially infection, may be influential. These abnormalities occur in clusters in time and space. According to Record (1951), there is a seasonal incidence of anencephalic births, the peak being from October to March. Guthelch (1962) compared the spina bifida figures for Manchester with those of Record for Glasgow (1961) and found a peak incidence from December to May, taking the time of initiation of the defect back to the period March to July. This difference in time of birth might be accounted for by the longer period of gestation characteristic of the infants with spina bifida, and would support evidence suggesting a common cause. On the other hand Kalter (1963) noted that although anencephalic births are more frequent from October to March the same trend is not seen with hydrocephalus or spina bifida. In the infants of the present series the probable dates of conception were spread over all months of the year, and the seventeen-month period under

review is too short a time to indicate any trend of this sort. Leck and Record (1966) added two observations regarding the seasonal incidence of anencephaly. From 1958 they noted that the summer trough had filled in. They felt there must be a specific cause for this. They noted also that amongst surviving siblings there was no such seasonal pattern of birth, but that abortions in these mothers reflected the same seasonal incidence as did anencephaly, suggesting that similar factors were involved.

Two outbreaks of meningocoeles are of interest from the aetiological point of view. Both were superimposed on the general run of meningocoeles. Boris, Blumberg, Feldman and Sellers (1963) published data on an outbreak in Atlanta in August, September and October, 1962, the rate rising from 76 to 441 per 100,000 live births. Lucey, Mann, Simmons and Friedman (1964) reported an outbreak in Vermont, the rate rising from 99, in the period 1952 to 1961, to 232 per 100,000 births in 1962. This would suggest some specific causal agent. Boris et al. write:-

> "The cluster of spinal cord anomalies in this limited period cannot be explained statistically by chance alone. Some teratogenic factor at work briefly in the community during the early gestational period may account for the outbreak".

These two reports were published in June, 1963, and June, 1964, respectively. No teratogenic factor was recognized. Record (1961) noted an abnormally high incidence of anencephaly in Scotland in the five years prior to his report, also suggesting some special causal agent. Several authors have noted a high rate of anencephaly in more densely populated

areas. Pleydell (1960) found the rate twice as great in urban as in rural areas, and three times as great in industrial belts. In France there is a drop in anencephalic births from west to east, which may be associated with falling population density (Lamy and Prezal, quoted from Mufarrij and Kilejian, 1963). Hewitt (1963) reports that mortality from spina bifida is two to three times greater on the Atlantic than on the Pacific Coast of the U.S.A. Here again population density may have a bearing on aetiology and lend some weight to the theory that at least some anencephalic births may be of infective origin. In Patrick's series (1967) five infants with defects of dorsal mid-line fusion were born to 133 mothers with coliform renal-tract infection during the ante-partum period compared with no such defective infants born to 500 mothers with no urinary-tract infection. Whether the infection itself was the noxious agent is uncertain as these mothers were past the organogenetic stage when their infection was diagnosed. The cause of these defects may lie somewhere between environmental and genetic factors in that under certain adverse environmental circumstances in the early weeks of pregnancy the degree of penetrancy of an abnormal gene may be enhanced and the abnormality become manifest.

Polyhydramnios is known to be a common accompaniment of foetal abnormality, and in particular of nervous system defects and oesophageal atresia. In this series 13 mothers out of the total of 20 having infants with defects of mid-line fusion (65 per cent.) suffered from polyhydramnios. It was present in seven of the nine mothers with anencephalic foetuses. Wacker (1963) reported an incidence of hydramnios in

association with anencephaly of 33 per cent., Marcus and Brandt (1960) of 50 per cent., and Comerford (1965) of 90 per cent.. Pinkerton (1961) reported an incidence of 30 per cent. in all nervous system lesions. Conversely, Scott (1961) found a 41 per cent. incidence of grossly malformed infants in 318 mothers with hydramnios, and Moya, Apgar, James and Berlen (1960) a 26.6 per cent. incidence with, in addition, a 17.7 per cent. incidence of other pathological conditions.

The reason for or mode of development of hydramnios is not understood. It was formerly thought to be due to inability of the foetus to swallow amniotic fluid and thus allow its return to the maternal circulation. Nichols and Schrepfer (1966) considered that polyhydramnios is of complex aetiology and not a simple failure to swallow. They observed that infants with oesophageal atresia can have normal amounts of amniotic fluid, and that anencephalics with no swallowing reflex can ingest hyapaque sodium from amniotic fluid.

The sex of the foetus with anencephaly or spina bifida is most often female, in the ratio of 3 to 1 and 2 to 1 respectively (Kalter, 1963). The reason for this is not known. It was suggested that more male foetuses died at an early stage, reducing their numbers when anencephaly would be obvious. It was also thought to be hormonal as a result of pituitary and adrenal deficiency, but this is not borne out by the nuclear chromatin findings which reveal the same sex as that indicated by the genitals (Polani and Claireaux, 1957; Perrin and Benirschke, 1958). There is as yet no satisfactory explanation for the preponderance of females with defects of mid-line

fusion.

Diagnosis of such an abnormality prior to delivery is important. The main aim should be not to endanger the mother's life or damage her in any way. In the present series no mother was at any risk in delivering the anencephalic infants, but with two hydrocephalic infants the head caused obstruction in labour and required perforation before delivery could be effected.

The mothers of babies with defects of mid-line fusion tended to be older than those with healthy infants, the critical age being 30 years. This may be related to increasing parity. There was a higher incidence of mothers who were pregnant for the fourth time or more in the group with defective babies than in that with healthy infants. Edwards (1958) and Record (1961) also noticed this tendency for the older mother to have anencephalic babies. Record pointed out the difficulty of assessing age and parity since these two factors are themselves inter-related. He was able to distinguish, however, a higher rate of anencephalic babies in primigravidas under 25 years of age, and in all groups over 30 years, particularly in those mothers aged 35 years and over and in their sixth or subsequent pregnancies. In the present study the numbers are small and no pattern can be made out.

Genetic and Chromosomal Defects

These constituted 20 per cent. of the lethal defects in this series, accounting for 5.2 per cent. of the total perinatal mortality in the Unit. The rate per 1000 total births was 2.6. This is higher

than the incidence given in the First Report of the 1958 British Perinatal Mortality Survey (Butler and Bonham, 1963) of 1.2 fatal cases per 1000 total births, or in the report on Mortality and Morbidity in the First Year of Life, (Grundy and Lewis-Faning, 1957) of 1.4 per 1000 live births. It is considered that about 10 per cent. of all congenital defects may be genetic in origin (Kalter, 1963).

Four types of defect were seen in the Unit during the period of the Survey. These were Down's syndrome (4), achondroplasia (2), fibrocystic disease of the pancreas (one) and hypophosphatasia (one).

Down's syndrome constituted 10 per cent. of the lethal congenital defects in the series and accounted for 2.6 per cent. of the total perinatal mortality in the Unit. The rate was 1.3 per 1000 total births. The over-all incidence of mongols is stated to be between two and three per 1000 live births (Nelson, 1964). Carter and McCarthy (1951) pointed out that the total incidence tends to increase slightly after the neonatal period when a certain number are newly diagnosed and despite the fact that some die. Down's syndrome was the first defect in which specific chromosomal abnormalities were recognized. A variety of aberrations is now known to account for the general syndrome of mongolism.

The great majority of such infants are born of older mothers. Nelson (1964) states that

> "the average maternal age for such births is almost 10 years greater than for random ones"

and Carter and MacCarthy note that the mother over 45 years of age runs a 2.5 per cent. chance of having a mongol. Penrose (1962) found that in trisomy 21:22 advancing paternal age is a significant aetiological factor. In the infant of the younger mother translocation abnormalities are found and are sometimes evident also in the mother.

In 1962 Collman and Stoller in Australia implicated infective hepatitis as an aetiological factor, but Leck (1966) in Birmingham, England, found no association between the two conditions.

Three of the mothers of this series were of the older age group, being 37, 39 and 40 years of age whilst the fourth was aged 29 years. No pattern of maternal history was seen.

The prognosis in Down's syndrome is largely dependent on the presence or absence of other lesions. Neonatal death is the mode of loss rather than stillbirth. The two conditions particularly associated with mortality in mongols are congenital heart disease and duodenal atresia. Septum primum and ventricular septal defects are seen most often. Massive pulmonary haemorr ages have been noted in these cardiac deaths. (Butler and Bonham, 1963). In the present study congenital heart disease was present in two and duodenal atresia in one of the four mongols. One baby developed gangrene of the legs which was thought to result from an aortic embolism arising from thrombus in a patent ductus arteriosus. In the First Report of the 1958 British Perinatal Mortality Survey six of 12 mongols suffered from congenital heart lesions, and six from either oesophageal or duodenal atresia. In the report of Grundy and Lewis-Faning (1957) seven of 28 mongols suffered from congenital heart disease.

The control of this abnormality could be regarded as one of eugenics, even though the cause is not known. The majority of such infants are born to mothers whose age is outwith the optimal for reproduction. They could thus be avoided by the avoidance of pregnancy at this time of life. In the younger mother the chromosomal abnormality might be recognized if such examination were routine practice. We are however very far from establishing this as a routine procedure.

Two babies with achondroplasia were born in the Unit during the period under survey, one being stillborn and one dying neonatally. They accounted for 1.3 per cent. of the total perinatal mortality. The incidence was 0.6 per 1000 live births. In both cases the loss was probably due to accompanying hydrocephalus and nervous system damage during delivery. No surviving babies with this anomaly were seen during this period. Butler and Bonham (1963) reported achondroplasia as accounting for 0.6 per cent. of total perinatal mortality. The aetiology is uncertain. It may be due to a dominant or recessive gene and is considered by Roberts (1962) as a "bad risk" genetically.

Fibrocystic disease of the pancreas is increasing in frequency of recognition if not in frequency of occurrence. In the present study one baby died during the neonatal period from this disease, accounting for 0.6 per cent. of the perinatal mortality in the Unit. The incidence was 0.3 per 1000 births. Hydramnios was present. The baby, a male, was delivered at 38 weeks and weighed 3154 g.. He presented with intestinal obstruction due to meconium ileus, underwent ileal resection and ileostomy on his third day, and died on his 10th day.

The diagnosis was confirmed at autopsy. Meconium ileus or peritonitis is the usual presenting picture in the neonate dying of this condition. Nelson (1964) stated that the frequency of this disease is one per thousand to one in ten thousand of population. It is known that two other children, sisters, born in the Unit during the same period died subsequently of fibrocystic disease of the pancreas. This brings the incidence of known fatal cases of the disease to one in 1000 births in the Stobhill Unit. Roberts (1962) states that this is one condition which might be recognized in the heterozygote premaritally, offering thus the possibility of prevention.

Hypophosphatasia occurred once in the 17-month period under survey. This was a clinical diagnosis, the infant dying very shortly after birth and no investigations being carried out.

Miscellaneous Defects. A group of miscellaneous defects showing no pattern of aetiology or of tissue involvement comprised congenital heart disease (4), oesophageal atresia (3), multiple deformity (4) and renal agenesis (1).

Congenital heart disease accounted for 10 per cent. of lethal congenital defects in this series, and for 2.6 per cent. of the total perinatal mortality in the Unit. The rate was 1.3 per 1000 births. None of the infants was stillborn, all dying neonatally. The incidence of fatal cardiovascular lesions in the First Report of the 1958 British Perinatal Survey (1963) was 1.2 per 1000 total births, and in the report on Morbidity and Mortality in the First Year of Life (Grundy

and Lewis-Faning, 1957) was 2.8 per 1000 live births. McMahon's incidence (1953) was 3 per 1000 total births.

Little is known of the aetiology of the majority of congenital heart lesions. The embryological development is complicated, and this gives greater opportunity for maldevelopment than in areas where the processes involved are simpler. It is suggested that there is an hereditary tendency in that more than one generation may be affected, and that the incidence is higher amongst siblings of cases than in the general population. Roberts (1962) states that from an eugenics point of view the risk of recurrence however is "very low". Campbell (1961) found that the distribution of types of lesion associated with rubella was "quite unlike anything found under other conditions", reporting patent ductus arteriosus in 58 per cent., ventricular septal defect in 18 per cent. (these combined in 6 per cent.) atrial septal defect in 6 per cent., pulmonary valve stenosis in 6 per cent. and Fallot's tetralogy in 6 per cent. He states that maternal rubella is not a major cause of congenital heart disease, accounting for only two to four per cent. of cases and that other viral infections, including mumps, measles, epidemic hepatitis and poliomyelitis may be found to be responsible for similar malformations. The usual distribution of congenital heart lesions is given by Nelson (1964) from other reports as pulmonary stenosis with ventricular septal defect, 4 per cent. to 20 per cent., patent ductus arteriosus 10 per cent. to 17 per cent., coarctation of the aorta, 8 per cent. to 11 per cent., ventricular septal defect, 6 per cent. to 18 per cent. Rowe (1963) described 11 cases of pulmonary artery stenosis and

Menser, Dorman, Reye and Reid (1966) a case of renal artery stenosis resulting from maternal rubella. None of the four mothers in the present study gave a history of rubella or of exposure to rubella or other virus infections in the early weeks of pregnancy. One of the mothers suffered from diabetes mellitus. It is known that the infants of such mothers are more likely to show congenital defects than are those of healthy mothers (Driscoll, Benirscke and Curtis, 1960; Pedersen, Tygstrup and Pedersen, 1964).

The prognosis in congenital heart disease is dependent on the presence or absence of other abnormalities. In McMahon's series (1953) over one third of infants (31 of 83) with congenital heart lesions were stillborn as a result of malformations in other systems, often multiple and he considered that

> "the majority of cardiac anomalies were so gross as to make corrective surgery quite impossible".

Butler and Bonham (1963) reported that two thirds of infants with cardiovascular lesions showed malformations in other systems. Wallace and Sanders (1959) stated that 43 per cent. of deaths from congenital heart disease occur in the neonatal period, and 85 per cent. in the first year of life. Of the four babies in this series only one showed a second lesion, that of Rhesus haemolytic disease. This baby required exchange transfusion, with a cord haemoglobin level of 7.2 g. per 100 ml. and a bilirubin of 7.2 mg. per 100 ml. At the end of transfusion these values were 9.4 g. per 100 ml. and 4.0 mg. per 100 ml. It is evident therefore that the haemoglobin level was still unsatisfactory. Seventeen hours

later this baby died in congestive heart failure. He was found to have an inter-atrial septal defect of persistent ostium secundum type. Five further babies suffered from congenital heart lesions, but this was not regarded as the primary cause of death. Two suffered from multiple abnormalities *1,*2, two were mongols and a further baby died during exchange transfusion for Rhesus haemolytic disease. This brings the total number of cardiac lesions to nine in 153 perinatal deaths (5.9 per cent.) and six of these infants had other serious abnormalities.

Multiple deformities were seen in a total of four infants, two of whom are mentioned in the foregoing paragraph. The upper limbs deformities seen in the first case were similar to those associated thalidomide, but the time (1959) was a little ahead of the small outbreak in Scotland and the family doctor had prescribed no thalidomide. A third mother gave a history of rubella before conception. The possibility of a virus infection so damaging the ovum or persisting and damaging the conceptus is discussed in more detail in relation to virus infections in Part II. The main abnormality in the fourth case was a severe extension deformity of the cervico-dorsal spine.

*1 The defects included absence of arms, rudimentary fingers, imperforate anus, duodenal atresia, Meckel's diverticulum, patent foramen ovale, ventricular septel defect and patent ductus arteriosus.

*2 The defects included oesophageal atresia, large right ventricle, patent foramen ovale and anterior thoracic spina bifida.

Accidents of Labour

In the present study only 13 clear cut accidents of labour were considered to be the absolute cause of foetal or infant loss, accounting for 8.5 per cent. of the total perinatal mortality in the unit. It is more than probable that on several occasions marginal deviations from the normal course of labour set the seal on a situation which was already hazardous for the foetus. The numbers of such cases are not known and cannot be clearly assessed. They are included in Group II, as the abnormalities of labour were not considered to be in themselves sufficient to cause perinatal loss.

Abnormal Presentation. This was the most common accident of labour. Delivery in four of the five cases was ultimately by breech, which, without the increased hazard of the original malpresentation and manipulation, itself carries an increased risk of foetal mortality and morbidity.

Case No. 1 is of interest in that the fault, not an uncommon one, was that of anatomical inadequacy of the uterus to contain the foetus any longer. The foetus was the correct weight for the duration of gestation, so that one could assume a satisfactory physiological relationship between mother, placenta and foetus. Case No. 2 although immature has been included here because there was difficulty in delivery at the abdomen and autopsy showed a ruptured liver with subcapsular haemorrhage. The remaining three infants might have been rescued by Caesarian section as all were fresh stillbirths after manipulation and delivery by breech.

Broadly speaking there appear to be two groups of babies who are born by breech, the immature and the mature with some structural dis-

crepancy or disproportion between mother and foetus. One of the simplest forms of discrepancy is that of the large baby (as in case No. 4, weighing 4708 g. or 10 lbs. 4 oz.). Randall, Baetz and Brandy (1961) found that infants weighing between five and six pounds gave less difficulty than those of seven pounds. At the other end of the scale Bulfin (1960) found a considerable increase in mortality in big babies delivered by breech in primigravidae. At under 9 lbs. the mortality was 3.2 per cent. but at over 9 lbs. it was 28.5 per cent. Dugan and Redding (1963) gave an uncorrected perinatal mortality rate of 16.4 per cent. for breech delivery, but by excluding all infants under 1500 g. and all stillbirths and major anomalies their mortality rate was reduced to 3.4 per cent. Todd and Steer (1963) found a mortality rate of 3.4 per cent. in term babies. Siong Kian (1963) of Indonesia reports a perinatal mortality of 22.5 per cent. amongst infants weighing over 1500 g. and also a maternal mortality rate of 1.2 per cent.. Conditions of working must however be very different here from those of the relatively sophisticated surroundings from which reports more often issue. The reduction of perinatal mortality and infant morbidity from abnormal presentation is an obstetrical problem and much information is to be found in the literature on the importance of recognizing the type of difficulty, and assessing correctly the probabilities of successful vaginal delivery or the need for Caesarian section. Difficult and prolonged manipulations lead to foetal mortality whilst breech extractions, as opposed to spontaneous deliveries, and frank breech presentations are especially productive of birth injuries (Rubin and Grimm, 1963; Dugan

and Redding, 1962).

Prolapse of the Umbilical Cord. The incidence of prolapse of the cord is not very high but it carries a high foetal mortality rate, and without other complications should be a preventable cause of infant loss. The incidence is given by McPherson (1965) as 0.43 per cent. of 8,868 deliveries, Widholm and Nieminen (1963) 0.41 per cent. of 74,703 deliveries, Nelson and Burns (1963) 0.3 per cent. of 17,776 deliveries and Campbell (1962) as 0.79 per cent. of 1,900 deliveries. The over-all incidence in the present series of deliveries is not known since only the fatal cases have been taken into consideration. Only three cases were fatal, accounting for 2 per cent of the total perinatal mortality in the Unit. This, again, is an obstetrical problem on which there is much advice in medical literature. Since the prognosis for survival of the infant is dependent on the time from prolapse of the cord to the time of delivery (Campbell, 1962 and Nelson and Burns, 1963) it is important to be aware of the circumstances under which prolapse is likely to occur. In this way an early diagnosis can be made and delivery effected with expedition, vaginally if the cervix is fully dilated and the presenting part low, but otherwise by Caesarian section. The foetal mortality can be as high as 20 per cent. to 30 per cent. (Nelson and Burns, McPherson, 1965) as seen with forceps deliveries, or as low as 9.8 per cent. (Widholm and Nieminen, 1963) or 11 per cent. (Kalmbach, Ward and Dilworth, 1962) with Caesarian section. Nevertheless Caesarian section is to be avoided with gross immaturity or stillbirth. The latter finding is not always easy to determine as the foetal heart may be faint as a result of shock.

Prolonged Labour. From the paediatrician's point of view any labour in which the foetus becomes distressed is too long. For the obstetrician managing any individual case the definition of prolonged labour is difficult. This is in part due to the effect of minor abnormalities which contribute adversely to the outcome of labour so that no time limit can be universally applied. Nassar (1963) considers that no labour should last more than 24 hours. Jeffcoate (1961) found a foetal mortality rate of 3.4 per cent. in labours lasting over 48 hours. McClure Brown (1952), Jeffcoate, and Goodwin and Reid (1963) all stress this "grossly cumulative effect" of small hazards on foetal risk. The outcome must ultimately depend on the cause of the delay in labour, and on the management.

Maternal and foetal distress may develop. A distressed mother can be sedated and delivered operatively. A distressed infant should be delivered. Indications of foetal distress are becoming more refined largely as a result of the work of Hon and his associates (1959, 1962 a, b, c, 1963 a, b), Larks and Anderson (1962) and Millican, Urbach, Carrington and Lambert (1966) on the nature of the foetal electrocardiogram in pregnancy and labour and in the early stages of foetal distress. Estimations of the acid-base status of the foetus during labour are also being used as an indication of foetal distress, and may influence the management of individual patients. Nevertheless the foetal heart rate and meconium-contamination of the liquor amnii are the criteria on which most labour rooms must rely in the meantime. Butler and Bonham (1963) showed that where a forceps delivery was resorted to on account of the

finding of meconium the perinatal mortality rate was 130, and for bradycardia 114, compared with 100 as the Survey ratio. When bradycardia and meconium-staining of liquor amnii were both present a mortality ratio of 218 was found. In a clinical study of 10,968 vertex deliveries Fisher (1964) found that where there was meconium staining of the liquor and a bradycardia of less than 100, 30.5 per cent. of Apgar scores were five or less. With one or other finding the scores were higher, but still significantly lower than in the control group, where 4.1 per cent. of infants showed scores of five or less.

Bradycardia occurs normally during a contraction, but should not persist for longer than 30 seconds after the end of it.(Eastman and Hellman, quoted from Lee and Hon, 1963). Failure to accelerate in this interval may indicate cord compression, and failure to accelerate at all between contractions is evidence of gross foetal hypoxia. Temporary bradycardia is also seen as a result of compression of the foetal head during labour (Prystowsky, quoted from Wolkoff and Adkins, 1962). Tachycardia and irregularity may precede bradycardia and should call for most careful supervision. Nassar (1963) states for this reason that no trial of labour should be conducted unless the membranes are first ruptured. Fenton and Steer (1962) feel that meconium-passage alone or bradycardia alone does not indicate sufficient distress as to warrant interference. However in view of a perinatal mortality of 22.2 per cent. associated with the finding of thick meconium and a foetal heart rate of 110, they advocate delivery within 30 minutes. Once both factors are present foetal survival is directly correlated with the time interval between

their onset and delivery.

Maternal distress can be relieved to some extent by sedation, glucose, oxygen and correction of acidosis. Romney and Gabel and Takeda, Gabel and Romney (1966) have shown that by the intravenous administration of 25 gms. of glucose followed by continuous infusion of a 20 per cent. solution bradycardia is corrected. They conclude that maternal glucose loading results in a "significant increase in placental glucose transport and can prevent the marked bradycardia of severe fetal hypoxia". They also note that whilst maternal inhalation of 100 per cent. oxygen increases placental transfer for about half an hour a decrease in oxygen transfer then takes place. It has been shown that hypoxia produces vasodilatation, with increased rate of flow through the foetal vascular bed and that high oxygen pressures cause the reverse (Goerke, McKean, Margolis, Glendening and Page, 1961). This may be the explanation of the effectiveness of administration of oxygen to the mother initially only. John (1965) reported that the foetal heart rate varies with the percentage of oxygen given, and that with 100 per cent. concentration it is always normal after bradycardia within three minutes. McClure (1960 has shown that in normal deliveries the administration of oxygen to the mother raises the oxygen level in the cord blood. In normal labour this may or may not be an advantage. If the cord is obstructed it is of no help, but if deterioration of placental function is present then extra oxygen in the maternal blood may succeed in raising the foetal oxygen-blood level to survival values.

Rupture of the Uterus. This may occur at the site of a previous

Caesarian section scar or may result from inability of the uterus to expel the foetus despite good contractions. In the present series one patient, a grand multipara had undergone a previous Caesarian section. The uterus ruptured at the 37th week of gestation, before the onset of labour and the amniotic sac was found at laparotomy to be intact in the abdomen. The second patient was 25 years of age and in her second pregnancy only. She was confined at home. There was delay in the second stage of labour, the exact duration of which was not known, and intrauterine death occurred prior to admission. Delivery was effected by forceps following craniotomy. At laparotomy the uterus was found to be ruptured into the right side of the broad ligament. Hysterectomy was carried out. This patient was at 41 weeks gestation and was 146 cms. (4'9¼") in height. The infant weighed 3178 g. (7 lbs.). On the other hand the mother had delivered her first baby, weighing 3332 g. (7 lbs. 5½ oz.) without difficulty 18 months previously. Perhaps this exceptionally small height is an indication for hospital delivery, but it is difficult to say if the outcome would have been any different.

Haemolytic Disease of the Newborn

Six infants were stillborn and two died neonatally as a result of haemolytic disease of the newborn. The six stillbirths were all of 37 weeks gestation or more. In three patients (case numbers 16, 17 and 18) the antibody titre was known sufficiently early and was of such a level that amniocentesis would have been performed at the present time and intrauterine transfusion may have been indicated. In cases 6 and 8 the antibody titre was known too late to be of help, whilst in case no. 20 it is possible that early delivery might have saved the infant. In three of these six mothers this was only the second pregnancy. Patient no. 14 came into hospital for the first time already in labour and delivered a small, severely-affected infant. Death here was due to a combination of immaturity and haemolytic disease. In case no. 15 there is little doubt that with present knowledge intrauterine transfusion would have been carried out and would have offered those extra weeks of maturity which might have changed the outcome.

It is evident from this that the treatment of these patients has changed considerably in the past eight years. Bevis (1950, 1952, 1956) conceived the idea of examining amniotic fluid for evidence of haemolytic disease. This technique has been developed and is now an essential adjunct to the management of the Rhesus negative woman who is thought, on the grounds of her obstetrical history, husband's genotype and antibody titre, to have a severely affected foetus. Originally the findings were used to indicate the need for pre-term delivery. Freda (1965) reduced the perinatal loss in his series from 30 per cent. to 9

per cent. by the application of the results of spectrophotometric scanning of amniotic fluid. Barton and Stander (1963) state that the more darkly stained fluids corresponded to the more severely affected infants but

> "the distinction between patients with mildly affected infants and patients with unaffected infants could not be clearly made on the basis of the gross appearance of amniotic fluid".

Townsend, MacKay and Liley (1961) reported the same finding. Walker and Jennison (1962) used an absolute level of bilirubin in the amniotic fluid as an indication of the state of the foetus, finding that

> "where the bilirubin level was over 0.2 mgm. per cent. 87 per cent. of infants required exchange transfusion or died"

and Bower and Swale (1966) found that with a level of 0.4 mgm. per cent. foetal death was imminent. More recently such estimations have become of value in indicating those cases in which intrauterine transfusion is likely to be of help. Of intrauterine transfusion Liley (1963) writes

> "the aim of the exercise is simply to arrest deterioration if possible and gain a few extra weeks of gestation so that skilled paediatric care of severe haemolytic disease is not nullified by gross prematurity".

This is an important point, Dunn (1963) pointing out that

> "mortality amongst 13 babies delivered before 36 weeks gestation was ten times as high as for the whole series, accounting for seven of nine deaths. The susceptibility of these babies, usually severe cases delivered by Caesarian section, to develop respiratory distress syndrome was undoubtedly a major factor".

He found that little is gained by delivery before the 36th week.

The use of intrauterine transfusion theoretically is the ideal solution for the severely affected infant who is immature, and many successes have been obtained by its use.

The prevention of this disease is now possible. In 1961 Finn, Clarke, Donohoe, McConnell, Sheppard, Lehane and Kulke demonstrated the removal of 50 per cent. of Rhesus positive chromium ^{51}-tagged adult red cells from the blood of Rhesus negative male volunteers by anti- D gamma-globulin. Since then good progress has been reported by the same group of workers (1963, 1965, 1966) and now gamma-globulin is generally available for any newly-delivered Rhesus negative woman who is likely to become sensitized. In a recent paper Woodrow, Bowley, Gilliver and Strong (1968) reported the prevention of immunization from large placental haemorrhages, although Hughes-Jones and Mollison (1968) and de Wit and Borst-Eilers (1968) were not successful. Woodrow et al. think that the use of gamma-globulin may be of value in preventing sensitization from Rhesus-incompatible transfusions, saying that a "cautious approach seems justified".

Placenta Praevia

Placenta praevia was responsible for the loss of six infants in the present study, or 4.0 per cent. of the total perinatal mortality. Bleeding in five of these mothers occurred at between 31 and 33 weeks gestation and there was little chance of carrying on these pregnancies to a reasonable maturity. They were thus inevitable losses as a result of immaturity and shock from haemorrhage and anoxia. In the sixth mother a malpresentation with a high head was diagnosed at 41 weeks, but nevertheless normal labour was attempted, and was accompanied by a haemorrhage fatal to the foetus.

Macaffee (1960) noted that 100 years ago the foetal mortality from placenta praevia was 60 per cent. and the maternal mortality 30 per cent.. In 1939 the foetal mortality was still 54 per cent. but the maternal mortality was reduced to 5 per cent.. In 1960 foetal mortality was reduced to about 10 per cent.. This is due to the recognition that many of these patients can be given bed rest for a period of from one to four weeks (Foote and Fraser, 1960), thus adding a little maturity, and to the freer use of Caesarian section.

Intra-partum Sepsis

Three infants died of infection acquired during the intra-partum period, accounting for 1.9 per cent. of the total perinatal mortality of the Unit. One of these infants was stillborn, autopsy showing evidence of intrauterine bronchopneumonia although no organism was isolated. Two died neonatally, both of staphylococcal infection, aged 6 days and 16 days, weighing 2424 g. and 1530 g. respectively. All three showed features which are associated with intra-partum infection.

In particular all showed considerable delay in delivery following rupture of the amniotic membranes. In one the delay was only 21 hours, but in the others it was 34 hours and 57 hours, both beyond the accepted limits of safety. This limit has been put as low as 12 hours by Emig, Napier and Brazie (1961) and Lanier, Scarbrough, Fillingim and Baker (1965). The majority of workers find that 24 hours is the limit after which the danger of foetal infection becomes likely (Hepner and Stephens, 1955; Pryles, Steg, Nair, Gellis and Tenney, 1963; Tyler and Albers, 1966), whilst others considered 36 hours or even 48 hours as the time lag after which one should expect infection in utero (Anderson, Green, Neligan, Newell and Russell, 1962; Breese, 1961). The incidence rate of infection in these reports varied from 20 per cent. to 50 per cent. and Hepner and Stephens found a 10 per cent. neonatal mortality rate with membrane rupture of 24 hours duration. Anderson et al. found that where there was maternal pyrexia of over 99.6°F. 50 per cent. of infants were infected. It is doubtful if the length of labour itself with intact membranes has any effect on the acquisition of infection by the

foetus (Emig et al.; Pryles et al.; Tyler and Albers). However, in the presence of distress, which may be a result of abnormal labour, foetal lung infection may occur from infected amniotic fluid, again if the membranes have been ruptured long enough for infection to have occurred from the perineum, vagina or cervix. This is the usual mode of access of bacteria to the foetus in utero, but there is increasing evidence that maternal bacteraemia can spread to involve the foetus (Kobak, 1930; Osborne, 1958; Kraft, Haberman and Montgomery, 1963; Robinson, Krause, Johnson, Zwicker, 1964; Patrick, 1967). Gonococceal infection is acquired as the foetus tranverses the cervix, as is herpes simplex, although recently transplacental transfer of the herpes simplex virus has been described (Mitchell and McCall, 1963). The prepondera-ting organisms at the present time are Gram-negative rods (Pryles et al.; Buetow, Klein and Lang, 1965; Berman and Bankier, 1966). Berman and Bankier found a high coincidence of coliform neonatal meningitis with maternal infection, especially of the urinary tract. Presumably such organisms could gain access to the foetus either via the maternal blood stream, or from the perineum, labia or vagina contaminated from infected urine, especially where the membranes have been ruptured for several hours prior to delivery. The organisms may also originate from the pool of hospital infection, at present mainly coliform, but at the time of this study, Staphylococcal.

Two points thus emerge. Firstly, good prenatal care should reduce the incidence of maternal infections which can be passed on to the foetus; in particular genito-urinary infections should be dealt

with prior to delivery. Secondly, constant bacteriological surveillance of Maternity Units and their Nurseries will not only reveal sources of infection, but will give an indication of the probable identity of the infecting organism when an infant does become ill, so that treatment can be started without delay.

The main problems to be decided are at what point the mother should receive an antibiotic, and on what indications treatment should then be continued or started in the newborn. It would seem only reasonable to continue a course of treatment in the newborn infant started before birth and with the same drug as was used in the mother. It is therefore of importance to choose for the mother a drug with a wide range of activity, or to which the maternal organisms are known be sensitive, and certainly one which will not produce neonatal complications when the infant takes up independent existence.

Any mother with a known infection would ordinarily be on treatment and those whose membranes are ruptured for 24 hours before delivery should receive antibiotic therapy. Foul-smelling liquor is considered by most workers to be an indication for maternal and foetal medication. In addition to this, of course, labour should be induced (Lebherz, Hellman, Madding, Anctil and Arje, 1963) and delivery effected within 12 to 24 hours (Lanier et al.), provided that there is reasonable maturity.

At the time of birth "opacification" of the foetal surface of the placenta is an indication of probable foetal infection (Benirscke and Clifford, 1959). In addition immediate examination of frozen sections of the proximal and distal ends of the umbilical cord for

arteritis and phlebitis, and of the placenta, or chorionic membranes is considered to be of value in determining whether an antibiotic is to be administered to the newborn infant. Leucocytic infiltration, independent of other focal lesions such as haemorrhage, at both ends of the cord was regarded by Fujikura and Benson as indicating severe infection (1963). Robinson et al. were able to find bacteria in Gram-stained preparations of cords and placentae in vessels or at their periphery where leucocytes were present. Emig et al. and Pryles et al. claimed that where there was inflammation of the cord, membranes or placenta there was a 10 per cent mortality rate from sepsis.

Krafft et al. regarded all infants of under 2500 g. as being particularly liable to infection and Breese considered infants delivered by breech, weighing 2500 g. or less and with long-ruptured membranes and inflammation of the amniotic membranes to be in need of a prophylactic antibiotic. Oh, Keller, Klein and Kunstadter (1964) reported that prophylactic antibiotics in premature infants for ruptured membranes slowed down bacterial growth, but did not prevent it.

Positive culture of cord blood is not considered necessarily to be indicative of neonatal infection. Krafft et al. however think that blood culture from the infant is of importance in certain "suspect" groups. Kobak (1930) found foetal bacteraemia in infants of bacteraemic mothers and this would appear to be the case in my own series of patients (Part V) in whom cord blood specimens could show a heavy growth of organisms, without any subsequent neonatal illness. More investigation requires to be done on this subject, with follow-up blood cultures on the infant

itself.

Administration of an antibiotic to the mother does not appear to be a very effective way of preventing infection in the baby (Lanier et al.) although most authors recommend it. Demethylchlortetracycline reduced infective morbidity such as endometritis, parametritis and post-partum pyelonephritis in the mother (Lebherz et al.) but did not reduce perinatal mortality. On the other hand, as has already been pointed out, it would be of importance to continue the same drug in the infant in order to produce any effect. Therefore if there is sufficient indication for antibiotic administration to the mother on account of septicaemia or localised genital tract infection then this is also sufficient indication for antibiotic administration to the baby for a reasonable period.

Various drugs and combinations of drugs have been used, varying from one Maternity Unit to another, and changing with the recognition either of ineffectiveness or the production of iatrogenic disease, and with the introduction of new drugs. Chloromycetin, tetracycline, oxy-tetracycline and penicillin with streptomycin have all been used prophylactically and therapeutically, chloromycetin disastrously. Ampicillin is the most recent drug to receive attention in respect of maternal and foetal blood levels and amniotic fluid levels in reports from Blecker, Edgar, Melville and Peel (1966), MacAulay, Abou-Sabe and Charles (1966), Bray, Boe and Johnson (1966 and Still and Adamson (1967). It seems probable that cephaloridine may take its place for both maternal and infant administration.

Brelje, Kaltreider and Kassir (1966) made a very reasonable

approach by using vaginal pessaries with long-ruptured membranes. The agent incorporated was nitrofurazone. This was not effective but the method would seem worth a further trial with other agents. If the efficacy of a drug administered to the mother is to be measured in terms of its level in amniotic fluid then the local administration of antibiotic or antiseptic agents must be as effective as systemic administration to the mother. It seems probable that the foetal blood level is of primary importance.

Intra-partum sepsis is a cause of perinatal mortality which should be preventable theoretically. We know the cause and the sequence of events in most instances. Thus with careful supervision and close cooperation between the obstetrician and paediatrician stillbirths and deaths from intra-partum infection should not occur.

Perinatal Deaths, Group II Infants

The cause of death in the infants of Group II was related to uterine environment in the widest sense, or more accurately to the failure to establish or maintain physiological well-being between mother, placenta and foetus. Evidence of this inadequate relationship is seen in Table I where 66 per cent. of these pregnancies failed to reach 37 weeks gestation. It is apparent that after this stage the relationship can be sufficiently unsatisfactory as to cause stillbirth, or, less often, neonatal death.

In Table II it is seen that the percentage of babies of low birth-weight is greater than of those of under 37 weeks gestation, indicating a tendency to retardation of intrauterine growth. Whilst this was the trend in the majority of Group II infants some showed acceleration of growth.

Maternal age was significantly related to perinatal loss, there being more mothers over 30 years of age amongst those with infants dying perinatally than with healthy infants. This factor however was not as highly significant as was that of parity. The mother who was pregnant for the fourth time or more was more likely to have an infant who died in the perinatal period. This is an interesting point as the primigravid patients showed more severe illness than those patients in their second and third pregnancies. It is possible that with more careful antenatal supervision both on the mother's and the obstetrician's part much loss in these primigravid patients was averted. The woman with the bigger family is probably more casual about attendances at the ante-

natal clinic and will be unable, on account of home circumstances, to accept hospital admission unless she is fairly ill. The physiological well-being of the second pregnancy is well-recognized. Butler and Bonham (1963) refer to the "high biological efficiency" of the second pregnancy.

The previous obstetrical history of these patients showed only one significant factor, the previous birth of an infant or infants of low birth-weight. This is also found in mothers where the baby of the current pregnancy is of low birth-weight (see Part II), and also in the histories of mothers with renal tract infection in the current pregnancy. There appears to be a group of mothers whose pregnancies tend to be associated with perinatal deaths, low birth-weight live-born infants and renal-tract infection. The relationship is not easy to understand. All three are related to increasing maternal age, and even more closely to parity. Maternal renal and cardiac reserve determine to a considerable extent the success of a pregnancy. Herwig, Merril, Jackson and Oken (1965) claim that pregnancy is a very delicate test of renal function. It seems probable that the development of infection in the kidney may convert renal function which is marginally adequate to a state of insuff-iciency. Mackay (quoted from Herwig et al) states that where the blood urea is over 60 mg. per 100 ml. foetal death is inevitable. The amniotic fluid level is higher than that of the maternal serum.

Cardiac reserve is also tested during pregnancy. It has been shown that where the cardiac volume is small there is a tendency to low birth-weight babies, although this may only be in keeping with the small

build of these mothers (Terris, Gold, Schwartz and Hall, 1965). Cardiac output is maximum at the 32nd week of pregnancy (Cohen and Thomson, Burwell, Strayhorn, Flickinger, Corlette, Bowerman and Kennedy, Palmer and Walker and Hamilton, quoted from Vorys, Hanusek and Ullery, 1963) and if it is unable to meet the demands of pregnancy the foetus will be in jeopardy at an early stage. Both renal and cardiac function must determine the adequacy of placental function, although undoubtedly the placenta itself has limits of reserve and may be the primary cause of perinatal loss.

The illnesses present in pregnancy may be complications only of that particular pregnancy, may be carried over from one pregnancy to the next, e.g. iron-deficiency anaemia or renal-tract infection, or may be chronic diseases in which the pregnancy itself is the complication, e.g. diabetes mellitus. In the present group of mothers with perinatal deaths each mother had more illnesses and more severe illness than those mothers with healthy infants

Whilst most of the illness was related to the pregnancy miscellaneous illnesses of severe constitutional nature also made a contribution indicating the diversity of causes of perinatal loss.

Ante-partum haemorrhage was the most frequent abnormality in the mothers of these infants who died perinatally. However it is probable that in some of these cases the bleeding indicated only the onset of labour and that the termination of pregnancy was due to other cause. This distinction would not always be clear. Nevertheless if the maternal haemorrhage involves ex-sanguination of the foetus then this is the

essential cause of perinatal death. Pre-eclamptic toxaemia was rather less frequent but made a considerable contribution to maternal morbidity in these perinatal deaths. Discussion of individual maternal illnesses is included in Part II.

Three further factors have been considered in relation to the severity of maternal illness. These are maternal age, parity and maturity. Increasing age did not have a bearing on the severity of maternal illness, nor was there any apparent relationship between the severity of illness and the degree of immaturity. However the parity of the mother was of importance. The most severely ill mothers were primigravidae and women who were pregnant for the fourth time or more. The mothers who were pregnant for the second and third times were less often involved in serious illness. This has already been noted and is an accepted finding. Why this state of well-being should exist is difficult to explain. Conditions must exist in the primipara which predispose to severe illness, as with pre-eclamptic toxaemia. These conditions must be absent in the second pregnancy, as a result of the first pregnancy. Subsequently with increasing parity, especially if pregnancies are at short intervals, anaemia may develop, which predisposes to ante-partum haemorrhage, or renal tract infection may become established. In addition to this the mother's work load is increasing with each child. It is not difficult to envisage the general slackening of good care and healthy environment to which the highly parous mother must submit, and to see why she may become seriously ill. On the other hand it is probable that the illnesses in the multipara will be of a different nature from

from those in the primigravida and that one form of illness classified as severe, such as anaemia (with a haemoglobin level of less than 8 Gm. per 100 ml.) is less dangerous in itself than for example a profuse ante-partum haemorrhage or eclamptic fits.

The severity of maternal illness was finally considered in relation to a gestation period of over 42 weeks. None of the mothers showed severe or even moderately severe illness, and only three of six showed mild illness. This means that post-maturity itself is a risk to the foetus. This fact is beginning to have widespread acceptance. In all Maternity Units it seems probable that a component of perinatal mortality is due to prolonged pregnancy. It is my feeling that, whilst we can now keep alive very immature infants, the margin of post-maturity by which foetal life is lost is much smaller. Plainly more attention should be given to the date of onset of the last menstrual period, both by the mothers and their obstetricians. In addition an objective test of adequacy of placental function to foetal well-being is of primary importance to this problem. The following information has been collected in order to stress the need for work in this field.

The human foetus is mature at 40 weeks gestation. Before this time it is immature, and after this time it is post-mature, chronologically speaking. At any time dysmaturity may supervene, being a qualitative alteration in the state of the foetus as a result of abnormality in the maternal-foetal-placental relationship, probably due to pathological processes.

In this section, only the problem of the post-mature baby is

discussed -

> "That of the average foetus during prolonged pregnancy, rather than the one suffering obvious deprivation from placental insufficiency" (Gruenwald, 1964).

The post-mature foetus is exposed increasingly to two hazards as 40 weeks is reached and passed. Firstly, there may be a continued very good interrelationship between the mother, placenta and foetus, in which case the foetus will continue to grow and in due course will give rise to difficulties of delivery. This occurs particularly in primigravid patients aged 21 to 25 years (Mead and Marcus, 1964) and the difficulty is most often a cephalopelvic disproportion (Evans, Koeff and Morley, 1963). In the writer's experience these deliveries tend to end as traumatic mid-cavity forceps extractions or as Caesarian sections. Foetal distress was present in labour in 13.3 per cent. of the cases of Mead and Marcus who were delivered at 42 weeks and over. Magram and Cavanagh (1960) and McClure Browne (1963) also noted the increase of foetal distress after the 42nd week and Lucas (1965) stated that anoxic deaths were doubled in post-term deliveries compared with term deliveries. The case is familiar of the mother who has a stillbirth or a damaged infant on account of it's large size at 40 weeks and in whom labour is therefore induced early in subsequent pregnancies. It seems only reasonable to apply the same principle to the post-term mother with the increasingly big baby. It seems to the writer that even in some of these patients the placenta is not functioning as well as would appear from the size of the baby, as sudden stillbirth can occur where

there is no gross difficulty in labour.

A second hazard in which there has been increasing interest in the past few years and with which I am more concerned is that which takes place in the foetus as a result of decline in the adequacy of placental function after the optimal period of human gestation is passed. Gruenwald (1964) writes -

> "Prolonged pregnancy is increasingly unfavourable to the average foetus..... This is not a phenomenon that begins at 42 or 43 weeks or any definable time, but rather a continuation of a trend which starts shortly before term, and assumes significant proportions somewhat later, depending upon the particular circumstances of a given pregnancy".

The 37th or 38th week of pregnancy seems to be the point about which all physiological processes are at their best, and subsequently there is gradual deterioration.

Gruenwald writes -

> "It is well known that the increase in (foetal) weight is linear to about 38 weeks gestation, and then declines. McKeown and Record (1953) have shown that this decline is not the result of a decreasing growth potential of the foetus, since the previous, more rapid, rate is resumed after birth when supplies are plentiful".

Presumably then, in utero supplies have become meagre and there is "decline in placental adequacy" and the foetus does not thrive.

McClure Brown (1962) states that the volume of liquor amnii is progressively reduced after the 37th week, until by the 43rd week there may be 100 ml. or less. Elliott and Inman (1961) found that the amniotic fluid volume in the healthy young mother was about 1000 ml. at the 38th week, after which it declines at the rate of 145 ml. per week, there remaining rather less than 250 ml. by the 43rd week. In pre-eclamptic toxaemia and essential hypertension they found a peak volume of only 500 ml. at 37 weeks, with subsequent decline and the lowest volume reached before 43 weeks gestation. Gruenwald considers that after the 38th week no further improvement can be brought about in the chance for survival of the foetus. If it is not delivered by the 40th week then the danger of intrauterine death increases from day to day, and if death does not occur antepartum, it may occur during labour, particularly if the labour is stressful (Magram and Cavanagh; Gruenwald, 1964; Smith, Greene and Touchstone, 1966). McClure Brown (1963) states that the changes of post maturity include -

> "Calcification of the placenta, diminution of liquor, slowing of maternal placental circulation in some cases, impairment of placental transfer and possibly lowered available oxygen" and cessation of growth of the baby.

In the present study six infants died perinatally of "environmental" causes at over 42 weeks gestation. It is noteworthy that in none of these mothers was there any severe or moderately severe illness. Three mothers suffered from mild illness, and in three no illness was apparent. This constitutes 4 per cent. of the total perinal

deaths for the unit and 7.2 per cent. of infants dying from "environmental" causes. McClure Brown (1963) found a 3.5 per cent. of incidence of pregnancies lasting over 42 weeks, and Magram and Cavanagh found a 4.4 per cent. incidence of pregnancies lasting over 43 weeks. Most authors are in agreement that increased perinatal mortality is associated with post-term delivery (McClure Brown 1962a and b, 1963, Gruenwald 1964, Greene, Smith, Touchstone, Kyle and Duhring 1965, Lucas 1965, Smith et al. 1966). Evans et al. state that post-term delivery raises only the question of cephalopelvic disproportion, whilst Magram and Cavanagh and Mead and Marcus found a greater incidence of foetal distress without increased perinatal mortality. It would seem to the writer, however, that cephalopelvic disproportion and foetal distress are the beginnings of events which might easily lead to stillbirth, neonatal death, or permanent cerebral damage. Smith et al. state -

> "The development of foetal distress in post maturity occurs late and heralds almost immediate foetal death. Delivery must be accomplished before distress occurs if a healthy baby is ultimately to be obtained".

McClure Brown (1963) found that when a patient was "past dates" only, perinatal mortality at 41 weeks was 1.05 per cent.. This was doubled by 43 weeks, trebled by 44, and more than quintupled by 45 weeks. In the presence of toxaemia or chronic hypertension the perinatal mortality rate rose earlier, being doubled at 42 weeks, trebled at 42½ weeks, quadrupled at 43 weeks, and more than quintupled at 44 weeks.

Further, he found that -

"The combination of two or more conditions each of which in itself conduces to placental insufficiency may be lethal for the foetus unless delivered without delay".

In addition McClure Brown (1963), Lucas, and Scott and Usher (1966) have recognised that the infants of primigravid patients are in particular danger, especially if the mother is over 35 years of age. The infant of the multipara over 35 years of age is also at increased risk.

How then is one to recognize and manage such cases in a practical sense?

Silverman (1963) has pointed out the importance of educating women to note the date of the beginning of each menstrual period. McClure Brown (1963) stresses the importance of beginning at the beginning. If the mother is seen between her sixth and twelfth week of pregnancy then the size of the uterus is unmistakable. The mother can be instructed to note when foetal movement is first felt, which would confirm the duration of pregnancy. Abdominal girth can be measured. Accurate weighing should be done at each visit. If there is any doubt about the maturity of the foetus X-ray examination for ossification centres can be carried out when it is thought that the 36th week has been reached. At term there is not infrequently a little "show" or a few contractions in these patients, and then nothing further happens. From this time on the foetus is in danger. The mother may now herself notice that she is losing weight, especially if she has been

warned of this possibility. If antenatal weighing has been accurately done this suspicion is easily confirmed. If, in addition, her abdominal girth is no longer increasing or is decreasing McClure Brown feels that delivery should be effected within a week. If foetal movements are less, and if on auscultation foetal heart beats are missed, then the foetus is in imminent danger.

This is a very "clinical" approach to the problem, and yet this loss of weight is undoubtedly firmly based on changes in the hormonal state of the mother secondary to similar changes in the foetus and placenta. The woman will herself be able to appreciate the changes if she is instructed in what to look for and should be told to report to her clinic when she is at all suspicious, if indeed she is not already in hospital as an elderly primigravida or with toxaemia, or hypertension.

One could do no better here than to quote Gruenwald (1964) again -

> "Obstetricians will derive little comfort from the realization that the untoward effects of prolonged pregnancy upon the foetus are not a disease entity in the usual sense, but, rather, the more severe form of a change affecting all pregnancies of a similar duration... From the point of view of obstetric practice, there is a legitimate desire to define the abnormal state and develop driteria by which it can be predicted and treated.

Greene et al. (1965) stress the urgent need of a dependable method

for examination of placental function, stating that it -

> "could reduce perinatal mortality and morbidity and contribute to the solution of the problems of mental retardation, cerebral palsy, and congenital malformation... By the time suggestive signs and symptoms appear intra-uterine death may be imminent".

Several tests have now been devised for the assessment of placental function and foetal status. Pregnanediol levels in blood and urine have been used by Patti, Bonanno, Frawley and Stein (1963) and in the urine by Lau and Jones (1964). Urinary oestriol excretion rates are now being used more frequently, (oestriol accounting for 90 per cent. of oestrogen excretion, Lencioni, Bianco, Amezaga and Badano, 1965) by Greene and Touchstone (1963), Breborowicz, Krzywinska and Pisarski (1965), and by Schindler and Herrmann (1966) who also examined amniotic fluid levels. Endocrine cervical cytology has been combined with a study of oestriol and pregnanediol excretion by Lencioni et al. and direct visualization of the cervix for signs of "ripening". Smith et al. perform abdominal amniocentesis on all patients found to have low oestriol excretion and have always found the "truly post-mature" infants to be surrounded by meconium-stained amniotic fluid. Greene and Touchstone (1963) and Greene et al. (1965) describe a method of estimating oestriols which is more reliable and less time consuming than most. They found in 88 diabetic pregnancies that where the level of urinary oestriol excretion was above 12 mg. per 24 hours within 48 hours of delivery there were no perinatal deaths. At levels between

4 mg. and 11.9 mg. per 24 hours there were nine neonatal deaths amongst 39 patients, and at levels under 4 mg. after the 33rd week there were six perinatal deaths amongst 12 mothers. They consider therefore that serial oestriol estimations should be an integral part in the supervision of the pregnant diabetic patient. Schindler and Herrmann quoted values of urinary oestriols in normal pregnancies of one to two mg. per 24 hours at 14 weeks gestation, and of 26 to 40 mg. at term, stating that this "represents the work of the fetal-placental unit". Heys, Scott, Oakey and Stitch (1968 a, b) have described the successful application of serial urinary oestriol excretion estimations to the saving of foetuses in danger of intrauterine death before term.

For the diagnosis of post-maturity one would look particularly at the primigravida over 35 years of age, and the multipara over 35 years, with pre-eclamptic toxaemia or hypertension, and possibly with some additional illness, who has reached 38 weeks gestation, is losing weight, feeling less foetal movement, and with stationary or decreasing abdominal girth. In such patients urinary oestriol determination should be done at least on alternate days, if not daily. Further confirmation would be obtained by finding meconium-stained amniotic fluid on abdominal amniocentesis.

At this stage Smith et al. say that labour is contra-indicated and Caesarian section is correct. Before urinary oestriols reach a dangerously low level, the patient should have bed rest, as this is known to increase the adequacy of placental function (McClure Browne, 1962; Smith et al.) and the reverse is also true that hard physical activity

is detrimental to placental function.

There is little doubt that no patient with the above findings should be allowed a trial of labour. Artificial induction will probably fail, for the same reasons that spontaneous labour did not occur. At it's simplest, this would mean that a reduction in the volume of amniotic fluid and in the size of the foetus would so reduce uterine resilience that there would be no stimulus for the onset of effective contractions and it would seem that this state of minimal uterine activity might even be accentuated by the further loss of amniotic fluid resulting from surgical induction of labour. Further if labour did ensue the outlook for the meconium-surrounded, and deprived foetus would seem hopeless. If labour did not ensue then the danger of infection has been added and the end is a Caesarian section after all.

From the ill-defined term "postmaturity" there has emerged a fairly clear clinical picture of what it constitutes. One should perhaps stress again that one is not discussing here the postmaturity which gives rise to large babies and difficult deliveries, but the opposite process, in which maturity has been reached, and those physiological processes, the essentials of pregnancy, have begun to regress and yet the foetus remains in utero. By the awareness of this picture, by careful clinical observation, and by assessment of urinary oestriol output, possibly combined with amniocentesis, it should be possible to manage these cases successfully without any fear of foetal loss or damage.

In 42 infants of Group II there was no apparent adequate cause of perinatal loss as judged by the foregoing classification. Certain

features however were recognizable in some cases.

These included cases of intrauterine death where the clinical findings were subsiding by the time the mother was admitted to hospital. From the history of these cases it seemed probable that there had been a fairly severe pre-eclamptic toxaemia in three and hypertension in two of these mothers. The diagnosis of pre-eclamptic toxaemia is probably the most difficult to make after intrauterine death as this is the illness par excellence which resolves following termination of pregnancy or death in utero.

Secondly two patients, both aged 38 years and with previous pregnancies in their early twenties, had intrauterine deaths. This is not necessarily a well-recognized association, but does suggest that such patients might be regarded as elderly primiparae and given special care, perhaps with early delivery based on serial oestriol excretion estimations.

Finally two broad groups of mothers were recognized who tended to overlap. These were patients with bad obstetrical histories and with termination of the current pregnancy at under 32 weeks gestation. In these patients there may be hormonal, renal, cardiac or placental inadequacy or dysfunction whereby foetal life cannot be supported beyond a certain time. Or, in others, the foetus may be genetically abnormal. It seems probable that if these babies survive they form part of that group of defective, immature infants described by Heimer, Cutler and Freedman (1964) and Drillien (1965).

SUMMARY

1. A study of perinatal mortality involving singleton babies born in the Maternity Unit of Stobhill General Hospital, Glasgow, was undertaken. The mortality rate was 4.9 per cent. of 3,093 deliveries. Stillbirths outnumbered neonatal deaths by 87 to 66.

2. In the 66 live-born infants death occurred at under four hours of age in 57.5 per cent. and at under seven days in 86.4 per cent.. This indicates that perinatal loss was closely associated with factors already present in utero or occurring at the time of delivery.

3. Infants of short gestation constituted 50 per cent., and of low birth weight 65 per cent. of perinatal deaths.

4. Two groups of infants were distinguishable: viz.

   Group I in whom there were well-recognized abnormalities (congenital defect, accidents of labour, haemolytic disease of the newborn, placenta praevia and intra-partum sepsis) which accounted for 45.8 per cent. of the total perinatal mortality;

   Group II in whom no gross structural or mechanical abnormality was present, and which accounted for 54.2 per cent. of the total perinatal mortality.

5. Congenital defects comprised 26.1 per cent. of the total perinatal mortality and of these, defects of dorsal mid-line fusion constituted one half. The types and incidence of congenital defect are summarized in Figure 1.

6. Group II infants were lost, apparently, as a result of adverse environmental conditions in utero. A study of their characteristics revealed the following information:-

a) Sixty-six per cent. were of under 37 weeks gestation and 77 per cent. weighed 2500 g. or less at birth. This indicates a broad, but not invariable, tendency to retardation of intrauterine growth.

b) The mothers of Group II infants tended to be older and more highly parous than the mothers with healthy infants. There was an increased frequency of previous low-weight babies amongst them.

c) Compared with the mothers of healthy infants they suffered more illnesses, including certain serious and diverse conditions such as ante-partum haemorrhage, pre-eclamptic toxaemia, urinary-tract infection, thyrotoxicosis, diabetes mellitus, virus infections. The contribution of the main illnesses to total maternal morbidity is shown in Figure 2.

d) Severe maternal illness was found in primiparae and in mothers who were pregnant for the fourth time or more. It was not related to increasing maternal age. From 28 to 42 weeks gestation the incidence of severe maternal illness was fairly constant, but after this time no mother showed severe or moderately severe illness. From this it is inferred that postmaturity of over 42 weeks is in itself a danger to the foetus.

7. Males predominated over females by two to one in the infants of Group II. Male foetuses were associated with an increased incidence of pre-eclamptic toxaemia with ante-partum haemorrhage, and of ante-partum haemorrhage with anaemia.

8. The mode of delivery was not significantly different in these infants dying perinatally from that of infants who survived. However, breech delivery and Caesarian section were both characterized by immaturity in Group II infants.

9. The use of analgesia and anaesthesia had no association with perinatal mortality in this series.

10. A group of 42 mothers showed insufficient evidence of illness to account for perinatal death. Amongst these were recognized mothers with intrauterine deaths where the clinical findings were subsiding by the time of the first examination; mothers with pregnancies late in life after a long interval with no children; and mothers with poor obstetrical histories who produced little more than late abortions. This indicates that the causes of perinatal mortality are numerous, sometimes cumulative, and not fully understood.

From this study it was evident that the individual care of patients is important, and that much work is needed, in particular on the prevention of congenital defects and on the maternal illnesses most closely associated with pregnancy.

PART II

PERINATAL INFLUENCES RELATING TO LOW BIRTH-WEIGHT BABIES AND TO THEIR DEVELOPMENT IN THE FIRST YEAR OF LIFE

PART II

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INTRODUCTION

"Natural selection almost inevitably causes much extinction of the less improved forms of life". These words of Darwin were published in 1859. He was not referring in particular to the human species. Nevertheless his words provoke some thought as to the result of interfering with this process of natural selection. In the past 20 years many more low birth-weight infants who would have died in the normal course of events, have been kept alive. It is of some importance therefore not to be content with mere survival but to judge what the end result of low birth weight is likely to be. Much skill, time and money is involved in the saving of these infant lives. Whilst all may appear well when viewed from the nursery, the view from the first birthday, from school or from work may be quite different. Hutchison (1940) said "I have a strong suspicion that of those (premature infants) who survive a large proportion turn out to be defective, either physically or mentally". If in fact the "Premature Nursery" regularly produces individuals who are at the lower end of the spectrum of human achievement it could be argued that little is being achieved. Gesell and Amatruda (1960) write:

> "Development is the business of the infant and child; it is his task. And if he fails at this task it is a very serious matter. There is no second chance, he cannot do it later and make up for

lost time. There can be no light-hearted, off-hand extenuation; failure of normal development in infancy is insuperable because of the indivisible unity of life, growth and age".

While something may be gained by care in therapy and in the maintainance of a suitable environment for these infants, the main need is for research into the maternal aspects of the problem. Even the best paediatric care is of little avail if a pregnancy results in little more than an abortion.

Much damage can be done through the unthoughtful introduction of routine practices or un-tried drugs both for the mother and infant. Whilst it is not possible to avoid this entirely, it should be possible to guard against such damage on a large scale. Smith (1960) writes

"amongst the problems waiting to be solved is the elimination of iatrogenic disease by more diligent precautions against the side effects of drugs. Application of routine measures to entire nursery populations must not be substituted for attention to the individual newborn infant".

In this section, Part II, of my thesis the situation in the Stobhill Maternity Unit is assessed. Maternal factors are considered first, after which the main early and late neonatal characteristics of these babies are examined. A report on certain aspects of physical and mental development of a group of these infants during the first year of life is presented. The inter-relationship of some of the characteristics is examined. The results serve to show that the foregoing paragraphs are not without foundation. Much more social, medical and obstetrical research and help is needed to prevent low birth weight.

From the paediatrician's point of view immaturity is the main problem and the one from which most other difficulties originate.

MATERIALS AND METHODS

From January 1st, 1959 to May 31st, 1960, 3,093 singleton infants were born in the Stobhill Maternity Unit at over 28 weeks gestation. Three hundred and two of these babies (9.8 per cent.) weighed 2500 g. or less at birth. Information concerning these 302 infants and their mothers in the perinatal period was collected, some retrospectively, most concurrently, and transferred to punch cards. For purposes of comparison information derived from the group of 100 healthy infants and their mothers (already utlilized in Part I of this thesis) is again used. These infants of the control group were selected only on the basis that their weight was over 2500 g. at birth and that they were fit to go straight to their mother's bedside after delivery without any period of special care in the nursery.

Consideration has been given at four main points chronologically. Firstly, the maternal characteristics during pregnancy and delivery were compared in these two groups of babies. The duration of gestation was based on the date of the last menstrual period. Secondly, the main characteristics of the low-weight babies at birth and under four hours of age were appraised. The control group was not used at this point since it comprised infants selected on the basis that they were known to be healthy at birth. Thirdly, the characteristics of these two groups of infants after four hours of age were compared. Fourthly, the physical and mental progress of 85 of the low birth-weight babies was assessed during the first year of life at an Out-patient Clinic set up for the purpose. The following plan shows the factors considered, tabulated according to these four periods.

PLAN OF PRESENTATION OF PART II

Pregnancy and Delivery

Maternal

Age
Parity
Height
Obstetrical History
Illnesses
Delivery Details

Illnesses include:

Ante-partum Haemorrhage
Pre-eclamptic Toxaemia
Thyrotoxicosis
Diabetes Mellitus
Virus Infections
Heart Disease
Operative Procedures

Neonatal Characteristics

General

Duration of Gestation
Birth Weight
Intra-uterine Growth
Sex
Congenital Defect
Birth Injury

Under 4 hours

Respiratory Abnormality
Oedema
Hypotonia
Cyanosis

Over 4 hours

Respiratory Distress
Cerebral Irritation
Cyanotic Attacks
Collapse
Jaundice
Sepsis

Progress in the First Year of Life

Physical

Weight
Congenital Defects
Anaemia
Infection
Rickets

Mental

Motor
Adaptive
Language
Personal-Social
Retardation in more than two fields
Other features

Recapitulation of Perinatal Mortality and Infant Morbidity

Detailed summary
Over-all summary: gestation
Over-all summary: birth weight

Inter-relationship of Certain Characteristics

The main factors characteristic of each of these four periods have been examined for significant inter-relationships.

A brief comment is added on the relation of intrauterine growth to perinatal mortality in these low birth-weight babies as it was thought to be more suitable for inclusion here than in Part I.

Assessments of developmental progress were made on 85 infants who attended the Follow-up Clinic during the first year of life. These assessments were based on the lines of developmental diagnosis set out by Gesell and Amatruda (1960) as shown in Figures 3, 4, 5 and 6, which provided normal standards for comparison. In the ultimate appraisal a list of tests was compiled as shown in Table XXV. The tests were adhered to as being either positive or negative. If, at any visit up to and including the first birthday, the infant failed to attain a positive result in motor, adaptive, language or personal-social behaviour, this was scored as a negative in the over-all assessment of the year's progress, regardless of whether or not that infant had scored a positive in the same group at any other time in the first year. Where the infant's age lay between two testing ages, the two groups of tests, one on the young side and one on the advanced side were taken into consideration. It was not found difficult to decide if an infant were lagging at the early stage or progressing well towards the next. In the end each infant was recorded as scoring either normally or sub-normally in each of the four fields separately, using as a control group all infants scoring normally in that field. The small group of infants scoring subnormally in three and four fields was finally compared with that group scoring normally in all four fields.

No attempt was made to allot a figure to the results as it was felt that the test areas were too widely spaced, and the first year of life too small a spread of time for such an assessment to be made with any accuracy with the tests of Gesell and Amatruda as used in this study. It was also felt that it would be of interest to deal with these four fields of motor, adaptive, language and personal-social behaviour separately instead of making the usual over-all assessment of the Development Quotient.

Correction was made, as is the usual practice, for the chronological immaturity of each baby.

For the ultimate appraisal of scoring results a separate assessment was made on two occasions without reference to the child's name. In every case there was absolute agreement of the two assessments where abnormality existed in one and two fields only, or in more than two fields. There was minimal disagreement on the border-line between the one-and-two abnormality groups and also between the three-and-four abnormality groups. In such cases a final decision was made after a third re-assessment. Five groups of infants thus emerged for consideration - those with retardation in (i) motor development, (ii) adaptive development, (iii) language development, (iv) personal-social development and (v) three and four of these fields. Where necessary comparison was made with the remaining low birth-weight babies not showing retardation in the field under consideration, and the fifth group was compared with infants showing no retardation in any field.

In the final section these characteristics are inter-related and

have been analyzed statistically where it seemed that there might be a significant relationship. The resulting tables are too numerous to include, but some of the findings are illustrated as figures. It was hoped that by making these comparisons some associations might be recognized whereby treatment of the early condition would prevent or modify the development of the later condition.

Five main comparisons were made. Firstly, characteristics of the pregnancy were considered in relation to neonatal abnormality at under four hours of age; secondly, neonatal abnormalities at under four hours ofage were related to neonatal abnormalities at over four hours of age; thirdly, characteristics of the pregnancy and neonatal state were related to progress in the four fields of development (motor, adaptive, language and personal-social) in the first year of life; fourthly, characteristics of the pregnancy and neonatal state were related to general retardation of developmental progress (that is, retardation in more than two fields); fifthly, developmental progress in the first year of life was related to intrauterine growth status.

RESULTS

Maternal Characteristics of Low Birth-Weight Babies

Age

Table XXVI shows the age in 5-year groups of the 302 mothers of low birth-weight babies and of 100 mothers of infants weighing over 2500 g. at birth. In the low birth-weight group significantly more mothers were over 30 years of age than in the control group of babies ($p < 0.02 > 0.01$).

Parity

Table XXVII shows the parity of the 302 mothers of the group of low birth-weight babies and of the 100 mothers of infants weighing over 2500 g. at birth. A preponderance of mothers pregnant for the fourth time or more was found in the low birth-weight group. The difference is significant at p value < 0.01.

Maternal Height

There was no significant difference in the numbers of mothers of low birth-weight babies and those of the control group when analysed statistically at 150 cms. (5 ft.) and less and over 150 cms., nor at under 150 cms. and 150 cms. and over.

Previous Obstetrical History

Table XXVIII shows the previous obstetrical history of the 176 parous mothers with low birth-weight infants and of the 59 parous mothers with infants weighing over 2500 g. in their current pregnancy.

Miscarriage, stillbirth and illness in a previous pregnancy were

not significantly related to a subsequent small baby, but a history of a previous small baby was almost four times as common in the low birth-weight group as in the control group. The difference is significant at p value 0.01.

Illness in the Present Pregnancy

Table XXIX shows the numbers of mothers who experienced some illness, and those who remained well. The difference between the normal and low-weight group is small and not significant statistically ($p < 0.20 > 0.10$). The difference becomes significant ($p < 0.05 > 0.02$) if more than two illnesses were experienced during pregnancy (Table XXX).

Table XXXI shows the type and incidence of illness occurring in the mothers of the small babies as compared with the controls. Ante-partum haemorrhage and pre-eclamptic toxaemia are both significantly more common in the mothers of the small babies than in those of the bigger babies. The period of gestation at which ante-partum haemorrhage occurred was not significantly different in the two groups. Pre-eclamptic toxaemia however occurred significantly earlier in the mothers of the low-weight babies. Miscellaneous maternal illnesses occurred in 44 (14.6 per cent.) mothers of low birth-weight babies compared with 7 (7.0 per cent.) mothers of the normal-weight babies. The types of illness are shown in Appendix J. None of the other illnesses considered was significantly more frequent in the low birth-weight group than in the "normal" birth-weight group.

Characteristics of Labour and Delivery in Low Birth-Weight Babies

Table XXXII shows some of the particulars of labour in 302 mothers

of low birth-weight babies and 100 mothers with normal birth-weight babies. There is a significant difference at two points. Firstly, more mothers of small babies were in hospital before going into labour than were mothers of bigger babies. Secondly more of the small babies were born by abnormal vaginal deliveries, breeches preponderating. The Caesarian section rate was similar for the two groups.

Duration of Membrane Rupture Prior to Delivery

Table XXXIII shows the interval of time elapsing between the rupture of the amniotic membranes and delivery. This interval was longer in significantly more mothers having small babies than normal-weight infants ($p < 0.02 > 0.01$).

Neonatal Characteristics of Low Birth-Weight Babies - General

Duration of Gestation

Table XXXIV shows the gestation periods of these 302 low birth-weight babies. All were by selection of at least 28 weeks maturity. It is noteworthy that 139 (46 per cent.) were born at over 37 weeks gestation. These babies are considered in Part III, "The Small 'Term' Baby". Fifty-seven (18.8 per cent.) were born at under 32 weeks gestation. Table XXXV shows the numbers of babies and the percentage mortality within each gestation group. It is seen that as the gestation period increases the percentage mortality decreases from 61.5 per cent. at 28 and 29 weeks to 17.1 per cent. at 40 weeks and over.

Range of Birth Weights

Table XXXVI shows the range of birth weights of these 302 small infants. It is seen that over-all the number of infants in each birth-weight group increases, so that only two infants (0.7 per cent.) weighed 500 g. or less, and at the other end of the table 176 (58.3 per dent.) weighed between 2001 g. and 2500 g. Mortality rates decrease from 100 per cent. at 1000 g. and less, to 17 per cent. at birth weights between 2001 g. and 2500 g. (Table XXXVII).

Intrauterine Growth Status

Table XXXVIII shows the intrauterine growth status of [o]99 low birth-weight infants lost perinatally. It shows that intrauterine growth retardation was a common finding, almost 75 per cent. of infants

[o] One foetus was not weighed at birth, but was known to be less than 500 g.

being on the low side of normal, and 25 per cent. above normal weight for the duration of gestation. When the infant's weight was under 60 per cent. of the expected weight mortality was as high as 75 per cent.. In all other groups the mortality rate was fairly constant, ranging from 28.3 per cent. to 33.3 per cent. However, intrauterine deaths in the group of infants who were under 60 per cent. of expected weight numbered 9 of 15 thus weighting the figures. Table XXXIX shows the retarding effect of pre-eclamptic toxaemia on the rate of intrauterine growth.

Sex Incidence

Table XL shows the sex distribution of these two groups of babies. There is no significant difference in the numbers of male and female infants amongst the low birth-weight babies.

Stillbirth

Fifty-one stillbirths occurred amongst these 302 low birth-weight babies, an incidence of 16.9 per cent.

Incidence of Congenital Defects.

Thirty-eight of 302 low birth-weight babies (12.6 per cent.) showed congenital defects at birth. In 23 (7.6 per cent.) the defect was of a type almost invariably incompatible with life and in 15 (5 per cent.) the defect was essentially non-lethal. The conditions seen are shown in Table XLI.

Birth Injury

Sixteen (5.3 per cent.) of 302 low birth-weight babies showed traumatic birth injury. In 15 this was superificial bruising, and in the 16th a tentorial tear and bilateral subdural haematomata were found

at autopsy, which also showed bilateral renal agenesis. No exact information was available on the total number of intracranial injuries because of the lack of post-mortem examination.

Type and Incidence of Common Clinical Abnormalities in 251 Live-Born Low Birth-Weight Babies at Birth and Under Four Hours of Age

Table XLII summarizes the most frequent abnormalities found in 251 low birth-weight babies in the first four hours of life. Six deaths occurred in this period.

Respiratory abnormality (difficulty in onset and maintenance of respiration, sub-optimal aeration of the lungs), was the commonest finding in these babies, occurring in 66 (26.3 per cent.). Oedema was the next most common finding, occurring in 60 (23.9 per cent.), hypotonia in 40 (15.9 per cent.) and cyanosis in 38 (15.4 per cent.).

Type and Incidence of Common Clinical Abnormalities in 245 Live-Born Low Birth-Weight Babies at Over Four Hours of Age

Table XLIII summarizes the main abnormalities found in the 245 surviving low birth-weight babies after the first four hours of life. Comparison is made here with a control group of 100 infants of normal birth weight whose condition at birth gave rise to no anxiety. The conditions are listed in order of time of development rather than in frequency sequence. Forty-three deaths occurred in this period.

Respiratory distress, cyanotic attacks, sudden collapse and jaundice were all characteristics of low birth-weight babies.

Age of Discharge from Hospital

Table XLIV illustrates the delay in discharge from hospital occasioned by low birth weight. Ninety per cent. of 100 babies weighing

over 2500 g. at birth were dismissed by their 10th day and the remainder by the 20th day, with one exception where the baby was retained on account of maternal illness. Only 63 per cent. of low birth-weight babies were dismissed by the 20th day, and almost 20 per cent. required hospital care for over five weeks after birth.

Study of the Progress of Low Birth-Weight Babies in the First Year of Life

Characteristics of Low Birth-weight Babies in the First Year of Life : Physical Development

Weight

Table XLV shows the weight progress of these low birth-weight babies, classified according to their percentage of expected weight at birth for the duration of gestation, and their percentage of expected weight at follow-up examination. The findings are compared with known standards. The majority (52.4 per cent.) were at times below and at times above their expected weight for age in the first year of life, whilst 34.5 per cent. were consistently underweight, and 13.1 per cent. consistently overweight.

Correction of Intrauterine Growth Retardation in the First Year of Life in Relation to the Severity of Retardation. Fifty-eight low birth-weight babies who showed intrauterine growth retardation were subsequently reweighed during the first year of life. Table XLVI shows the number of these babies who reached 100 per cent. of their expected weight for age during the first year and those who failed to do so, classified according to the percentage by which they were undergrown for the duration of gestation at birth. The p value is between 0.20 and 0.10, indicating that as many severely undergrown babies caught up in the first year as did those with lesser degrees of intrauterine growth retardation.

Age by which Intrauterine Growth Retardation was Corrected in Relation to the Severity of the Retardation. Twenty-nine babies with varying degrees of intrauterine growth retardation reached 100 per cent.

of their expected weight for age by their first birthday. Table XLVII shows the ages in weeks by which they did so. Those babies with greater degrees of retardation took no longer to reach 100 per cent. than did those whose weights were nearer normal at birth. The majority (22 of 29, or 76 per cent.) had reached 100 per cent. by or before the age of 27 weeks. Broadly speaking the greater the degree of intrauterine growth retardation the faster is growth after birth.

Intrauterine Growth Acceleration. Twenty-six babies whilst under 2500 g. were overweight for their maturity at birth. They were re-weighed during the first year of life. Thirteen (50 per cent.) were still over-weight by their first birthday, and 13 had fallen below 100 per cent. of their expected weight for age. In 11 of the latter babies the correction had occurred by or before the age of 27 weeks.

Weight Progress of Twelve Babies Showing the Severest Degrees of Intrauterine Growth Retardation. Twelve small-for-dates neonates were under 70 per cent. of their expected weight at birth, the range being from 42 per cent. to 68 per cent.. In Appendix K they are listed in order of the degree of retardation. The gestation period is shown and their subsequent weights, as percentages of expected weight for age during the first year. It is noteworthy that 10 of these babies were of more than 37 weeks maturity, whilst only two were immature, case number 77 at 34½ weeks and case number 83 at 36½ weeks. Three of the infants remained small whilst nine made good weight gains to within normal limits. Some details of the mothers are given in the table. No pattern of age, parity or illness is seen. Of the three infants who

remained small, one (case no. 74) suffered from the stunting effect of maternal rubella at 16 weeks gestation, whilst the mothers of the other two were under 5 feet in height (case numbers 77 and 82).

Congenital Defects Found after Dismissal from Hospital

Fourteen of these low birth-weight babies were found later to have congenital defects which were not evident at birth.

The most important of these was fibrocystic disease of the pancreas occurring in an apparently healthy baby, who died at the age of two years. Cardiac murmurs were the most frequent abnormality found. One baby developed pyloric stenosis which required operation. The remaining defects were of a minor nature. Four babies had umbilical herniae and three had naevi. This brings to 52 (17.2 per cent.) the total number of congenital abnormalities in these 302 low birth-weight babies.

Anaemia in Low Birth-Weight Babies during the First Year of Life

Haemoglobin estimations were done on those babies attending the Follow-up Clinic who were pale. Fourteen of 85 babies (16.5 per cent.) were found to have haemoglobin values of 80 per cent. or less (Sahli). Four of these babies were found to be anaemic at more than one visit despite the recommended oral administration of iron.

One baby (case number 85) whose mother had rubella at the 16th week of gestation showed a haemoglobin value of 35 per cent. at seven weeks of age. She showed no further anaemia after transfusion.

Appendix L shows the details of these fourteen infants. Their numbers are small, but their consideration indicates three points relevant

to the development of anaemia in the low birth-weight baby. Firstly, it is seen that eight of the fourteen babies were of under 32 weeks maturity. Secondly, three infants born near full term, (case numbers 86, 95 and 90) were only 42 per cent., 60 per cent. and 63 per cent. of their expected weight at birth for the period of gestation, but at the time of finding anaemia had all gained weight rapidly to 97 per cent., 103 per cent. and 99 per cent. of their expected weight at 23 weeks, 20 weeks and 17 weeks respectively. It is noteworthy that five of the 12 smallest-for-dates neonates (Appendix K) appear in Appendix L also. Case number 89 represents an intermediate state of these two processes. Born at 35½ weeks with some iron stores from the mother, but increasing from 86 per cent. at birth to 118 per cent. at 20 weeks of expected weight for age, there was also a relative iron deficiency. Case number 92 indicates the third factor of importance in producing anaemia in low birth-weight babies. Although she was born at 36½ weeks gestation and was 94 per cent. of her expected weight at birth, she suffered a severe attack of gastro-enteritis at 12 weeks of age, followed by otitis media. When seen at the clinic at 32 weeks she was only 86 per cent. of her expected weight and her haemoglobin was 55 per cent. Thus, immaturity, rapid increase in weight and infection each play a part in the "anaemia of prematurity".

Persistent Anaemia. Four babies showed haemoglobin values of less than 80 per cent. at more than one visit, despite the recommended administration of iron by mouth after the first finding of anaemia. Three of these babies were of under 32 weeks maturity at birth, three had either

respiratory or gastro-intestinal infection between visits, whilst one baby (case number 94) showed only mild upper respiratory-tract infection and no acceleration of weight gain between visits. He, however, was of only 31 weeks gestation and the haemoglobin value was never lower than 75 per cent.

Infection in Low Birth-Weight Babies in the First Year of Life.

Type and Incidence of Infection. Fifty-two of 85 low birth-weight babies (61.2 per cent.) seen during the first year of life gave a history of one or more attacks of infection, amounting to at least 74 episodes in all, compared with 27 of 39 (69.2 per cent.) "normal" birth-weight babies, with 27 episodes in all.

The incidence of attacks of respiratory, gastro-intestinal and a miscellaneous group of infections is shown in table XLVIII. It is seen that respiratory tract infection, particularly bronchitis, is the only type which predominates significantly in the low birth-weight babies. These babies with bronchitis were investigated in more detail.

Duration of Gestation in Infants with Infection in the First Year of Life.

Table XLIX shows the duration of gestation in 52 low birth-weight infants with a history of infection in the first year of life and of the remaining 33 low birth-weight babies who had no infection. The difference in incidence at under and over 32 weeks was not statistically significant ($p < 0.30 > 0.2$).

Birth Weight of Infants with Infection in the First Year of Life. Table L shows the birth weights of 52 low birth-weight babies with infection and 33 with no infection in the first year of life. No difference is

seen in the two groups (p value, taken at 1,500 g. level, < 0.50 > 0.30).

Duration of Gestation in Low Birth-Weight Babies with Bronchitis in the First Year of Life. Table LI shows the duration of gestation in 17 low birth-weight babies with bronchitis during the first year of life. It shows that this illness was significantly more frequent in babies of under 32 weeks gestation, and that thereafter there is no peak incidence. This type of bronchitis therefore is associated with immaturity ($p < 0.02 > 0.01$).

Birth Weights of Infants with Bronchitis in the First Year of Life. Table LII shows the birth weights of these 17 babies who developed bronchitis, compared with the remaining 68 babies with no bronchitis in the first year of life. Below 2000 g. a larger percentage was affected. The difference is statistically significant, the p value being $< 0.02 > 0.01$.

Incidence of Neonatal Respiratory Abnormality and of Respiratory Distress in Low Birth-Weight Infants with Bronchitis in the First Year of Life. Table LIII shows the incidence of respiratory abnormality at birth and in the first four hours of life, and of established respiratory distress after the first four hours in these 17 infants with bronchitis, and in 68 with no bronchitis in the first year of life. Eight of 17 babies with bronchitis (47 per cent.) had shown early respiratory abnormality compared with only 11 of 68 (16.2 per cent.) babies with no bronchitis. The difference is statistically significant at p value < 0.01. Four of 17 babies with bronchitis (23.5 per cent.) had suffered respiratory distress at over four hours of age compared with only 3 of 68 (4.4 per cent.) with no bronchitis. The difference is

statistically significant at p value $< 0.02 > 0.01$. Thus respiratory abnormality at birth and in the first four hours of life, and respiratory distress later are related to the development of bronchitis in the first year of life.

Rickets in Low Birth-Weight Babies in the First Year of Life

No clinical evidence of rickets was seen in the 85 low birth-weight babies seen at the Follow-up Clinic. Eighty-one infants underwent X-ray examination of their wrists, 36 on one occasion only and 45 on more than one occasion. In three there was a suspicion of widening, cupping and irregularity of the lower end of the ulna (Figure 7) with subsequent changes suggesting a healing progress (Figures 8 and 9). Radiological evidence of rickets was thus found to be minimal in incidence and degree in these low birth-weight babies.

Characteristics of Low Birth-Weight Babies in the First Year of Life - Mental Development

Motor Development

Twenty-eight of 83 babies (33.7 per cent.) considered to be adequately tested showed retardation in motor development in the first year of life.

Adaptive Development

Fifteen of 83 babies (18.0 per cent.) showed retardation of adaptive development during the first year of life.

Language Development

Ten of 83 babies (12.0 per cent.) showed retardation of language development during the first year.

Personal-Social Development

Seven of 84 babies (8.3 per cent.) showed retardation in personal-social development during the first year of life.

Retardation in More than Two Fields of Development

Seven of 81 babies (8.6 per cent.) considered to be adequately tested in all four fields, showed retardation in three or four of them. Of the remainder, 31 (38.4 per cent.) scored abnormally in one or two fields, and 43 (53 per cent.) showed no retardation.

Other Features

Convulsions. Four of the 85 babies (4.7 per cent.) followed at the clinic suffered from convulsions. Two babies suffered from febrile convulsions, one from "teething convulsions", a diagnosis made by the family doctor, and the fourth from fits associated with general mental

retardation.

Cerebral Palsy. One baby suffered from cerebral palsy. Motor retardation was pronounced, whilst adaptive retardation was less marked. Language and personal-social development were within normal limits.

Screaming. Four infants were difficult to assess developmentally as they screamed almost throughout their examination. All four were at an age when the normal reaction should have been one of smiling friendliness, and it was felt that this frightened screaming represented an abnormal response.

Apparent Retardation due to Congenital Defect and Illness. One infant showed retardation of adaptive development on first examination at the follow-up clinic at the age of 18 weeks. This was considered to be due to a unilateral microphthalmia and coloboma. In other fields she tested well. At her second examination she was ill with bronchitis and performed poorly those tests which she could be persuaded to do at all.

Shyness. One baby whose mother had a clinical attack of rubella when 16 weeks pregnant, was retarded in developmental progress in the early weeks of life as a result of severe anaemia. Subsequently she showed marked shyness, all natural reactions being brought to a standstill at the hospital clinic. Consequently she still tested poorly at one year of age although it was felt that potentially she was within normal limits.

Lack of Concentration. One baby showed marked lack of concentration. This was complained of by her mother in the first place at the age of 34 weeks, and was subsequently a notable feature of this infant.

These six findings, convulsions, cerebral palsy, screaming, apparent

retardation due to congenital defect and bronchitis, anaemia and shyness, and lack of concentration were all considered to be related to low birth-weight directly or indirectly.

Language Retardation. One infant who showed retardation in language development was the child of a mother who was deaf and dumb as a result of tuberculous meningitis. The disability was regarded as of environmental rather than inherent origin.

Recapitulation of Perinatal Mortality and of Infant Morbidity in the First Year of Life in 302 Low Birth-Weight, Singleton Babies

Detailed Summary According to the Duration of Gestation and Birth Weight

Tables LIV and LV summarize the perinatal mortality and infant morbidity in the 302 low birth-weight babies who are the subject of Part II of this thesis. They specify the type of abnormality present according to the duration of gestation (Table LIV) and the birth weight (Table LV). The tables show that one third of these babies died in the perinatal period. A further 4.2 per cent. (14) were known to have non-lethal congenital defects at the time of discharge from hospital. The remaining 188 showed no definite abnormality at the time of dismissal.

Eighty-five of these babies were assessed at intervals in the first year of life. Fifty per cent. of these 85 babies were within normal limits physically and mentally, and 49.4 per cent. suffered from some physical or mental defect, or both.

Projecting these numbers on to the 188 apparently intact babies dismissed home, and again on to the total of 302 low birth-weight babies, it means that one third (95) of these babies were within normal limits, one third showed some physical or mental abnormality during the first year of life, and one third died perinatally.

Over-all Summary according to the Duration of Gestation

Table LVI shows the total perinatal mortality and infant morbidity according to the duration of gestation, and expressed as a percentage of the number of infants in each gestation group. At under

32 weeks there were no normal infants. The situation improves, until at 37, 38 and 39 weeks 51 per cent. of these babies survived and were within normal limits in the first year of life. Beyond this time the prognosis deteriorated again, 63.3 per cent. of infants born at 40 weeks and over either dying perinatally or showing some physical or mental abnormality during the first year.

Over-all Summary According to Birth Weight

Table LVII summarizes the perinatal mortality and infant morbidity in these 302 low birth-weight babies, according to their weight at birth, and expressed as a percentage of the numbers of infants in each birth-weight group. At under 1500 g. no normal babies were seen. Improvement in outlook began in the 1501 g. to 2000 g. group, but here there is still a 76.9 per cent. chance of perinatal loss or infant morbidity. Between 2001 g. and 2500 g. this chance is reduced to 55.1 per cent..

Study of the Inter-Relationship of Maternal, Neonatal and Infant Characteristics

Characteristics of the Pregnancy Related to Neonatal Abnormality (respiratory, oedema, hypotonia, cyanosis) at Birth and Under Four Hours of Age

Duration of Gestation

Respiratory abnormality and oedema were significantly related to a short gestation period (Figures 10a and 10b). The relationship of hypotonia was much less marked, and cyanosis was not related to short gestation.

Birth Weight

The relation of birth weight to these four neonatal abnormalities was only that of the increasing numbers of babies seen in each birth weight group over-all as the 2500 g. level is reached. The lower birth-weight babies were not particularly characterized by these four findings.

Maternal Illness

Maternal illness was no more frequent in babies with these four abnormalities than in those without, nor was any particular maternal illness involved.

Characteristics of Low Birth-Weight Babies (respiratory abnormality, oedema, hypotonia, cyanosis) at Birth and Under Four Hours of Age Related to Characteristics (respiratory distress, cyanotic attacks, collapse, jaundice, cerebral irritation, sepsis) at Over Four Hours of Age

Respiratory Abnormality

This was significantly related to the subsequent development of respiratory distress, cyanotic attacks and sudden collapse (Figure 11).

Oedema

Oedema was significantly related to subsequent respiratory distress, cyanotic attacks, collapse and jaundice (Figure 12).

Hypotonia

This was significantly related to respiratory distress, cyanotic attacks, collapse and jaundice (Figure 13).

Cyanosis

Cyanosis was significantly related to respiratory distress, cerebral irritation, cyanotic attacks, collapse and jaundice (Figure 14).

Characteristics of Pregnancy and the Neonatal Period Related to Developmental Progress in the First Year of Life

Duration of Gestation

Immaturity affected personal-social development to the greatest extent, and adaptive and motor development to a lesser extent. Language development was unaffected by maturity at birth. At 37 to 39 weeks gestation a group of infants stood out as being retarded in motor, adaptive and language development. These are mature, low birth-weight babies. That is, they suffered from intrauterine growth retardation (Figure 15a, b, c, d).

Birth Weight

The birth weights of retarded babies in the four fields of development covered the range of survivors from 1001 g. to 2500 g., without any peak incidence. However, amongst the infants testing normally was a high number in the birth-weight group 2001 g. to 2500 g. (Figure 16a, b, c, d).

Maternal Illness

Motor and adaptive retardation were associated with an increased incidence of maternal illness. Personal-social development was less closely associated with maternal illness, and language development was unaffected. No particular type of maternal illness was involved (Figure 17).

Neonatal Abnormality under Four Hours of Age

An increased incidence of neonatal abnormality at under four hours of age was found in association with retardation in adaptive development

only (Figure 18), but there was no relation to any specific abnormality.

Neonatal Abnormality after Four Hours of Age

Again neonatal abnormality after four hours of age was more frequent in those babies with retardation of adaptive development than in those who tested normally (Figure 19).

Characteristics of Pregnancy and the Neonatal Period Related to Retardation of Developmental Progress in More than Two Fields

Duration of Gestation

Five of these babies suffered from the apparently non-specific retarding effects of gross immaturity, with a gestation period of under 32 weeks. The two remaining babies were born at 35 weeks gestation (following an ante-partum haemorrhage) and at 40 weeks gestation (following maternal rubella at the 16th week of pregnancy (Figure 20).

Birth Weight

No pattern of birth weight is seen in the retarded infants, but the normally-testing babies illustrate that the nearer the birth weight is to 2500 g. the better is the outlook for normal developmental progress (Figure 21).

Maternal Illness

This was not significantly increased in these retarded infants compared with those who developed normally. No specific illness was involved.

Neonatal Illness

Neonatal illness at under four hours of age was not significantly increased in these retarded infants.

No particular abnormality at this time was associated with general retardation.

Neonatal Illness

Neonatal illness at over four hours of age was significantly increased in the retarded group, but no particular abnormality was

associated with this general retardation (Figure 22a).

In infants showing adaptive retardation cyanotic attacks after the first four hours were more frequent than in those with normal adaptive development ($p = 0.05$ using Yates modification) (Figure 22b).

Developmental Progress in the First Year of Life Related to Intrauterine Growth Status

No influence was seen in developmental progress in the first year of life as a result of intrauterine growth retardation or acceleration. The number of low-weight infants born between the 37th and 39th weeks of gestation who showed developmental retardation was not significantly different from the number of such infants in other gestation groups.

DISCUSSION

Maternal Characteristics

Three hundred and two of 3,093 mothers (9.8 per cent.) delivered in the Maternity Unit of Stobhill Hospital, between January 1959 and May 1960, gave birth to low-weight babies. This incidence is at the middle of the range of other reported series (Dunham, 1955).

Age has a bearing on the birth of low-weight babies, the mothers of this series being more often over 30 years than the mothers of normal-weight babies. Drillien and Richmond (1956) found a maternal age of under 20 years or over 35 years to be associated with low birth weight. This seems to be the common finding (Woodbury, 1953; Anderson, Brown and Lyon, 1943; Norregaard, 1953; quoted from Dunham). Battaglia, Frazier and Hellegers (1963) and Israel and Deutschberger (1964) found a high incidence in girls in their early teens. In the present series of mothers there were no young girls and there was no evidence of an increased low birth-weight rate at under 20 years of age. The mean birth weight in primigravid patients is lower than in multigravidae (Drillien and Richmond). This was not seen in the present study where low birth-weight was associated with the fourth or subsequent pregnancy. Many factors are involved both in the age and parity of such mothers. For instance the same workers found that birth weight is highest in the second pregnancy and that this is maintained in social classes I and II,

but falls of in subsequent pregnahcies in classes III, IV and V. The essential fault may be either in the ovum or sperm prior to conception or in the developing conceptus and its environment. Some causes of low birth weight are of inherent or genetic origin, and those one might expect to be influenced by maternal or paternal age, whereas other causes of low birth weight are due to faults of environment which one could expect to be associated with parity. The first attempt at embedding of the fertilized ovum and the subsequent accommodation of the maternal organism to the demands of the growing foetus may be difficult. The second attempt is usually better, changing to the "high biological efficiency of the second pregnancy" (Butler and Bonham, 1963), and then progressing again to a less accommodating maternal organism, perhaps where concomitant increase of maternal age results in inadequacy of cardiac, renal or hormonal reserves. Thus it is evident that age and parity are variable parameters in their relation to birth weight. However, these findings do indicate that the woman over 30, particularly if primigravid or with three pregnancies already, merits rather special antenatal supervision.

At the two values considered in this study, of 150 cms. (5 ft.) and less, and less than 150 cms. maternal height did not influence birth weight. However, small infants were born of mothers of 145 cms. and 146 cms. It is found that such small women tend to marry men of below average height, and have small progeny. Baird (1959) found the critical height in Aberdeen to be 5' 1". Discussions ebb and flow as to how much of this effect is genetic, and how much due to generations of

malnutrition, overwork and poor medico-socio-economic background.

The obstetrical history showed that almost 40 per cent. of mothers of low birth-weight babies in this series had previously had at least one low birth-weight baby. This tendency has been referred to as "habitual prematurity" (Corner, 1960). It could reasonably be concluded that the same factors are at work in each of these pregnancies implicating an inherent deficiency in the mother's metabolism such as renal, cardiac or endocrine dysfunction. In some way the mother is unable to meet the requirements of a full-term, full-size foetus. These infants should be distinguishable from those whose birth weight depends on sheer accidents (such as the necessity for maternal abdominal or genital-tract operations, or the development of inter-current infections before the 37th week of pregnancy) and from those who are genetically defective or otherwise mal-formed. Nevertheless in the present study there was no significant relationship with abortions, which one might expect if surviving low birth-weight infants were genetically defective. There is a small group of mothers with recurrent abortions, who ultimately, with hormone therapy or a Shirodhar suture, proceed to 31 or 32 weeks gestation and produce a small live-born infant, who may die in infancy, or survive only to be of low intelligence. This type of group is evident, and has already been mentioned, amongst the mothers of the infants of Group II in Part I.

There was no excess of illness in previous pregnancies in the mothers with low birth-weight babies in their current pregnancy. Despite

this over-all finding it is well known that some illnesses do tend to repeat themselves in, or continue through several pregnancies. Perhaps, therefore, if individual illnesses had been taken into account some relationships would have been uncovered. This illustrates the defect of grouping miscellaneous findings under one heading. It would require a very careful prospective study in patients returning to the same hospital in several pregnancies to determine relationships between abnormalities in earlier and later pregnancies.

Multiple, but not single, maternal illness was significantly associated with the low birth-weight group. This may indicate the importance of good ante-natal care, both in quality and quantity. If one prevents the preventable, treats the treatable, and reduces to minimal severity that which cannot be entirely cured one may succeed in limiting maternal illness to a level which is compatible with the birth of a mature, normal-weight infant. In addition some conditions are inter-related, and by treating one we may be preventing another. This implies early and regular ante-natal care of good quality. It is well known that inadequate ante-natal care leads to an increase in immaturity, low birth weight and perinatal mortality. It would seem to be on this basis of prevention, early recognition of abnormality and early treatment, that the importance of ante-natal care lies. Nesbitt (1959) would take maternal care back further, to three months prior to conception stating that:

"Restoration of all demonstrable medical, anatomic, psychologic, endocrinologic and other defects to normal,

prior to and during pregnancy, will enhance the probability of perinatal salvage".

Two types of illness occurred significantly more frequently in the mothers of low birth-weight babies than in the mothers of the control babies; these were ante-partum haemorrhage (not due to placenta praevia or local cervical lesions) and pre-eclamptic toxaemia. The number of miscellaneous illnesses occurring in the mothers of low birth-weight babies was also in excess of that seen in the mothers of normal birth-weight babies.

It will be remembered that ante-partum haemorrhage made the biggest percentage contribution to maternal illness in the mothers of the infants of Group II dying perinatally, in Part I of this thesis. In the latter mothers male foetuses outnumbered female foetuses by two to one and this was noted to be related particularly to pre-eclamptic toxaemia with ante-partum haemorrhage and ante-partum haemorrhage with anaemia.

Uterine haemorrhage may be the result of separation of the placenta or membranes as a primary abnormality, or may occur simply because the pregnancy is terminating from some other cause. It has long been said, for instance, that ante-partum haemorrhage is a sequel to pre-eclamptic toxaemia but Jeffcoate (1966) writes that there is no such thing as a toxaemic haemorrhage. He considers that the hypertension and albuminuria found in such cases are the result of renal ischaemia from blood loss, and not its fore-runners. Armenia (1963) has pointed

out that separation of a small part of the amniotic membranes followed by their prolapse into the cervical canal will open up the cervix and may lead to bleeding and the termination of pregnancy. It is possible also that urinary-tract infection may lead to bleeding through reflex stimulation of uterine activity (Mitchell and Benson, 1957) or from the direct effect of coliform endotoxin (Wiederman, Stone and Pataki, 1962).

Anaemia predisposes to ante-partum haemorrhage, particularly where it is due to folic acid deficiency (Hibbard, 1963), manifest as megaloblastic anaemia or found in subclinical form by the excretion of an excess of formiminoglutamic acid in the urine. Nevertheless Clayton (1966) pointed out the low incidence of accidental haemorrhage in Nigeria, where the incidence of megaloblastic anaemia is high. Rhodes (1965) also noted the preponderance of male over female foetuses in association with accidental haemorrhage and ante-partum haemorrhage of doubtful origin, suggesting that the explanation might lie in the different metabolic use of folic acid by the male foetus or its placenta. Hobbs and Acheson (1966) noted a preponderance of males in threatened miscarriages. Rhodes, and Scott (1966) think it possible that the abnormality is primarily an immunological disease equated to the runt syndrome, and that the male foetus is less well-tolerated for embedding than is the female.

It is advantageous to delay delivery following ante-partum haemorrhage if this is at all possible so that the foetus can recover from ischaemia before it has to make the adjustment to extra-uterine life (Reid, 1959). I think there is a tendency for those infants who survive to suffer not only as a result of immaturity but also as a

result of cerebral ischaemia which may produce mental deficiency of quite severe degree. Table XXXI shows that in this series the time at which bleeding occurred in the mothers of low birth-weight babies was not significantly different from that in the mothers of normal-weight babies, in contrast to the finding of Wilkerson, Donnelly and Abernathy (1966) who found a significant relationship between bleeding in the first three months of pregnancy and subsequent low birth weight. However if the bleeding proceeds to termination of the pregnancy then obviously the earlier in gestation that this occurs the lower will be the birth weight.

An understanding of the aetiology of pre-eclamptic toxaemia and its effective treatment or prevention is far from realized. In an editorial in the British Medical Journal (1961) it is said:-

> "The archaic and confusing terminology of the 'toxaemia of pregnancy' has persisted over the years, though it has done little other than provide this aspect of obstetrics with an aura of obscurity".

Beaudry and Sutherland (1960) state the clinical criteria for the diagnosis of pre-eclamptic toxaemia as follows:- a blood pressure of 140/90 mm. of Hg. or more, or a rise of 30/15 mm. of Hg. above the pre-existing, well-documented level on at least two readings together with either oedema or albuminuria or both. These criteria are fairly generally accepted. Cobo (1964) would add highly increased uterine contractility as a fourth constant feature. Difficulty arises where ante-natal care is not sought early enough to determine what the non-

pregnant or early blood pressure level has been. This is complicated also by the fact that the hypertensive woman is inclined to develop an overlying toxaemia in the later weeks of pregnancy (Gate, 1960, Adams and Finlayson, 1961). Moreover the retrospective diagnosis of pre-eclamptic toxaemia can be difficult in cases of intrauterine death where the findings are subsiding before the condition of the mother is adequately assessed. This was seen in some instances in the present study.

This indicates the broad lines on which a diagnosis of pre-eclamptic toxaemia is made. It serves to indicate that the essence of the abnormality is not understood. Whilst these variable findings might be due to varying degrees of severity and different times of onset of one basic pathological process, they might well include a number of entities, the separate causes of which are obscured by the broad criteria and terminology used.

Pre-eclamptic toxaemia as usually defined occurs with significantly greater frequency in the mothers of low birth-weight babies, and its time of onset in such mothers is earlier than in those of the normal-weight babies of this series. With the exception of Beaudry and Sutherland all writers are agreed that the foetus or infant of a toxaemic mother shows intrauterine growth retardation. This was evident in the present series. Nevertheless Varga and Fields (1961) state that toxaemia does not otherwise affect the baby; once delivery is over survival is largely dependent on maturity. Delivery at under 34 weeks, and especially at under 32 weeks, is a very precarious time

for the survival of the foetus and for its normal development.

More recent studies have tended to contradict this observation of Varga and Fields. Freedman (1961) and Drillien (1965) have described a fairly clear-cut group of mentally defective infants, mostly males, born in the early third trimester of mothers with pre-eclamptic toxaemia. Wallace and Mickie (1966) described a group of 14 mothers with low urinary oestriols at the beginning of the third trimester, and found that six of these babies had neurological damage. Hertig (1962) has found low steriod excretion levels in pre-eclamptic toxaemia. Further the infants of mothers with pre-eclampsia have a tendency to hypoglycaemia in the neonatal period which may result in permanent cerebral damage (Cornblath, Odell and Levin, 1959; Brown and Wallis, 1963; Neligan, Robson and Watson, 1963; Haworth, Coodin, Finkel and Weidman, 1963; Banker, 1966; Creery, 1966). Drillien (1967) considers that the high incidence of severe mental retardation seen in very small infants born in 1953 and 1954 was due to iatrogenic hypoglycaemia, the result of withholding all sustenance from these babies for several days after birth. Cornblath, Forbes, Pildes, Luebben and Greengard (1966) have found a much improved survival rate amongst infants of 1500 g. and less with the intravenous administration of fluids starting at two to 15 hours of age. Naeye (1966), in an autopsy study of 11 small infants of toxaemic mothers found identical evidence of hypoplasia involving in particular the adrenal cortex. This may be related to a deficiency of oestrogen production, possibly the result of placental dysfunction. Schwers, Eriksson and Diczfalusy (1965) have illustrated extensive foetal con-

jugation of oestrogens, and hydrolysis of these conjugates by the placenta.

Aherne and Dunnill (1966) made a detailed quantitative anatomical study of 50 placentae with interesting results. They reported on normal placentae, those of hypertensive patients, and those of small infants of normotensive mothers. They measured the villous surface, the foetal capillary surface, the chorionic villous surface, the volume of the intervillas space and the volume of the foetal capillary bed. The villous surface and volume of the intervillas space were low in the placentae of hypertensive women, and exceptionally low in those normotensive women with small infants, whereas the volume of the foetal capillary bed was bigger in hypertensive mothers, and smaller than normal with a small foetus. The foetal and chorioni villous surfaces corresponded very significantly with the weight of the foetus, so that growth inhibition may be due to primary placental hypoplasia. It would seem that the foetus of the hypertensive mother attempts to compensate for placental ischaemia by increasing the volume of the foetal capillary bed. Where this is not achieved the infant remains small. These studies are undoubtedly of much value, and it is to be hoped, will be extended.

In twin pregnancy the demand on the placenta is greater than in the singleton pregnancy so that there may be a relative placental ischaemia, and in hydramnios there may be placental stretching which could produce ischaemia. Jeffcoate (1966) has referred to "hyperplacentosis" as a known factor in the aetiology of pre-eclamptic toxaemia, and has included such conditions as hydrops foetalis, diabetes mellitus, as well as

multiple pregnancy under this heading. In these conditions the conceptus is almost always large for the duration of gestation and probably makes excessive demands on the placenta thus creating a state of relative placental ischaemia. This may be the result of excessive demands from a profoundly anaemic foetus in an attempt to compensate for deficiency of carrying-power of essential metabolites (perhaps primarily oxygen) in the blood, or from the foetus of the diabetic mother as a result of the increased total foetal metabolism accompanying intrauterine-growth acceleration. It is well known that the mother of the severely-affected haemolytic baby develops a pre-eclampsia-like syndrome (Scott, 1966) and that the diabetic mother is more prone to develop pre-eclamptic toxaemia. This relative "ischaemia" in the diabetic mother may be accentuated by progressive microangiopathy. These may link up with Jeffcoate's group of toxaemic patients with "hyperplacentosis". The situation may by one not of primary hyperplacentosis, but rather of relative foetal deficiency of essential metabolites, which in turn results in an attempt at compensation, at least on the part of the foetal capillary bed in the placenta.

It is tempting to think that renal and placental ischaemia could both be relieved, not merely by resting the patient in bed, but in bed on her side. Cardiac output can be reduced in late pregnancy by restriction of venous return through pressure of the uterus on the inferior vena cava when the patient is supine (Robbins, Estrara and Russell, 1960; Vorys, Ullery and Hanusek, 1963: Wright, 1962). It seems possible that renal or placental ischaemia could result from this or even from direct pressure on the aorta or pelvic vessels supplying the uterus.

Govan (1962) has given details of water excretion in normal and pregnant patients in different positions after water-loading, and has succeeded in producing a diuresis of 112 per cent. in one oedematous patient (but with no hypertension or albuminuria) lying on her side, and of only 24 per cent. when supine. Even in the non-oedematous patient he found that there was 100 per cent. excretion of a water load with the patient lying on the side, 50 per cent. in the dorsal position, and only 30 per cent. if standing or moving about gently. This may indicate the means whereby improvement is brought about in toxaemic patients by admission to hospital, and again by complete bed rest, but perhaps we should now advise such patients always to lie on their sides. In addition it might be informative to record the arterial blood pressure in the arms and in the legs with the patients in these different positions, just as the venous pressure has been recorded in the legs; a low pressure in the legs, improving in the side position, might be demonstrable. One is reminded here of a multiparous mother of twins, delivered at term and both babies weighing over 7 lbs., whose lax abdomen allowed the babies to lie alongside her in her antenatal bed for many weeks. She did not suffer from any hypertension or pre-eclamptic toxaemia.

In the present state of knowledge the only cure for pre-eclamptic toxaemia is termination of pregnancy. Short of this only non-specific measures can be taken. These are often, although not invariably, effective enough to gain an extra week or two of maturity for the foetus. In 1952 the Master of Rotunda wrote that "antenatal care seems to be of little value in protecting against fulminating eclampsia". Hamlin (1962)

pointed out that the severest pre-eclampsia is seen in the poorest clinic attenders, or those mothers who had sought no ante-natal care. He allotted to each Sister certain patients, for whose continual care they were responsible throughout their pregnancy. They visited them at home immediately if they defaulted from the clinic. In this way the incidence of severe pre-eclampsia was greatly reduced. It is early and regular ante-natal care which offers most hope of early diagnosis and effective treatment.

Dalton (1960) made a general inquiry of ante-natal patients between the 20th and 30th weeks of pregnancy and found that of those patients who were unwell because of nausea, vomiting, headache, backache, vertigo, fainting, paraesthesiae, lethargy and depression one in four subsequently developed pre-eclamptic toxaemia; by contrast only one in 10 of the patients who remained well during the early period subsequently developed toxaemia. She thought the former patients should be started on a "toxaemic prophylactic regime". Clahr, Pear and Gabaef (1960) considered that "constant proteinuria is usually detectable before any other signs of pre-eclampsia appear", and provided their patients with albustix for home-testing between clinic visits. They were instructed to report to hospital on the finding of a level of 100 mg. of albumen per 100 ml. of urine. This was not the finding in the Stobhill patients; proteinuria was absent until late.

Oedema, as judged by tightness of the wedding ring is accepted widely as being of early prognostic import in the subsequent development of pre-eclampsia. Hamlin found that with oedema of the ring finger by

the 31st week there would be hypertension by the 37th or 38th weeks, and regarded a weight gain of over 8 lbs. between the 20th and 30th weeks as pathological. On the other hand Baird, Thomson and Hytten (1962) and Rhodes (1962) do not consider excessive weight gain to be any indication of the impending development of pre-eclampsia.

In the Stobhill patients hypertension was most often the earliest abnormality and a level of 140/90 mm. of Hg., not subsiding with rest in bed at home, was usually the indication for admission to hospital. Hamlin agrees that the blood pressure is a most important indicator, and would regard as suspicious a level of 130/85 mm. of Hg., believing that the usually accepted level of 140/90 mm. of Hg. is already too high.

These remarks indicate that at each visit examination should include blood-pressure measurement, urine-testing for albumen, weighing, and a careful clinical examination for oedema with a specific question as to whether the patient feels better or worse than when not pregnant, and whether her wedding ring is tight.

It has been stated that in order to treat a disease effectively one does not require to know its cause. The true nature of pre-eclamptic toxaemia and its effective treatment are still undiscovered. It is evident from its considerable frequency and its adverse effect that its control is of great importance to the welfare of the foetus and infant. Progress on these lines would lead to reduced perinatal mortality and to an improvement in neonatal and childhood morbidity rates. This is the most important and oldest of the outstanding problems in obstetrics, and the one which still remains unsolved.

Maternal thyrotoxicosis is a well known cause of infertility, abortion and low birth weight (Scott, 1966). It also leads to neonatal difficulties in the form of neonatal thyrotoxicosis or hypothyroidism where the mother is on treatment. In the present series of low birth-weight babies one infant was born of a thyrotoxic mother, weighing 1300 g. at 29½ weeks gestation. There was minimal thyroid enlargement but no other evidence of hyper- or hypothyroidism. The baby gained weight very slowly, and was not discharged home until his 89th day, being then only 2250 g., after which he made fairly good progress during his first year. This mother was being treated with potassium perchlorate. The action on the foetal thyroid was considered to be a chemical one, similar to that of the thiouracil group of drugs.

The principles of treatment of thyrotoxicosis in pregnancy are indeterminate. Herbst and Selenkow (1963) recommend therapeutic doses of an antithyroid drug and in addition full thyroid replacement therapy as in this way the patient should achieve a balanced thyroid status compatible with normal pregnancy. Hawe and Francis (1962) think surgery is best, but found that "careful treatment with antithyroid drugs substantially reduced foetal loss". Reis and De Costa (1961) considered that thiouracil was contraindicated, but that iodine in moderate doses and surgery if necessary offered the best result. The foetal thyroid is known to take up radioactive iodine^{131} from the 12th week of pregnancy (Hodges, Evans, Bradbury and Keetel quoted from Reis and De Costa, 1961) so that there is only a very short period of grace during which thiouracil might not damage the foetus. Plainly this is the

field of the physician, whose co-operation should be sought early, and who in turn may consult with a surgeon. Only in this way will the patient and her foetus have the best opportunity of remaining within reasonably healthy limits until term.

Rheumatic heart disease, although decreasing in incidence, is still a problem in pregnancy, and is still a risk to the life and well-being of the foetus. In the present series of low birth-weight babies 11 mothers (3.6 per cent.) suffered from chronic rheumatic heart disease compared with two mothers in the control group of 100 normal-weight infants. In addition two mothers developed cardiac failure, at 37½ weeks and at 36 weeks, due to severe megaloblastic anaemia and severe hypertension respectively. Both infants died perinatally. These two mothers had reached a later stage of gestation than that at which cardiac failure is expected from chronic heart disease, probably because of the special nature of the causes. Gilchrist (1963) reports that rheumatic valvular disease accounts for 94 per cent. of heart lesions seen in pregnancy, whilst the remainder comprise mainly congenital heart lesions and the cardiac myopathies of pregnancy. The danger periods for the foetus and mother are between the 28th and 32nd weeks of pregnancy, when cardiac output reaches its maximum (an increase of 40 per cent. to 50 per cent. of normal), during labour, and, for the mother, post-partum. Gilchrist recommends the full use of ante-natal beds often for months at a time. Since the cardiac output has increased to maximum by the 32nd week there is nothing to be gained by termination after this stage (Vorys, Hanusek and Ullery, 1963), and Caesarian section is not indicated.

Gerbie and Skom (1961) say that maternal lives are in fact saved by not performing Caesarian sections on these patients and that vaginal delivery, but with a shortened second stage, is the ideal mode of birth.

It is scarcely necessary to say that the successful management of these patients during pregnancy requires the attention of a physician experienced in heart disease.

It is well known that the diabetic mother runs an increased risk of pre-eclamptic toxaemia and hydramnios, and of foetal mortality and morbidity. The risk to the foetus is of abortion or premature delivery or, after the 37th week of gestation, intrauterine death. The risk to the liveborn infant is of respiratory distress, congenital malformation and early hypoglycaemia.

The outlook for the survival of the foetus improved greatly from 1940 to 1960 both in London (Peel, 1961) and in Houston, Texas (Paton, 1962). From mortality rates of just over 30 per cent. there has been a reduction to 14 per cent. Peel points out that this is due to a decrease in intrauterine deaths from 22.4 per cent. at the beginning of the period to 3.7 per cent. in the 1958 to 1960 period. Williger (1966) quoted the figures of Gellis and Hsia, reporting a 20 per cent. neonatal mortality rate between the 32nd and 34th weeks of gestation and a 25 per cent. stillbirth rate after the 37th week. It seems probable that the figure for neonatal deaths will be reduced by the present time with the improvement in paediatric care of these infants and in particular with the revised treatment of respiratory distress. Nevertheless even in 1960 a foetal mortality rate of about 30 per cent. was reported by McLendon and Bottomy,

and of 23.4 per cent. in 1966 by Williger. The infants who are now reported to show a high perinatal mortality rate are those of the unrecognized prediabetic mothers. Barnes (1963) however did not find the high rate reported in other series. Almost 30 per cent. of the infants of his series weighed over 9 lbs. at birth, and he considered that obstetrical difficulties resulting from this, or from toxaemia, hydramnios, early induction of labour with resultant prematurity and respiratory distress are the cause of loss in other series. Driscoll, Benirscke and Curtis (1960) reported that 52 per cent. of neonatal deaths in diabetic mothers were due to hyaline membrane disease. Farquhar (1962) found that the bigger babies had a better outlook than the smaller ones and thought that the better prognosis once diagnosis was made and treatment established was due to disappearance, as a result of treatment, of some harmful factor in maternal metabolism. Some such patients develop a frank diabetic state with acidosis during pregnancy. Acidosis is reported by McLendon and Bottomy to be associated with a high foetal mortality rate. It was present in 16.2 per cent. of their mothers with intrauterine death, andconversely where it occurred the foetal survival rate was only 53.8 per cent.

Congenital malformations are said to be three times more common in the infants of diabetic mothers than in the general population (Pedersen, Tygstrup and Pedersen, 1964). Driscoll, Benirschke and Curtis (1960) reported a 17 per cent. incidence of fatal congenital malformations. Pedersen, Tygstrup and Pedersen found a high number of severe bony deformities of limbs and were careful to make the point that

these were not due to thalidomide. In connection with congenital malformations it should be mentioned that the oral hypoglycaemic agents are suspected of teratogenicity and are contraindicated in the pregnant diabetic patient.

In the present series three infants died in the perinatal period whose mothers were diabetic. In one case, which has already been mentioned, the mother also had a placenta praevia and labour terminated at 31½ weeks, the foetus being 158 per cent. of expected weight for the duration of gestation. This is the only infant of a diabetic mother encountered amongst the low-weight babies of Part II, the low weight being due to gross immaturity and in spite of considerable acceleration of growth. The remaining two infants were bigger babies dying perinatally and are considered here rather than in Part I. The first was delivered at 37 weeks, weighing 3458 g. (138 per cent. of expected weight). The mother was an uncooperative, unstable diabetic, seldom free from glycosuria and acetonuria. The baby was stillborn. The second baby was also delivered at 37 weeks, weighing 2948 g. (111 per cent. of expected weight). Delivery was by Caesarian section and respiration was never adequately established. A cardiac murmur was noted. This baby died at 48 hours of age. Thus in these three babies are seen most of the threats to infants of diabetic mothers.

The nature of the abnormality existing in the placenta and foetus as a result of maternal diabetes is not fully understood. Peel (1961) considered that there was no placental insufficiency as experimentally no alteration was found in uterine blood flow, oxygen saturation

of cord blood or cord haemoglobin. Since then however the urinary oestriol excretion of diabetic mothers has been estimated serially and found to show a decrease towards term, particularly where the foetus is in danger of intrauterine death (Greene, Smith, Kyle, Touchstone and Duhring, 1965). The production of oestrogens is regarded as representing the work of the foeto-placental unit and thus a fall in excretion may indicate one form of placental insufficiency or dysfunction, despite the normality of oxygen transfer. Driscoll, Benirscke and Curtis (1960), expecting adrenal enlargement in infants of diabetic mothers, reported only that this was "not impressive".

The serial estimation of maternal oestriol excretion as a criterion offoetal well-being will become an essential part of the good management of pregnancy in the diabetic patient. In particular it is valuable as an objective and quantitative indicator of the need for the termination of pregnancy before intrauterine death occurs. Progress is being made in setting up such a test as a routine laboratory procedure, accurate and not unreasonably time-consuming, by Heys, Scott, Oakey and Stitch in Leeds (1968 a and b).

The factor which affects the foetal outcome the most is the adequate control of the diabetic state with the avoidance of acidosis (McLendon and Bottomy, 1960; Oakley, 1961; Peel, 1961; Paton, 1962). The duration and severity of the diabetic state are not thought to be of consequence. Peel considers it essential to admit these patients to hospital between the 30th and 32nd weeks of gestation in order to ensure this rigid control. His patients are rested in bed for 20 hours

daily and in the absence of complications delivery is effected at the 38th week. This is done either by Caesarian section or by surgical rupture of the membranes and vaginal delivery if the previous obstetrical history, current state of diabetic control and obstetrical assessments are considered satisfactory for a smooth labour. This was the state of affairs seven years ago. It is probable that foetal survival rates would be enhanced by the serial assessment of maternal urinary oestriol excretion, so that termination of pregnancy could be timed on this basis rather than at any particular week of gestation.

With complications bed rest in hospital can reduce the severity of hydramnios and of pre-eclamptic toxaemia. In these cases the direct assessment of foetal well-being is of even more importance as the 38th week is unlikely to be reached with a live foetus. Termination at 35 to 37 weeks may meet with success provided that good paediatric care is available. Before this time the dangers of immaturity, hyaline membrane disease and neonatal death are very considerable.

Hypoglycaemia occurs in some infants of diabetic mothers as a temporary upset. It is not however an invariable finding. It is regarded as being due to activity of the hypertrophied and hyperplastic foetal islets of Langerhans, stimulated by the high level of circulating glucose from the mother, in relation to the limited glucose supply of the neonate. This enlargement was found by Driscoll, Benirscke and Curtis in 81 per cent. of infants, and was most marked in those infants who were the heaviest for gestational age. Untoward signs in the new-born such as irritability, poor colour or cyanotic attacks should call

for investigation and for the intravenous administration of glucose if indicated, to tide the infant over this early difficulty. The administration of 30μg. per kilo of glucagon has been reported to produce hyperglycaemia in vaginally-delivered infants but a larger dose (300μg. per kilo) is required to raise the blood sugar level of infants born by Caesarian section or distressed during labour (Cornblath, Nicolopoulos, Ganzon, Levin, Gordon and Gordon, 1961. This offers a therapeutic alternative to the administration of glucose. Oral dextrose and intramuscular hydrocortisone have also been found to be satisfactory (Creery, 1966). Farquhar (1965), however, states that most of these babies can restore their blood sugar level to normal spontaneously in a few hours after birth.

All workers are agreed that a successful pregnancy in diabetic patients can be hoped for with considerable justification, but only providing that there is good ante-natal care, proper timing and mode of delivery and good paediatric care to follow.

In the present series of perinatal deaths and surviving, low birth-weight babies five mothers underwent operative procedures during pregnancy. These included two abdominal operations (a laparotomy for intestinal obstruction due to adhesions, at under 16 weeks gestation, and an ovarian cystectomy between the 24th and 26th weeks) and repair of a cervical laceration (at under 16 weeks). In none of these patients was labour precipitated by the operative procedure, but in the case with omental adhesions spontaneous rupture of the membranes and bleeding occurred at 31½ weeks, the infant was delivered by Caesarian section

but respiration was never established. In the remaining two patients labour was precipitated by the operative procedures of vaginal cystectomy at 32 weeks and ovarian cystotomy at 36½ weeks gestation. Four infants survived. It is seen that termination of pregnancy is not an invariable accompaniment or result of surgery. The maintainance of good anaesthesia and adequate oxygenation of the mother and foetus are essential (McCorriston, 1963). Lloyd (1965) found that surgical procedures other than those on the uterus and adnexa did not upset a pregnancy, whilst Shnider and Webster (1965) were less confident about this, stating that premature labour and delivery depended on the nature of the surgical disease rather than on the operation or anaesthetic technique per se. Levine and Diamond (1961) and Lloyd considered that post-operative anti-abortive therapy was not helpful.

It is generally agreed that elective operations should not be carried out during pregnancy, and particularly not during the first trimester as some anaesthetic agents may be teratogenic (McCorriston).

Since Gregg's report in 1941 of the finding of cataracts in infants of mothers who had suffered from rubella during pregnancy an enormous amount of information on the effects of this disease and other virus infections has accumulated. Whereas the rubella syndrome was orginally regarded as comprising four basic defects, deafness, blindness, microcephaly and congenital heart disease, it has now been shown to cause intrauterine growth retardation, and the "expanded rubella syndrome" of thrombocytopenia, bone deformities, hepato-splenomegaly, encephalitis, choreoretinitis, mental deficiency, intestitial pneumonia and profound

deafness (Monif, Asofsky and Sever, 1966; Phillips, Melrick, Yow, Bayatpour and Burkhardt, 1965; Friedmann and Wright, 1966). In addition as a result of the continued presence of living virus in these infants it has caused outbreaks of rubella amongst nurses and attendants caring for these infants (Phillips et al.; Hambridge, Shaffer, Marshall and Hayes, 1966).

Since 1960 at least 33 articles have appeared on rubella in pregnancy, half of them since 1965. Thus it is seen that rubella is the virus disease about which we have the most information and from which ideas regarding other virus infections originate. One mother in the present study suffered a clinical attack of rubella at the 16th week of gestation. The infant, a girl, was born at 40 weeks gestation and weighed 1858 g. (4 lbs. 1⅔ oz.), 58 per cent. of her expected weight. She developed a severe anaemia in the first weeks of life but after blood transfusion made a good recovery. In retrospect the appearances in the blood film are in keeping with those described by Cooper, Green, Krugman, Giles and Mirick (1965) of bizarre red cell morphology including fragmentation of erythrocytes. In addition one deformed infant was born to a mother who had suffered from rubella during the previous year but it was not clear from the case record what the relationship was to the time of conception. She was delivered at 41 weeks of an infant weighing 2354 g. (74 per cent. of expected weight). The abnormalities included a small head, flat nose, microstomia, short neck, absent scrotum and hypospadias, undescended testes and "meningitis", no organism being isolated. The suprarenals were distended with blood. The infant

was chromatin-negative. He died at 8 days of age. It seems probable retrospectively that this infant's defects may have resulted from persistent rubella virus. Whitehouse (1963) described embryopathy in a mother who suffered from rubella almost a month before her last menstrual period.

Other virus infections in the mother known to produce disease, congenital defect, immaturity or low birth weight are at least 10 in number. These are cytomegalic inclusion disease, herpes simplex, herpes zoster, influenza, infective hepatitis, measles, mumps, poliomyelitis, vaccinia and varicella. Undoubtedly more viruses will be recognized as being the cause of foetal mortality and infant morbidity as time passes. Nevertheless their contribution to the total number of congenital defects at the present time is reported by Kaye and Reaney (1962) as only 1.0 per cent. to 1.5 per cent.. Campbell (1961) states that the contribution of rubella to congenital heart disease is only between 2 per cent. and 4 per cent.

Herpes zoster in a 30-hour old infant, affecting the 5th cranial nerve has been described by Adkisson (1965). Recovery was uneventful. The mother gave no history of varicella or of herpes zoster, but the acquisition of infection was regarded as being transplacental. In the present study one stillbirth occurred at 31 weeks in a mother who had suffered herpes zoster at 18 weeks, with a suspected intrauterine death at about 22 weeks gestation. The foetus was badly macerated.

One case of maternal poliomyelitis was seen in the present study, in which the infant was born at almost 40 weeks gestation, but

weighed only 1803 g. (3 lbs. 15 oz.), 54.4 per cent. of her expected weight. The maternal infection had occurred at under 16 weeks gestation.

Passive immunization with gammaglobulin is helpful in some infections; the purposeful exposure of female children to rubella is sometimes recommended, and vaccination is of value in other infections. A warning is given regarding the use of the oral poliomyelitis vaccine in the pregnant woman as it contains a living virus and may thus damage the foetus. This is an aspect which is applicable also to the rubella vaccine which is now being developed. Ideally it would seem that no pregnancy should be undertaken for several months following any virus infection - and as a corollary to this it would be reasonable not to vaccinate any young married woman with a living virus in the second half of her menstrual cycle.

It is of interest in considering the labour details of these mothers of low birth-weight babies to find that more of them were in hospital prior to the onset of labour than were the mothers of the healthy, normal-weight infants. This probably means that they were being rested in hospital on account of some abnormality of pregnancy and shows that if the main illnesses were eminently curable considerable numbers of these pregnancies might continue to term. It is not the case by any means that the immature baby is always delivered as an emergency.

Breech deliveries were common amongst the low-weight babies. It is felt that this is a concomitant of immaturity, and that in the normal course of events conversion to vertex presentation occurs towards term.

The duration of membrane rupture prior to delivery was found to be prolonged in these babies. This was accounted for in part by the abnormality of "premature spontaneous rupture of the membranes" where delay was in terms of days or weeks, and probably also by the low level of activity of the uterus in the early part of the third trimester. For those small babies born near term it would seem that their small size probably does little to stimulate the contractions necessary to expel them within "normal" time.

Neonatal Characteristics

It is apparent from my results that some babies were of low birth weight on account of immaturity alone but that many were of low birth weight for the duration of gestation; that is, they suffered from intra-uterine growth retardation. The fact that almost 50 per cent. of these babies weighing 2500 g. or less at birth were of over 37 weeks gestation implies a degree of dysmaturity, manifest as retardation of growth in utero. It can be inferred reasonably that many of the babies who were of under 37 weeks maturity were also growing more slowly than normal in utero. Drillien (1959) stated that between 37 per cent. and 46 per cent. of low birth-weight babies were of greater maturity than 38 weeks. Colman (1962) found that 31 per cent. of so-called "premature" infants were of over 37 weeks gestation and Scott and Usher (1966) found 39 per cent. of infants of 2500 g. and less to be of over 37 weeks maturity. Markany, Monroe and Sutherland (1961) stated

that 8000 infants were born each year in the U.S.A. who showed intra-uterine growth retardation. Retardation is by far the commonest type of dysmaturity seen. Acceleration of growth may also occur as seen in the infants of diabetic mothers. Several other babies at about 30 to 33 weeks gestation also showed a high weight/maturity ratio, as already mentioned in Part I of this thesis. Some may be due to an abnormality such as maternal prediabetes while others may in fact be within normal limits. The foetal weight estimations of Scammon and Calkins and of Streeter (both quoted from Potter, 1961) may be rather low at this period of gestation.

Retardation of intrauterine growth has recognized causes also, such as rubella. In vitro the viruses of rubella and of poliomyelitis inhibit mitotic activity in tissue cultures (Plotkin, 1965; Naeye and Blane, 1965). An example of both of these conditions was seen in this series. In hepatitis and measles Siegel (1966) has found that low birth weight is due to short gestation. Gruenwald, Funakawa, Mitani, Nishimura and Takeuchi (1967) have observed an absolute increase in birth weight which was not due to an increased duration of gestation, in association with improved economic and health conditions. The reverse was not seen in Rotterdam shortly after the 1939-1945 war (Smith, 1962) when near-starvation levels of nutrition did not reduce birth weight significantly, but rather produced anovular amenorrhoea. Perhaps the findings of Gruenwald et al. in Japan illustrate the middle course in nutritional states, rather than extremes. Certainly it is generally agreed that the small, mal-nourished, overworked mother of poor

intelligence and low medico-socio-economic status is more likely to have a low birth-weight baby than the tall, well-nourished mother of better intelligence and higher medico-socio-economic status (Baird, 1959). Raihi and Kauppinen (1963) make the point that the living conditions of pregnant women should be adjusted to their physical capacity, in which the heart volume is probably of greatest importance, increased prematurity rates, renal insuffiiency and low urinary excretion of oestrogens being associated with a small heart volume. It seems probable that the mother from the higher socio-economic stratum will be better able to arrange her domestic responsibilities to suit her limitations than will the mother of poorer socio-economic class.

It has already been shown that pre-eclamptic toxaemia produces a low weight/maturity ratio, which is probably the result of placental dysfunction or foetal adrenal subnormality. Prednisoline administration to the mother is now thought to result, in some instances, in failure of placental growth followed by increased numbers of abortions, stillbirths and low birth weight babies. Experimentally, Blackburn, Kaplan and McKay (1965) showed this failure of development in rat placentae accompanied by an increased abortion rate. The present series includes one infant weighing 1300 g. at 39 weeks gestation (42 per cent. of expected weight) whose mother received prednisoline therapy in Canada in the hope of preventing Rhesus iso-immunization. The baby was thin, "dry" and alert, and made good progress during the first year of life. She showed no signs of adrenal insufficiency, a finding which is consistent with present thought (Warrell and Taylor, 1968).

Thus it is seen that a variety of conditions can cause intra-uterine growth retardation, viz. rubella and other virus infections, drug therapy, pre-eclamptic toxaemia, poor environmental circumstances, and that the babies of these pregnancies whilst being of low birth-weight may or may not be mature.

At the present time there is not a little confusion as to the meanings of the terms prematurity, immaturity, postmaturity and dys-maturity. Warkany, Monroe and Sutherland (1961), Silverman (1963), Engleson, Roath and Tornblom (1963), Yerushalmy, Van den Berg, Erhardt and Jacobziner (1965) and Scott and Usher (1966) are all aware of this difficulty. More rigid definition and usage of these terms is required. It would be accurate to consider maturity, immaturity and postmaturity as having a purely chronological meaning, taking 40 weeks gestation as indicating "maturity", less than 37 weeks as "immaturity", and 42 weeks and over as postmaturity. One can superimpose on all these terms the qualitative character, "dysmaturity", which may be in the nature of intra-uterine growth retardation or acceleration. The term "prematurity" should not be used since there is no such thing as a "premature baby", only a premature labour which results in an immature baby. The term low birth-weight can be used as a clinical indication for the need for special care, but should not be used as a parameter in medical investi-gations. Plainly the birth weight reflects only the summation of all factors acting during a pregnancy and, with certain exceptions, notably diabetes mellitus and severe haemolytic disease of the newborn, the bigger the birth weight, the better has been the pregnancy over-all.

Thus by using birth-weight as a parameter we are introducing a process of selection from the start. It is thus not to be wondered at that birth weight is usually found to be more closely related to the survival and subsequent progress of the infant than other factors. It is my regret that when I started this study the importance of this type of classification, according to the duration of gestation, was a good deal less clear to me than it is now. However it is only as a result of this study that these thoughts have emerged. It seems probable that the number of infants who weighed over 2500 g. at birth but who were of under 37 weeks gestation was quite small. Nevertheless they would make an interesting and perhaps important study in themselves.

The effects of postmaturity and dysmaturity on the foetus may be similar, but in the former placental function has reached its physiological maximum and begun to decrease, whereas in the latter the physiological normal has never been established, probably as a result of pathological cause or inadequate maternal accommodation to the foetus so that the foetus suffers from deprivation. Where dysmaturity and postmaturity co-exist the foetus is in great danger of intrauterine or intrapartum death. In addition McCance (1962 a, b) states that, in rats, "The younger the animal the more serious a nutritional setback will be, and permanent effects from undernutrition during foetal life are a distinct possibility".

No inquiry was made into the smoking habits of this series of patients but in retrospect it seems that this may be another factor influencing the development of the foetus. Indeed it has been shown by

several authors (Herriot, Billewicz and Hytten, 1962; O'Lane, 1962; Goldstein, Goldberg, Frazier and Davis, 1964; Levinski, Nellist and Takenaga, 1966) that cigarette smoking in pregnant women is associated with the birth of infants whose mean weight is lower than that of the infants of their non-cigarette smoking controls, and whose gestation period is significantly shorter. Savel and Roth (1962) did not find that gestation was shortened. Kumar and Zourlas (1963) found increased uterine contractility in more than half of patients whilst smoking, but were unable to detect any oxytocic effect of nicotine on isolated human myometrial strips. An increase in foetal heart rate during smoking has been demonstrated which might lead to the birth of a small infant if this is the treatment to which it is subjected several times daily. Goldstein et al. covered this possibility in suggesting that smoking causes foetal vasoconstriction. They also su gested that it has a direct toxic effect on the metabolism of the foetus, or causes an elevated carbon monoxide level, resulting in reduced oxygenation. In addition they considered that the reduced calorie intake resulting from smoking might cause low birth-weight. Finally these workers thought that the association might be with low socio-economic status, where more mothers are known to be heavy smokers. It seems probable however that there is also a specific association between cigarette smoking and low birth weight, and that this may be through an immediate effect on placental circulation (Herriot et al.) or on foetal cardiac output, or both.

Congenital defects of diverse nature were seen in 12.6 per cent.

of these 302 low birth-weight babies. In 7.6 per cent. these were lethal or potentially lethal, and in five per cent. essentially non-lethal. McDonald (1962) found an 8 per cent. incidence of gross malformation in 204 low birth-weight babies at birth, and serious defects in a further 9 per cent. of survivors. Defects of midline fusion were present in 5.4 per cent. of McDonald's series, and oesophageal atresia in 1.5 per cent. In the Stobhill series midline fusion defects, most often anencephaly, preponderate and were found in 3.6 per cent. of 302 low birth-weight babies. Multiple defects were second in order of frequency, and oesophageal atresia was not uncommon, occurring in 1.0 per cent. of these small babies. The subject of midline fusion defects has been discussed in Part I on perinatal mortality.

In oesophageal atresia it is agreed that low birth weight is one of the main factors to affect the outlook adversely, (Hays, 1962; Waterston and Bonham-Carter, 1962). Other difficulties which influence the outcome adversely are associated defects and pulmonary complications, to both of which the low birth-weight baby is prone. Temporary operative procedures, and staged procedures are recommended by these authors.

Eye defects in low birth-weight babies have attracted a lot of attention perhaps as a result of the high incidence of retrolental fibroplasia during the last decade. In the present series only one gross defect was seen at birth, a unilateral microphthalmia and coloboma. Coloboma has been described as occurring with multiple defects by Angelman (1961) but the aetiology in his four cases was not known. More frequently the defect is a squint of paralytic type (Brown, 1960). Myopia is also

common (Brown, and Graham and Gray, 1963). Cataracts and optic atrophy are seen. Cataracts may be the result of rubella, or of other virus infections whose presence or significance are not yet recognized. Optic atrophy is thought to be associated with anoxia, cerebral haemorrhage, subdural haematoma, haemorrhage into the optic nerve or its sheath, or to increased intracranial pressure to all of which low birth-weight babies are liable.

It is well known that all congenital defects are not detectable at birth (Lock, Gatling and Wells, 1961). During the first year a further 14 infants of 85 examined were found to have abnormalities. This figure does not take into account those babies who were not seen after discharge from hospital. By projecting this finding on to the number of survivors (188) the total incidence of congenital defect in these 302 low birth-weight babies could have been as high as 69, or 22.8 per cent. The incidence of fatal congenital defect in the perinatal period is 0.58 per cent. (Butler and Bonham, 1963) and the over-all incidence in live-born infants in the first year of life lies between 1.53 per cent. (Grundy and Lewis-Faning, 1957).

Superficial birth injury in the form of extensive bruising was seen in 16 of 302 low birth-weight babies. It is my impression that this type of injury is not usually associated with cerebral birth injury such as haemorrhage, tentorial tears or general anoxic damage. Bruising can be an additional hazard to low birth-weight infants in that it adds unconjugated bilirubin to the circulation raising the bilirubin load to a dangerous level for the development of kernicterus. One gram of

haemoglobin produces 35 mgm. of bilirubin (Brown, 1962). Thus where the total blood volume is only 200 ml. the lysis of 1 g. of haemoglobin could raise the serum bilirubin level to 17.5 mg. per 100 ml. Under normal circumstances the liver has to deal only with the haemoglobin of "physiological" red-cell breakdown, but in these low birth-weight babies it is dealing also with haemolysis from bruising, with anoxia, hypothermia, hypoglycaemia, and a deficiency of glucuronyl transferase, all characteristic of the low birth-weight baby. Thus it seems of importance to reduce bruising to a minimum in such babies, perhaps by a gentle forceps delivery, and then to watch very closely the bilirubin level and the clinical condition of the baby with a view to exchange transfusion.

Respiratory difficulty at birth and in the first four hours of life was present in 66 of 251 live-born, low birth-weight infants in the present series. It was associated with immaturity, but no specific maternal illness was involved. It was associated with development of established respiratory distress, cyanotic attacks, sudden collapse and jaundice in the later neonatal period. These are closely related findings tending to overlap in causation and time of occurrence, and are either dependent on each other or, more probably, on the common denominator of immaturity. Oedema, hypotonia and cyanosis were also closely related. The main abnormality about which these findings are centred is the respiratory distress syndrome. This is the prime cause of mortality in live-born immature babies, its incidence amounting to 3.9 per cent. in live births (Cohen, Weintraub and Lilienfeld, 1960), and its

mortality rate being between 50 per cent. and 60 per cent. of cases, prior to modern therapy. In the present series respiratory distress was present in 23 of 245 infants (9.4 per cent.) 9 of whom died, a mortality rate of 39.1 per cent.

Many authors consider that there is a "high risk" mother for the subsequent development of respiratory distress in the infant. The mother is delivered prematurely, may suffer from pre-eclamptic toxaemia, ante-partum haemorrhage or diabetes, and may have undergone Caesarian section. Rogers and Gruenwald (1956) and Cohen, Weintraub and Lilienfeld found this high incidence in infants of 2500 g. and under, stating that it was particularly common with pre-eclampsia and bleeding. "Very small prematures" are not exempt from this syndrome, as sometimes is the impression (Silverman and Silverman, 1958; Avery and Drolette, 1958). The severest form of the disease is seen three times more frequently in male infants weighing between 1500 g. and 2000 g. at birth than in female infants (Miller, 1963). Infants born by Caesarian section are known to be at increased risk, but this may be related only to the reason for the operative delivery (Moss, Duffie and Fagan, 1963), particularly ante-partum haemorrhage (Cohen, Weintraub and Lilienfeld) and to their immaturity. The latter workers found a high risk in mothers with previous stillbirths, but not with previous low birth-weight babies or miscarriages. This is an interesting finding. It is known that the immature baby has an increased risk of respiratory distress. It is also known that the mother with an immature baby has not uncommonly had previous low birth-weight babies. There may be a special group of

low birth-weight babies who are prone to respiratory distress and have stillborn siblings, but such a relationship was not seen in the present series.

Pre-eclamptic toxaemia, diabetes and ante-partum haemorrhage are all regarded as being accompanied by intrauterine "asphyxia". One must regard this in a different light from the "normal" state of intra-uterine hypoxia which Romney, Kaneoka and Gabel (1962) describe as only anoxic when compared with adult criteria for extra-uterine existence, postulating that the foetal capacity to tolerate hypoxia or anoxia may not be a matter of foetal adaptibility but an expression of different biological needs. Likewise Dancis (1959) states that the foetus exists in utero under standards that are anoxaemic by post-partum standards. It seems probable that substances other than oxygen have more importance during intrauterine life. Miller and Bundy (1962) state that the foetal distress of pre-eclamptic toxaemia is hypoxic. Cox (1963) on the other hand says that the environment must not be blamed entirely and that "the metabolic rate of the foetus itself determines oxygen utilization". Plainly if placental function is sufficiently deranged, as in pre-eclampsia, diabetes and ante-partum haemorrhage, the resulting further reduction in oxygen below the level of physiological hypoxia may produce foetal asphyxia. The foetus in this condition tends to be apnoeic at birth. Cohen, Weintraub and Lilienfeld considered respiratory distress to be the result of intrauterine asphyxia. Potter (1959) likewise states, in speaking of twins that she had

"long felt that the main conditions responsible for the

development of hyaline membranes must already exist at the time of birth".

We know anyway that the infants of mothers with these three conditions (pre-eclampsia, diabetes and haemorrhage) tend to require more than minimal resuscitation, and this is particularly the case if delivery is by Caesarian section. Some suffer from the effects of repeated administration of analgesics or of deep anaesthesia to the mother and are apnoeic at birth. This, however, was not seen in the present study and it would appear that analgesia and anaesthesia, as used in the Stobhill Maternity Unit, were not responsible for morbidity or mortality in the newborn. Brady and James (1962) think that bradycardia lasting longer than one minute after a contraction is over will always be associated with a depressed infant. The Apgar score over the first five minutes is usually low. Very few of these babies have a "clear" period prior to the onset of respiratory distress although originally this was thought to be the case. Miller and Calkins (1961) state that apnoea should be timed as they have noted that fatality rates amongst infants with severe respiratory distress are significantly higher if "self-sustaining, spontaneous breathing" is delayed for more than one minute after birth. They feel, however, as do Apgar and James (1962), that estimations of respiratory rate, colour and retraction are more indicative of developing respiratory distress. Initial tachypnoea or bradypnoea is also of significance. These infants are also oedematous, often severely so (Hutchison, Kerr, McPhail, Douglas, Smith, Norman and Bates, 1962) and this may worsen during the course of the disease (Gregg and Bernstein,

1961). The association of oedema with respiratory distress is shown in the present study. Whether the distress is a result of oedema of the lungs, or whether both are primarily associated with immaturity is not known. Morison (1952) found pulmonary oedema in such infants at autopsy, as well as ascites, increased volume of cerebrospinal fluid and hydrothorax. Experimentally, Avery (1963) did not find that severe and prolonged hypoxia produced the histological picture of hyaline membrane disease. Nevertheless cyanosis, presumably indicative of hypoxia, was seen frequently in the babies of this study and, unlike the experience of Gregg and Bernstein, was present in the first four hours of life. On the other hand one has been impressed more than once by the small extent of aerated lung found at autopsy in an infant whose colour has been considered fairly satisfactory during life.

Taylor, Scott and Govan (1951) found that the blood of the normal full-term infant reaches 85 per cent. of normal oxygenation by the end of the first hour of extrauterine existence, whereas the premature infant is incapable of achieving this level. Further if this level is not attained by this time neonatal deaths tend to occur. Fawcitt (1962) found in most low birth-weight babies within an hour of birth radiological evidence of well-marked areas of unexpansion up to complete atelectasis. Klaus, Tooley, Weaver and Clements (1962) found that most full-term infants achieve full functional residual capacity during the first few minutes of life. Thus there is objective evidence that the full-term infant adjusts to extrauterine ventilation rapidly, whereas the premature infant does so more slowly if at all. Whether

established respiratory distress results from this slow response or, as would seem to be more likely, the slowness and the distress are both the result of a basic incapability to meet the respitatory needs of extrauterine life is not clear.

The difficulty appears to be primarily pulmonary. Potter says that immaturity of the lungs is the most important factor in determining the death of immature infants. Atelectasis may be the primary abnormality, with the formation of membranes occurring secondarily (Gregg and Bernstein). It may, however, be the result not of one cause, but rather of a sequence of events. The factors involved may be slight or severe deviations from normal physiological processes.

Perhaps one can envisage the normal sequence of events occurring in the spontaneous vaginal delivery of a full-term infant. At the start of labour the foetus is in its "normal" hypoxic state, becoming a little "deprived" of essentials as a result of decreasing placental function, which starts about the 38th week. The first stage of labour is not too long (probably a good deal less than 12 hours in a multipara), with the mother in satisfactory condition and the foetal heart steady at 140 per minute. It slows during a contraction but recovers quickly when the contraction is over. With the transition to second stage, accompanied by more forceful uterine contractions and expulsive efforts on the part of the mother the cord blood supply is much more severely curtailed. Placental vascular resistance is increased during contractions, and instead of receiving 55 per cent. of the foetal cardiac output, the normal during pregnancy, it receives a much smaller quantity. It seems probable that the remainder is forced in increasing amounts

into the pulmonary circulation. Yao, Hirvensalo and Lind (1968) have confirmed that uterine contraction is the key factor determining placenta-to-baby blood transfer. It is probable at this stage of initial pulmonary perfusion that a foetus becomes cyanosed for the first time, or hypoxic to a degree which stimulates its respiratory centre. At the time of birth, with the sudden release of the chest from the vaginal tract there must be sudden full pulmonary perfusion, synchronous with the last effective uterine contraction. The infant cries and air ventilates the lungs, filling out the alveoli and lending support to the distension already produced by the filling of blood vessels. Thus in the first few seconds the anatomical changes necessary for normal pulmonary function are achieved, and in the first hour the physiological consequences of this are seen in the blood gas values. Pulmonary perfusion comes first, probably starting gently in utero, followed by sudden full perfusion at the moment of release from the vaginal tract, and backed-up immediately by air ventilation, to produce normal extra-uterine pulmonary function. Obstruction of air intake at the time of birth by amniotic fluid, blood or mucus will considerably reduce or prevent forceful pulmonary aeration.

One can perhaps envisage other deviations from normal which might occur. This may be as simple a matter as a long labour with strong but incoordinate contractions, so that whilst the lungs are undergoing the initial perfusion the foetus is becoming increasingly anoxic. In addition the mother may become acidotic, which is reflected in the foetus. Labour progresses beyond the optimal time for air ventilation of the

lungs, with resultant foetal distress, depression, and ultimately still-birth, if relief is not given. In cases of ante-partum haemorrhage or cord obstruction it seems probable that the abnormality would be absence or insufficiency of pulmonary perfusion from sheer blood deprivation. This same mechanism would be present in Caesarian section unless the infant were held below the level of the placenta for a sufficient time to allow pulmonary perfusion to take place. If the theory is correct that perfusion occurs in a small way during labour then the baby whose mother has been in labour before section should show a better respiratory response on delivery than the baby of the mother undergoing elective section. On the other hand the baby of the emergency section may be in poor condition for those reasons for which the section was carried out, and may thus be difficult to resuscitate. In addition, in Caesarean section there is no sudden release of the chest from the pressure of the vaginal tract, and this must reduce the force with which blood would normally reach the lung capillaries. The initial intake of air in such infants with no lung perfusion would probably meet with little effect, since the lungs are still in their relatively ischaemic foetal state, and air pressure alone may be inadequate for distension of such lungs. If respiration becomes established following cord clamping in an apnoeic infant the heart rate increases to about 180 per minute, later returning to normal. It seems possible that lung perfusion may be achieved even at this stage by the accompanying increase in cardiac output resulting from this temporary tachycardia. No such cardiac response is seen in the infant who is vigorous and breathing well before the cord is clamped

(Brady and James, 1962).

The situation is much worse in immature infants, where lung development itself is unprepared for extrauterine existence. The alveolar cells are thick and unsuited for diffusion and there is low perfusion due to inadequate capillary development. In addition enzyme systems for oxygen transfer are immature. The lung, as a result, is less compliant and more "spastic" than the full-term lung and has a high surface tension. It is plain that these circumstances added to pre-eclamptic toxaemia, ante-partum haemorrhage or diabetes, or Caesarian section for any of these three could not put produce a very precarious passage for such an infant from intrauterine to extrauterine life.

We have thus noted three fundamental factors, perfusion, ventilation and maturity, all of which can be easily disturbed with the production of various degrees of abnormality in the newborn. The underlying process, once started, appears to be cellular destruction in the alveoli and alveolar ducts up to 24 hours, and repair by cellular proliferation after 48 hours. This stage is considered to be an active reparative one rather than a purely reactive phenomenon (Boss and Craig, 1962). Barter (1962) compared the formation of hyaline membranes in the newborn with the cellular necrosis of kerosene aspiration, and thought the process of damage to be similar, with granular eosinophilic material in the cytoplasm of greatly swollen alveolar epithelial cells.

Evidence of tissue destruction is seen in the metabolic changes found in these babies. Beard, Panos, Burroughs, Marasigan and Öztalay (1963) withheld all calories and fluid for 72 hours form a series of new-

born infants. The normal infants developed only hypoglycaemia and acetonuria, but those with Apgar scores of one to three, and with low birth weight and pulmonary distress showed excess potassium excretion for six days, prolonged acidosis, early hypernatraemia and excess weight loss. Nicolopoulos and Smith (1961) also found evidence of excess tissue destruction in hyperkalaemia, excess excretion of sodium and shift of water from the cells to the extracellular tissues. They compared the reaction to that seen in the baby stressed by cold, or the adult stressed by anaesthesia or surgery.

Other theories on the actiology of respiratory distress and the formation of hyaline membranes were summarized by Aronson (1961). These include left heart failure, vasomotor hypotonia, toxic or anoxic capillary damage, decrease in plasmin activator, an abnormal lining substance causing increased surface tension, and autonomic nervous system dysfunction.

With regard to what has been postulated here concerning perfusion and ventilation ultimate myocardial failure would seem to be the result of the deviations from normal rather than the cause. Early right heart failure would seem to be more likely from a mechanical point of view, since pulmonary vascular resistance is increased. Right to left shunt of blood may occur in the pulmonary bed but Rudolph, Drorbaugh, Auld, Rudolph, Nadas, Smith and Hubbell (1961) considered that left to right shunt occurs across an abnormally patent ductus arteriorus and that left ventricular failure follows. In analysis of blood gases in seven infants with severe respiratory distress Strang and MacLeish (1961) found

convincing evidence of a right to left shunt. This however would be late in the course of the disease. Digitalis is of no help in preventing the development of pulmonary distress (Martin, 1963) and, contrary to what one would expect in left heart failure, is of little or no help in treating it (Jaco, 1963; Smith, 1965).

Vasomotor hypotonia, toxic and anoxic pulmonary capillary damage and decrease in plasmin activator are probably all the result of disturbance of these three basic physiological functions of the lungs. In face of this the postulate of the presence of an abnormal lung-lining substance, as a disease entity in itself, causing increased surface tension, seems unnecessary and excessive. By contrast Pattle, Claireaux, Davies and Cameron (1962) suggested that there was no lipo-protein layer, or surfactant, on the alveolar walls and that surface tension was thus increased. They found that the minimum surface tension of extracts from lungs with hyaline membrane disease was consistently higher than in normal lung. Finally, autonomic nervous system dysfunction has been held as primarily responsible for the formation of hyaline membranes. Aronson states that excess sympathetic activity causes leakage of plasma through pulmonary capillaries, with intra-alveolar clotting of fibrinogen to form dense membranes of fibrin demonstrable by fluorescent antibody technique and by electron microscopy. It seems certain that the fluid arises from within and not from outwith the alveolar lining. Buckingham and Sommers (1960) found hypersecretory changes in the terminal bronchioles and alveoli-lining cells in infants, with DNA incorporated ih the membranes, suggesting that the secretory products of the respiratory epithelium are

a part of hyaline membranes. They consider that this reflects autonomic nervous system dysfunction. Adams, Fujiwara and Rowshan (1963) found normal tracheal fluid present in the tracheae of lambs in which where there was no communication between eyes, nose or mouth and the trachea, showing that this fluid had not originated directly from the liquor amnii. They suggested that a process of ultrafilration with selective reabsorption or secretion goes on in the lungs in utero. Colebatch, Halmagyi and Starzecki (1963) found that amniotic fluid aspiration in lambs produced some of the features of the respiratory distress syndrome. However, as amniotic fluid aspiration may occur and interfere with initial aeration, this finding is quite in keeping and may indeed be a factor in producing or aggravating respiratory distress in some cases.

There is good evidence that there is capillary damage in these babies, both in the lungs and elsewhere. In the first place it has been shown by Baar (quoted from Gregg and Bernstein, 1961) that both the pulmonary and systemic oedema fluid of these babies is proteinaceous, containing 3.4 mg. per 100 ml. of protein. In addition there is known to be a smaller blood volume and shift of fluid to the tissue spaces, an increased volume of cerebrospinal fluid, and a tendency to the development of ascites and hydrothorax. The development of petechiae at the site of the suction-type electrodes used in electrocardiographic examination of these babies is not uncommon. It seems probable that this increased capillary fragility is the result of diminished oxygen tension in the blood. The hypoxic baby not uncommonly dies with haemorrhage from the

lungs or intestine.

Thus it is felt that the initial abnormalities of lung perfusion and ventilation, with the ensuing difficulty of diffusion is the basic process underlying respiratory distress in the newborn, and that other findings are a consequence of these abnormalities, and not the basic cause.

The question of lung expansion cannot be left without reference to cord clamping. Moss, Duffie and Fagan (1963) state that

> "the carefree manner in which the newly born infant is 'disconnected' from his 'oxygenator' without any assurance that respiration will ever begin is in contrast to the meticulous care with which the thoracic surgeon separates his patient from the pump-oxygenator".

Whilst finding the comparison striking, one must remember that the 'oxygenator' of the foetus will become of no avail in quite a short space of time after delivery of the infant. Nevertheless it appears that one might make good use of this brief interval.

Under normal circumstances cord pulsation continues until the change from placental to pulmonary oxygenation is complete (Moss et al.) and the cord should not be clamped before then. It follows that the apnoeic infant should not be separated from his placenta until he has received its blood by gravity drainage. The volume of blood transferred can be increased by 80 ml. in this way (Redmond, Isana and Ingall, 1965). Bound, Harvey and Babshaw (1962) found a significant decrease in the incidence of the pulmonary syndrome of the newborn in

the weight group from 1500 g. to 2000 g. by delaying cord ligation and allowing gravity infusion from the placenta. Gecher and Karlberg (1962) found placental transfusion beneficial on a haemodynamic basis and for increasing iron transfer. They suggest gravity infusion after all Caesarian sections. Taylor, Bright and Birchard (1963) found no benefit to premature infants from placental transfusion. Redmond et al. state that "placental transfusion is an inevitable physiological consequence of initial pulmonary expansion. In the present thesis the opposite view is put forward in that initial pulmonary expansion is thought to occur as a consequence of placental transfusion.

It has already been noted that there is experimental evidence that foetal pulmonary perfusion starts before delivery and is maximum at the moment of release from the vaginal tract. Greiss (1965) has shown in ewes that, during uterine contractions and maternal expulsive efforts, uterine blood flow is decreased, and that recovery varies with the duration of myometrial "diastole". Ramsay, Corner and Donner (1963) have shown by cine-angioradiography that placental blood flow is greatly reduced or ceases altogether during uterine contractions. This must hold back blood on both the maternal and foetal sides of the placenta with an increasing flow in the foetal pulmonary circulation as labour progresses. In 1965 Chu, Clements, Cotton, Klaus, Sweet, Thomas and Tooley described the "pulmonary hypo-perfusion syndrome", by which they meant hyaline membrane disease developing as a result of vasoconstriction under conditions of hypoxaemia, acidaemia, hypothermia and hypovolaemia. Smith (1965) finds that blood given during the course of the respiratory

distress syndrome may be beneficial, as do Bound et al. This may increase lung perfusion by increasing blood pressure and cardiac output, in a belated manner, or may have some less direct effect.

Finally one must express doubts about the value of cord stripping and point out the warnings of Lanzkowsky (1960) on late cord clamping. Such a practice is contraindicated where there is risk of intracranial haemorrhage, asphyxia with circulatory failure and materno-foetal blood incompatibility.

Jaundice occurs early in the course of respiratory distress, usually within 48 hours of birth (Hutchison, Kerr, McPhail, Douglas, Smith, Norman and Bates, 1962) and the bilirubin level may reach dangerous levels. Not only is the liver immature but there is depression of enzyme formation by anoxia and by acidosis, both of which also facilitate the passage of unconjugated bilirubin into the brain cells.

Paralytic ileus also occurs with respiratory distress (Dunn, 1963). The cause is not clear. Its importance lies in its recognition as being non-surgical and responsive to gastric aspiration and parenteral fluids if required. It subsides with the improvement of distress.

Exhaustion is seen in infants who are severely ill with respiratory distress. The posture of thes babies is unmistakable. They are unresponsive and flaccid, with arms to their sides, and marked chest retraction. The exhaustion is regarded as being due to the physical exertion demanded of the heart and muscles to attain adequate oxygenation from damaged lungs. The respiratory rate is raised and lung compliance markedly reduced, resulting in increased energy expenditure for each

breath. In 1963 Smythe suggested, as a result of his experience with neonatal tetanus, that continuous positive pressure respirators might be of help in reducing this burden on infants with respiratory distress. Colgan, Eldrup-Jørgensen and Lawrence used this method in 1960, and more recently Reid and Mitchell (1966) have reported favorably on its use in infants with recurrent apnoeic attacks.

The treatment of infants with potential respiratory difficulties should start in the labour room with the expectation of a depressed or immature infant in the types of mothers already outlined, namely those with pre-eclamptic toxaemia, diabetes, haemorrhage, Caesarian section, prolonged labour with incoordinate contractions, repeated analgesia or prolonted anaesthesia, or where foetal bradycardia is prolonged for more than one minute after the end of a contraction. In such circumstances a paediatrician, experienced in resuscitation of the newborn should be present in the labour room, so that the infant receives undivided attention such as cannot be given either by the obstetrician or anaesthetist. The mother may previously have been helped by oxygen administration, intravenous glucose, or correction of acid-base upset. Attention by the obstetrician to the time of cord clamping relative to the condition and position of the infant should result in optimal perfusion of the lungs under the circumstances prevailing. Reid (1959) considers it of importance to delay delivery following ante-partum haemorrhage for as long as several days if this is at all possible so that foetal circul-

ation can be restored and recovery made from the shock and anoxia of exsanguination, especially if maturity is "borderline".

Initial resuscitation comprises suction of the pharynx and administration of oxygen by a face mask or funnel. It was said in 1958 (Higgins) that this, with warmth, was often all that a full-term infant needed for the establishment of respirations. More active measures may be required if there is no sign of gasping after four minutes (Barrie, 1963). In addition Barrie feels that where there is no heart beat circulation of blood may be induced by external cardiac massage. Drugs may be required such as Vandid (25 mg. or 12.5 mg. for small infants) or Nikethamide (125 mg. or 62.5 mg. for small infants) given sublingually (Barrie, Cotton and Wilson, 1962) or into the umblical vein, muscles of the leg or into the heart. As the circulation is poor these drugs may not prove very effective. It is doubtful if the heart is a satisfactory site for injection except in extremis, since with the onset of respirations and increased cardiac activity there is increased blood supply to the myocardium and haemorrhage may occur from the site of puncture. Haemorrhage into the conducting system of the heart can occur in the newborn following ischaemia without any external assault (Hoch-Ligeti, and Diaz-Perez, 1962) Lethidrone should be used specifically where there is morphine or pethidine depression.

Endotrachael intubation may be followed by controlled positive pressure insufflation. Intra-gastric oxygen has been abandoned as it is not considered to be of any great benefit and carries a risk of gastric perforation. Coxon (1960) found no oxygen increase in the

arterial or portal blood of anaesthetized cats following the intra-gastric administration of oxygen. If positive pressure insufflation of the lungs is carried out the pressure must be controlled to within 15 cm. of water, with an occasional "puff" not exceeding 26 cm. of water, as there will otherwise be a considerable danger of emphysema and pneumo-thorax (Corner, 1962). Barrie found the ideal time and pressure for lung expansion to be 0.5 seconds at 40 cm. of water. It is possible at this stage that, where there has been foetal distress, there is already acidosis, and some effort to correct this has been made by the empirical administration of sodium bicarbonate. The primary need is for oxygen. Experimentally oxygenated blood has been given via the umbilical vein to asphyxiated lambs (Brandt, Cunningham and Harned, 1960) with no improvement; with the addition of endotracheal insufflation some resp-iratory effort was made, but death occurred within a few hours. In 1963 Goodlin administered oxygen to mice in a "foetal incubator" utilizing cutaneous respiration and found that survival was prolonged. He thought that this "might be a useful method to maintain the oxygen supply of an extrauterine fetus". In 1963 Hutchison, Kerr, Williams and Hopkinson reported good results from the use of hyperbaric oxygen in a series of infants who were apnoeic at birth and in whom the usual resuscitative measures had failed. In 1966 Hutchison, Kerr, Inall and Shanks reported that intubation was equally effective, but that hyperbaric oxygen had the advantage of not requiring highly-trained staff.

With the delayed onset of respiration subsequent respiratory distress should be expected. A watch is therefore kept on respiratory

and heart rates, and for the development of inspiratory retraction. These infants should be kept warm, and oxygen and humidity supplied on the least evidence of distress. With a rising respiratory rate and increasing retraction blood values of pco_2, ph, standard bicarbonate and base excess are estimated on capillary blood by the micro-Astrup method. Deviations from normal are corrected either by rapid or slow intravenous infusion. In many centres it is still the practice to use 10 per cent. glucose and 8.4 per cent. sodium bicarbonate via the umbilical vein, but this runs the danger of producing portal vein thrombosis. Smith (1965) prefers the early setting-up of a 10 per cent. glucose infusion by scalp vein or "cut-down", to run at 65 ml. per Kg. per 24 hours, and to add alkali as required. A continuous infusion also has the advantage of giving these babies fluids early, which is said to improve survival rates, especially amongst those of lowest birth weight. Nasogastric and oral feeding does not provide the same benefit (Cornblath, Forbes, Pildes, Luebben, Greengard, 1966). Hyponatraemia has been reported in the infants of pre-eclamptic mothers, caused either by low placental transfer (Johnston and Clayton, 1957) or by the salt-free diet of such patients (Alstatt, 1966), or both. It might therefore be worth estimating the serum electrolyte levels once or twice during the course of the illness and making the necessary corrections. Smith, and Bound, Harvey and Bagshaw (1962) consider that blood transfusion is valuable in some infants. Smith would raise the haematocrit value from below 40 to between 50 and 60, by use of a red cell concentrate. Micro-Astrup estimations can be made about two hourly. When metabolic acidosis is

corrected and oral feeding well established intravenous therapy is stopped.

Oxygen administration is at a level where cyanosis is just relieved. Avery (1962) allows oxygen concentrations of 60 per cent. to 80 per cent. if this is necessary to sustain life, saying the danger of retrolental fibroplasia "seems remote" under the conditions. Nevertheless one would have to proceed with great care, reducing the oxygen level with advancing recovery, yet still relieving cyanosis. The maintainance of 90 per cent. humidity is the routine practice. The use of detergents has been abandoned in the Stobhill Unit, and Smith is awaiting convincing evidence that such wetting agents are of value. A prophylactic antibiotic is usually given in our cases, as in Smith's, whereas Gairdner (1965) would only prescribe this if there were a history suggestive of infection or a positive blood culture. Vitamin K oxide 0.7 mg. is used routinely by Smith, but at Stobhill is only given on specific indications such as the presence of marked ecchymoses or recurrent apnoeic attacks suggestive of intraventricular haemorrhage.

The most recent addition to therapy is the relief of physical fatigue by the use of a positive pressure respirator. Reid and Mitchell (1966) used this method successfully for infants with recurrent apnoeic attacks. If this not only helps a neonate through severe respiratory distress but also prevents cyanotic attacks, then this is a considerable contribution to the subsequent welfare of these infants. In the present series cyanotic attacks at over four hours of age were the only abnormality found more frequently in infants with retardation of adaptive development

than in normal infants. Further MacDonald (1963) found a high incidence of cyanotic attacks in the neonatal period in children with cerebral palsy who had been of short gestation and birth weight of less than 1800 g. Using such apparatus close attention is needed to keep the airway clear. The usual biochemical corrections are carried out.

Despite successful correction of metabolic acidosis some of these infants deteriorate progressively and rapidly. There is uncorrected respiratory acidosis. Thus whilst great improvement has been brought about in the survival rate of these babies, the whole answer is not yet available.

It is said that once an infant recovers from respiratory distress there are no further consequences (Gregg and Bernstein, 1961). It has been noted however in the present series of low birth-weight babies that bronchitis in the first year of life was significantly related to respiratory difficulty at birth and respiratory distress in the hours after birth. Despite this fact it is obvious that a number of infants developed bronchitis who had no such upset in the neonatal period. Douglas and Mogford (1953), Drillien (1959) and Grewar, Medovy and Wylie (1962) also noted an increased incidence of respiratory tract infection in low birth-weight babies, usually bronchitis or pneumonia.

It has usually been accepted that low birth-weight babies are deficient in γ-globulins and that this is the reason why they are prone to infection. γ-globulins are not demonstrable in foetal blood until mid-pregnancy, and reach a maximum at the eight or ninth month of gestation (Vahlquist, 1960). It is claimed that a monthly dose of γ-globulin will

reduce the incidence of infection amongst "premature" infants, and will probably ameliorate severe infections and reduce mortality (Amer, Ott, Ibbott, O'Brien and Kempe, 1963).

Forming a link between bronchitis, respiratory distress and deficiency of γ-globulins in immature infants Hardie, Heese and Kench (1965) demonstrated low total protein concentration in the serum of infants with pulmonary distress, and an abnormally low proportion of γ-globulins. Both abnormalities were said to be present in cord blood at birth, and to become more pronounced as the disease progressed. This fall in serum proteins may be the result rather than the cause of the increasing oedema which occurs in the course of respiratory distress, the fluid being rich in protein as a result of anoxic capillary damage.

Thus there appears to be an immunity link between immaturity, respiratory distress and bronchitis in the first year of life. One is tempted to postulate a structural link also. Destructive changes are said to be always present in the first 24 hours of respiratory distress, and reparative changes after 48 hours. It seems possible that these structural alterations, in the presence of a lung which is still undergoing development would persist or fail to resolve completely during the first few weeks or months of life predisposing these infants to recurrent attacks of "bronchitis" which are so characteristic of the immature baby in the first year of life. Such attacks may be precipitated by bacterial infection, or infection may supervene later. A clinical picture which is not uncommon at the Follow-up Clinic is that of the smiling, afebrile, acyanotic child, with a good appetite, who nevertheless has

noisy breathing and indrawing of the lower ribs and interspaces, if not also of the sternum and soft tissues of the root of the neck. This picture is quite different from the child who is ill with acute bronchitis. This condition seems to subside during the first year of life and radiographic examination is seldom indicated. There are no informative reports based on autopsy studies.

Two papers have appeared, in 1960 (Wilson and Mikity) and 1963 (Baghdassarian, Avery and Neuhauser), describing a pulmonary disease of small "premature" infants characterized clinically by increasing dyspnoea, with the possibility of death in a few hours from cor pulmonale, or recovery in six to eight months time. Radiographic examination shows diffuse involvement of the lungs, with coarsely nodular or reticularly-streaked infiltrates, sometimes with a cystic appearance. Biopsy on two of Wilson's cases showed thickening of the interstitial septa like fibrosis. Thus there seems to exist yet a third pulmonary syndrome of "premature" infants but its relationship to the others is not known.

Jaundice is a feature of the low birth-weight baby and particularly of the immature low birth-weight baby. Its incidence in the present series was 20 per cent.. Its development was significantly related to respiratory abnormality at birth and in the first four hours of life, to oedema, hypotonia and cyanosis. In such infants the bilirubin level reaches a maximum later than in mature infants, (Hsia, Allen, Diamond and Gellis, 1953; Meyer, 1956) often about the sixth day, and the level is higher. Billing, Cole and Lathe (1954) state that the

serum level is often over 12 mg. per 100 ml., and Barton, Wilson and Wacker (1962) found levels of over 15 mg. per 100 ml. in infants of less than 35 weeks maturity, and over 20 mg. per 100 ml. in 2 per cent. of all infants weighing 2500 g. or less at birth. Similarly Grewar, Medovy and Wylie (1962) seldom found levels of over 20 mg. per 100 ml. in non-erythroblastic premature infants. The highest levels are found in infants of the lowest birth weights (Rapmund, Bowman and Harris, 1960), but this is probably only a reflection of their greater immaturity. The small mature baby is much less likely to suffer from jaundice than is the small immature baby, as is seen in Part III of the present study. Several contributory factors may raise the level. The danger of hyperbilirubinaemia in the neonate lies in the possibility of the development of kernicterus with subsequent frank mental retardation, choreoathetosis or "minimal cerebral damage". It may be the cause of deafness in children who were of low birth weight (Fisch and Norman, 1961) but Barton, Court and Walker (1962) found a retrospective history of severe neonatal jaundice in only 18 per cent. of severely deaf children.

The level of bilirubinaemia necessary to produce kernicterus is variable and indeterminate. In vitro 20 mg. per cent. is cytotoxic, but in vivo levels considerably below 20 mg. per 100 ml. have sometimes resulted in kernicterus and levels above 20 mg. per 100 ml. have sometimes been innocuous (Odell, 1959). The development of kernicterus is dependent on the transfer of unconjugated bilirubin from the blood into the cells of the brain, notably those of the corpus subthalamicum, hippocampus, striate bodies, thalamus, inferior olives, cerebellar nuclei and

cranial nerve nuclei. Selective deposition of bilirubin may depend on attainment of a specific state of maturation of neuronal enzyme systems. On the other hand non-pigmented areas may also be damaged (Nelson, 1964). Several factors are now known to influence this transfer of unconjugated bilirubin. The first of these, and the most potent so far as this study is concerned, is immaturity. This implies low plasma albumen concentration and probably also immaturity of enzyme systems or of other cellular metabolites by which mature brain cells are able to resist a certain amount of assault. Cyanosis and anoxia have been shown experimentally to increase the risk of kernicterus (Govan and Scott, 1953; Brown and Zuelzer, 1957). Anoxia may be anaemic as in haemolytic disease of the newborn or primarily anoxic as a result of insufficient pulmonary aeration. Metabolic and respiratory acidosis and hypoglycaemia also assist the passage of unconjugated bilirubin into the brain cells (Brown, 1962). These factors indicate why it is impossible to lay down any one level of serum bilirubin as being invariably safe or dangerous.

Even without these variables relating to the movement of unconjugated bilirubin into cells numerous factors influence the amount of unconjugated bilirubin which is available for transfer in the first place. These factors act by three different mechanisms. Firstly, there may be depression or deficiency of the enzyme glucuronyl transferase; secondly, there may be increased haemolysis producing a large bilirubin load for the amount of glucuronyl transferase available; thirdly, there may be competition for albumen, which is essential for conjugation, or active dissociation of bilirubin from albumen.

The enzyme glucuronyl transferase is deficient in the immature liver. It is also depressed by anoxia, hypothermia and hypoglycaemia, to all of which the immature baby is prone. In addition deprivation of fluid, resulting in under-perfusion of the liver, and deprivation of calories, as was practiced until recently in low birth-weight babies, also contribute to the liver's difficlty in producing adequate enzyme. The administration of some drugs may reduce enzyme production (e.g. novobiocin), through hepatic toxicity. The following drugs are also thought to depress enzyme production through hepatic toxicity, mainly due to individual idiosyncrasy:- all the phenothiazines, especially chlorpromazine, sulphonamides, tetracyclines, para-aminosalicylate and erythromycin estolate (Sherlock, 1968). In 1963 Iossifides, Smith and Keitel showed that chloromycetin did not interfere directly with bilirubin metabolism. It is known however to interfere with cellular oxygenation.

Increased haemolysis occurs in immature infants particularly as a result of bruising. Their susceptibility to extensive echymoses is well known. These add considerably to the circulating unconjugated bilirubin load. Any collection of blood in a neonate is liable to produce hyperbilirubinaemia with the exception of haemorrhage in the peritoneum, from where red cells are absorbed intact by the lymphatic system. As these bruises may not be due to hypoprothrombinaemia there would be no indication for the administration of vitamin K. Nevertheless Bound and Telfer (1956) tested out the effect of large and small doses of Synkavit with a view to preventing bleeding, "partly due to

hypothrombinaemia". Further it is now thought that some of the cerebral damage shown by immature infants is the result of slow oozing of blood into the brain substance and ventricles, and thus there might still be a case for the administration of some form of vitamin K.

Increased haemolysis may also be the result of administration of certain drugs to the mother or to the newborn infant. Synthetic vitamin K (Synkavit or tetra-sodium 2 - methyl naphthalene - 1 : 4 diol phosphate) is the best example of this. Its association with increased haemolysis was first noted in 1955 by Allison, working with rats. Bound and Telfer noted hyperbilirubinaemia in their group of babies who were given large doses (30 mg.) of this preparation. Corner, Berry and Neale (1960) reported a 2.6 per cent. incidence of kernicterus where Synkavit was in use, compared with an incidence of only 0.6 per cent. in Boston Lying-in Hospital where it was not used. Thewater-soluble preparation Vikastab (menaphthone dipotassium sulphate) was considered much safer. Hill, Kennell and Barnes (1961) noted serum bilirubin levels of over 12 mg. per 100 ml. in infants given Synkavit. In 1962 Wilson reported an increase in the number of exchange transfusions required for the infants of mothers who were being given 70 mg. or more of Hykonine (Menadione Sodium Disulfite) parentally just before delivery. She says these preparations cause haemolysis

> "in a manner very similar to that seen in individuals whose red blood cells are genetically susceptible to haemolysis by fava beans and certain drugs".

Haemolysis with Synkavit was shown to occur especially in rats deficient

in vitamin E (Allison, 1955) and in immature infants it is known that there is a deficiency of this vitamin. The red cells in such susceptible individuals may be defective in certain enzymes. An example of this is the enzyme glucose - 6 -- phosphate dehydrogenase which maintains the glutathione present in red cells in a reduced state. Reduced glutathione in turn protects the haemoglobin from the toxic effects of various drugs. Nitrofurantoin causes haemolysis in the newborn of mothers to whom it has been administered, if they have this individual or racial susceptibility.

Finally hyperbilirubinaemia may result from abnormalities of metabolism involving albumen. Conjugation of indirect bilirubin with albumen is an essential step before that of conjugation by glucuronyl transferase to form direct bilirubin. The albumen deficiency of immaturity is worsened by some drugs, administered either to the mother or the infant, whose de-toxification in the liver requires albumen binding, thus reducing the amount available for bilirubin binding. Some of these drugs produce dissociation of bilirubin from albumen. The long-acting sulphonamides are particularly contra-indicated for this reason in the mother and in the neonate. Sulphamethoxypyridazine (kynex) and Sulphadimethoxine (madribon and midicel) are notable examples, having been found in the neonate as long as four or five days after birth following administration to the mother prior to delivery (Brown, 1962; Wilson, 1963; Diamond, 1966). Sulphasoxazole (gantrisin) is also implicated, as are salicylates and phenacetin (Sherlock, 1968).

Sepsis in the newborn leads to jaundice due to accumulations of both conjugated and unconjugated bilirubin, the result of primary hepato-

cellular damage (Brown, 1962). In particular coliform sepsis is liable to do this, and the infection is very frequently pyelonephritis (Bernstein and Brown, 1962).

In the present series of low birth-weight infants none who were seen during the first year of life showed evidence of kernicterus, and in the statistical analysis there was no evidence of mental retardation in relation to neonatal jaundice. It seems that by careful management those factors which produce additional jaundice in the immature infant are being kept to a minimum. This matter requires constant survey.

The basic requirement for the reduction in the incidence of hyperbilirubinaemia is a reduction in the incidence of immature babies and all the complications which immaturity entails.

The immature baby should as far as possible be protected from birth trauma. A forceps delivery might reduce the amount of bruising of the scalp, and care in manipulation of legs, arms or buttocks might reduce haemorrhage in breech deliveries, which are not uncommon in immature infants. Prolonged apnoea should be avoided as far as possible by having present in the labour room a person skilled in resuscitation, to take care of the baby alone. Oxygen and warmth should be provided, and respiratory distress treated early and energetically. Fluid and calorie intake should be started early. This is most effective by intravenous administration. Damage to the portal system is avoided by using a superficial vein and not the umbilical vein. Drugs should be

used only on individual merits, and their administration not established as routine practice. In particular large doses of synthetic vitamin K, and sulphonamides are to be avoided. If vitamin K is given it usually suffices to use a dose of 1 mg. once (Denton, 1961), or even 0.5 mg. once, intramuscularly, to a small baby as is the practice in the Stobhill Unit.

An awareness of the possibility of infection, especially of the urinary tract, should always be maintained and the necessary investigations made. It is the usual practice in neonates, particularly those of low birth weight, to start treatment with a broad-spectrum antibiotic whilst awaiting the results of investigations. In this case it is obviously advantageous to know what the organism is likely to be. This can only be done by keeping a continual watch on the bacterial flora of the nursery and other babies, so that one may in this way have a very good idea as to the identity of the causative organism. Maternal infections should also receive consideration here.

It is recommended that a 12 - hourly watch be kept on the bilirubin level. If there is rapid increase or a level approaching 20 mg. per 100 ml. exchange transfusion is indicated. Van Praagh (1961) states that the situation of the lethargic, hypotonic baby, who wont suck and has no Moro reflex is not a "warning sign" but an "emergency situation", and that by the time irritability and stiffness appear there is already brain damage. Thus if the clinical condition of the baby indicated it, exchange transfusion would be carried out a considerably lower level of serum bilirubin than 20 mg. per 100 ml. Diamond (1966) confirms the

recommendation for the use of intravenous albumen in these babies (Dunn, 1961; Odell, Cohen and Gordes, 1962) with or without exchange transfusion. One gram of albumen per Kg. of birth weight, one hour before transfusion increases the bilirubin mass removed by 41 per cent. per Kg. of birth weight (Odell, Cohen and Gordes, 1962). This is not yet a standard practice but seems well worth a trial. Further, since oedema at under four hours of age is shown in this study to be significantly related to the development of jaundice in the later neonatal period, one is tempted to suggest the trial administration of albumen in the presence of oedema, and before jaundice has developed.

Sepsis was no more common in this series of low birth-weight babies than in the normal-weight babies. This is not the usual finding. The explanation seems quite clear in that in the Stobhill Maternity Unit the Nursery conditions as regards space and personnel could scarcely be bettered, whereas the maternity wards are less spacious and the mothers themselves often have infections. In addition there is continual movement of medical, nursing and domestic staff, and in particular visitors in the wards, all of which is reduced to an absolute minimum in the Premature Nursery.

Infant Characteristics - Physical Development

The post-natal increase in weight in those infants with the severest degrees of intrauterine growth retardation was probably the most striking feature of physical development. Well over one half of those infants who were under 75 per cent. of their expected weight at birth reached over 100 per cent. during the first year of life. Rather fewer babies with milder degrees of retardation reached normal weight during this time. It is possible that in some cases retardation is due not merely to deprivation in utero but to active depression of growth and that on release from this environment extremely active growth occurs. It is interesting also to note the speed with which this compensation took place. The adjustment was made in the majority by the 27th week of life, and this occurred relatively more rapidly in those infants with severe under-growth than in those who were more mildly affected. In no other sphere of development does the low birth-weight baby compensate with such speed. Further, it is on this characteristic that the later development of anaemia is to a large part dependent. This was evident in the present study.

Nevertheless despite this initial feature of rapid weight gain the tendency of premature infants to remain small in stature and in weight is well-known (Drillien, 1961; McLauchlan, 1963; Lubchenco, Horner, Reed, Hix, Metcalf, Cohig, Elliott and Bourg, 1963).

In the present study 14 of 85 low birth-weight babies showed anaemia (haemoglobin level of less than 80 per cent. (Sahli)) during

the first year of life. It has been noted in the results that four of these infants were of over 37 weeks gestation and two were of 32 to 37 weeks gestation, whilst eight were grossly immature.

A broad pattern emerged. Three of the infants born near term were only 42 per cent., 60 per cent. and 63 per cent. of their expected weight at birth for the duration of gestation, but by the 27th week of life, when anaemia was diagnosed, had gained weight rapidly to 97 per cent., 103 per cent. and 99 per cent. of their expected weights respectively. It seems reasonable to suppose that the body-tissue and blood requirements of iron accompanying this degree of growth had resulted in a sparse spreading of iron stores. Further it would seem likely that in a mature low birth-weight baby all placental activities are restricted to some degree and that iron transfer from the mother to the foetus is proportionately reduced. It is unlikely that a low birth-weight baby is bestowed with more iron per unit of weight than is the normal infant. In addition the small baby is increasing in weight not from 3.2 Kg. at birth to 7.4 Kg. at 28 weeks (0.6 Kg. per four weeks) but from some much lower weight, so that iron stores are unable to meet this expansion and one could reasonably expect an anaemic infant.

The eight grossly immature infants, all of under 32 weeks gestation, not only had this extra increase in weight to cope with, but had also a poor endowment of iron from their mothers, since by far the largest amount of iron is passed to the foetus in the later weeks of pregnancy. Widdowson and Spray (1951) have shown that a total amount of only 8 mg. of iron is demanded by the foetus in the first and second

trimesters, but in the third trimester 4.0 mg. per day are normally being transferred. Thus it is seen that the baby born in the early part of the third trimester is likely to be poorly endowed with iron from its mother.

In some of these babies there was evidence of infection and one infant (Case No. 92) demonstrated this well. She was born at 36½ weeks gestation and weighed 94 per cent. of her expected weight. She suffered a severe attack of gastroenteritis at 12 weeks of age followed by otitis media, and when seen at the clinic at 33 weeks of age was only 86 per cent. of her expected weight, with a haemoglobin value of 55 per cent.

Various studies confirm the reasons for these findings. Firstly it has been shown to be the case that throughout gestation the concentration of iron per unit of foetal weight is constant (Iob and Swanson, 1938; Widdowson and Spray, 1951). The transfer of iron requires the presence of the enzyme transferrin (aβ1- globulin) to carry the iron to the placenta, where placental ferritin is formed. Smith, Schulman and Morganthau (1952) have found high levels of transferrin in maternal blood compared with foetal blood, and high iron levels in cord blood compared with maternal blood. The placenta obviously plays an active part in iron transfer from mother to the foetus, and it would seem reasonable to suppose that where there is other evidence of placental dysfunction iron transfer is also reduced.

It is known that growth excites an increased demand for iron. This is seen with the greatly increased foetal growth of the third trimester as found by Widdowson and Spray. Gorten, Hepner and Workman

(1963) state that "this striking relation between iron absorption and growth continues from conception to maturity". It seems certain that growth stimulates the demand for iron, and not that iron produces better growth. Farquhar (1963) found no improvement in the heights, weights or general well-being of children on supplementary iron, although the haemoglobin levels were raised.

There is still doubt as to the side-benefits of raising haemoglobin values in infants. In 1960 James and Combes found that the prevention of iron-deficiency anaemia did not reduce the high incidence of common infections (respiratory and diarrhoeal), whereas in 1966 Andelman and Sered found that supplementary iron did reduce the incidence of respiratory in term infants.

At this stage it is of interest to note the estimations of Schulz and Smith (1958) regarding the iron requirement of a normal full-term infant in the first six months of life, and then to compare it with that of a small mature baby and a small immature baby. I have used the figures rather freely and have modified them to suit an infant of 3.2 Kg. at birth increasing by 0.6 Kg. every four weeks, to 7.4 Kg. at 28 weeks. For the small mature baby I have taken an extreme example of 1500 g. increasing to 7.4 Kg. at 28 weeks, figures not outwith those seen in the present study nevertheless, and for the immature baby 1500 g. at the beginning of the third trimester. Schulz and Smith state that the amount of iron needed can vary as much as 300 per cent., depending largely on the foetal body iron and on the rate of growth. These figures serve to indicate that the immature baby and stunted baby are in great need of

iron relative to the full-term, fully-grown baby.

1. Iron Requirements of the Normal, Full-Term Infant

Birth weight = 3.2 Kg.

Blood volume (85 ml./Kg.) = 273 ml.

	Mg.
Iron in blood (3.4 mg./g. haemoglobin) (Haemoglobin value 17 g./100 ml.)	= 158
Iron in tissues (6 mg./Kg.)	= 20
Iron store	= 35
Total Body Iron	= 211

At 28 Weeks

Weight = 7.4 Kg.

Blood volume (85 ml./Kg.) = 629 ml.

	Mg.	
Iron in blood	= 363	
Iron in tissue	= 44	
Iron store	= 35	(or more)
Total Body Iron	= 442	

Therefore extra iron required in 28 weeks

= 442 - 211

= 231 mg.

2. Iron Requirement of the Small, Mature Infant

Birth weight = 1.5 Kg.

Blood volume (85 ml./Kg. maximum) = 127 ml.

Mg.

	Mg.	
Iron in blood	= 73	
Iron in tissues	= 9	
Iron store	= 35	(maximum)
Total Body Iron	= 117	

At 28 Weeks:- as for normal full-term infant

Therefore extra iron required in 28 weeks

= 442 - 117

= 325 mg.

3. Iron Requirement of the Immature Infant

Mg.

Birth weight = 1.5 Kg.

Blood volume (85 ml./Kg. maximum) = 127 ml.

Iron in blood	= 73	
Iron in tissues	= 9	
Iron store (1st and 2nd trimester only) .	= 8	
Total Body Iron	= 90	

At 28 Weeks:- As for normal, full-term infant

Therefore extra iron required in 28 weeks

= 442 - 90

= 352 mg.

These comparisons can leave no doubt as to why the low birth-weight baby develops anaemia. This is supposing that the mother herself has normal amounts of iron with which to supply her infant.

It is now thought that the infants of iron-deficient mothers suffer diminution in transfer. This does not mean that the anaemic mother will have an anaemic infant (i.e. with a low haemoglobin level) but rather that the iron store of such an infant will be insufficient to maintain a normal haemoglobin level throughout the first year of life. Smith, Maletkos, Gibson, Roby, Caton and Reid (1955) state that in normal infants haemoglobin production for the first several months utilizes iron obtained transplacentally and not until three to four months of age can any dietary iron be identified in the blood cells. If the mother has an iron-deficiency anaemia during pregnancy the red cells of the infant are normal at birth, but because of inadequate iron stores iron deficiency generally appears within a few months of birth.

From the previous calculations the iron demand on the mother appears to be between 200 mg. and 300 mg. for the foetus in each pregnancy. There may be no iron loss in the mother, since she is conserving iron through amenorrhoea, or it may be substantial, e.g. 725 mg. (Owen and Glienke, 1962) or 965 mg. (Jacobs, Kilpatrick and Withey, 1965). Pritchard and Mason (1964) have shown that ferrous gluconate, 0.3 g. t.d.s. for four to six months will accumulate 500 mg. of storage iron which is readily available for synthesis. It is well seen from these two considerations that the woman with closely-spaced pregnancies will scarcely avoid becoming anaemic. It is known that the interval

between pregnancies is more closely associated with the development of maternal anaemia than is the number of pregnancies. Thus the infant of high birth order has come to have the reputation of proneness to anaemia, as has the infant of low birth weight, both terms requiring a good deal more definition for accuracy.

The largest part of the neonate's total body iron is contained in the blood, and it is therefore of importance to avoid blood loss at the time of delivery or as a result of careless cord-clamping.

Various considerations come together here in their potential effect on each other. Anaemia in the mother is associated with a number of pregnancies at short interval and with ante-partum haemorrhage. Mothers who are in their fourth or subsequent pregnancy and those with ante-partum haemorrhage have been shown in this study to have a higher perinatal mortality rate and low birth-weight rate than the control group. The low birth-weight babies are additionally handicapped by anaemia, the direct result of anaemia in the mother. Thus from maternal anaemia, which should be preventable, springs a whole range of maternal and infant abnormality.

Two basic abnormalities require attention in the prevention of anaemia in the infant in the first year of life. Firstly anaemia in the mother should be prevented. This can be done before depletion of iron stores becomes manifest through a falling haemoglobin. Jacobs, Kilpatrick and Withey (1965) state that 45 per cent. of women in this

country are in a state of "negative iron balance". There is thus a very good case for the prophylactic routine administration of iron to all women throughout pregnancy. This should probably be continued in the ensuing post-partum months, and it follows from this that a reasonable spacing of pregnancies would be advantageous. The development of anaemia having been averted it seems probable that some premature terminations of pregnancy would also be averted through avoidance of ante-partum haemorrhage. Folic acid deficiency is particularly associated with accidental haemorrhage (Hibbard, 1963) and vitamin C deficiency may be an associated factor in iron-deficiency anaemia of pregnancy. Klein (1962) and Stapp (1963) considered that although an increased incidence of anaemia was found amongst mothers of low birth-weight infants the low weight was not due to anaemia, but rather that both were due to low socio-economic status, lowered levels of general health, poorer nutrition, deliveries closer together, poorer medical care, heavier work loads and a higher incidence of complications of pregnancy.

In the present study an unusual finding was noted, viz. that more mothers of healthy normal-weight babies showed lower levels of haemoglobin than did the mothers of the low birth-weight babies. This may be due to the short gestation period of the majority of the latter babies, the maternal haemoglobin not falling until the third trimester when foetal demands on the maternal iron store are enormously increased. The time of greatest incidence of low haemoglobin levels is usually about the 34th and 35th weeks, a finding which was noted in this study. One third of the low birth-weight babies were born before this time, a

factor which must influence the results. It seems remarkable that this has not been evident in other series.

The question of iron-fortification of bread arises at times in the hope of reducing the prevalence of iron deficiency anaemia. Davidson, Lindsay and Roscoe (1944) and Fullerton, Mair and Unsworth (1944) reported an improvement in pregnancy anaemia from 1934 to 1944 in Aberdeen and Edinburgh, which they attributed to the iron-fortification of national bread. Elwood (1963) however found no improvement in the haemoglobin values of a group of mental patients on iron-fortified bread. It is possible that differences in preparation of the bread, particularly the fine milling of the latter, affected the outcome. On the whole it would seem much better to give iron where iron is needed.

The avoidance of haemorrhage at birth, and thus loss of iron, is of importance. The question of placental transfusion by gravity, and of cord-stripping has already been discussed.

It is agreed that all premature infants require supplementary iron (Potter, 1959; Sisson, Lund, Whalen and Telek, 1959; Schulman, 1959; James and Combes, 1960; Hammond and Murphy, 1960; Ross, 1962). This it will now be understood applies to all low birth-weight infants, whether mature or immature.

The time at which iron therapy should be started appears to be within the first few weeks of life. In the Premature Nursery at Stobhill Hospital iron therapy is now started at the age of three weeks. There is evidence that absorption is very good in the first three months

of life, and that this is stored and is of value in preventing later anaemia. Hammond and Murphy state that exogenous iron is being utilized before natural iron stores are depleted and that if iron is administered early the haemoglobin value will be raised by three months of age. This also prevents the anaemia which is common about the first birthday. Sisson et al. think that erythropoiesis starts between the third and seventh weeks, and that the original iron stores are sufficient for haemoglobin synthesis only up to the 10th week of life. In addition to this Gorten et al. showed that the iron absorption rate is 72 per cent. in the first month of life and falls to 30 per cent. by three months of age; premature infants absorb and utilize iron to a greater degree during the first 10 weeks of life than in later infancy or childhood. It would seem therefore that one cannot start iron therapy too early. These authors stress that

> "growth is associated with an increased demand for iron regardless of the haemoglobin level. Iron is used first for tissues, then for haemoglobin for the expanding blood volume"

and

> "a rate of growth in excess of normal increases the demand".

Thus one would certainly not wait for a falling haemoglobin level before administering iron, but rather start it as soon as the baby is able to deal adequately with milk and is gaining weight. The amount of iron passing through the intestinal mucosa is proportionate to need, and not to the dose (Gorten, Hepner and Workman, 1963).

Ross based the dosage of iron on the following formula:-

$$\text{mg. of iron required} = \frac{12 - \text{Hb. in g.}}{100} \times 80 \times \text{weight in Kg.} \times 314.$$

and added 25 per cent. of the calculated dose for storage. She states that when given on a body-weight basis failure is rare. Broadly her doses are 100 mg. daily up to six months, 200 mg. from six months to one year, 300 mg. from one to two years and proportionately thereafter, divided into 50 or 100 mg. doses. Iron absorption is improved when it is given in small doses such as 15 mg. or 30 mg. doses t.d.s. or q.q.h. It is best given one to two hours before feeding in order to avoid the formation of insoluble iron compounds with milk. This therapy should be continued for at least three or four months.

The form of iron used is variable; Ross recommends ferrous sulphate and Farquhar used ferric pyrophosphate for his full-term infants. Any of the common iron preparations is satisfactory and if one is impotable or causes gastric irritation, diarrhoea or constipation then another can be substituted and will probably be taken successfully, especially if the baby is first started on a small dose, increasing gradually over a few days. Intramuscular preparations might be of value if known to be safe (as iron-dextran was not), particularly in those infants where the oral administration of iron is not ensured. It is also helpful where there is gastroenteritis, in that it short-circuits the need for intestinal absorption.

A multi-vitamin preparation should be supplied, with particular attention to the vitamin C content. Mixed feeding with wheat and oat cereals, finely-ground meat and vegetable purees is encouraged early, especially as many of these mothers are inclined to delay on account of

the small size of the baby.

Folic acid deficiency has been noted in premature infants with non-iron-responsive anaemia (Vanier and Tyas, 1967) and its administration to such infants is not now uncommon, in doses of 2.5 mg. orally, daily. The need for folic acid should be based on the presence of iron-resistant anaemia and megaloblastic morphology in the buffy coat of blood smears. It can be confirmed by blood folate levels and responsiveness to folic acid (Strelling, Blackledge, Goodall and Walker, 1966). These workers gave folic acid by intramuscular injection in doses of 60 g. to 480 g. daily. They found this type of anaemia at the fifth to the 11th week of life, and noted it to be especially common in infants of the lowest birth weight. They concluded that premature infants have a small store of folic acid which rapidly becomes depleted.

It will be seen from Appendix L, which gives particulars of the anaemic babies seen in this study, that many of the variations in causes of iron-deficiency anaemia were seen. Gross immaturity with rapid growth after birth was the commonest finding. Intrauterine growth retardation followed by rapid growth after birth was a notable finding. Severe gastroenteritis and otitis media was associated with a low haemoglobin in another baby. Anaemia due to blood loss at delivery was not seen. When the Premature Baby Follow-up Clinic was started in 1959 there was no routine administration of iron to these babies. This is, however, now the practice, and it would seem not only justifiable but necessary for the welfare of these infants.

The incidence of rickets in these low-weight babies was minimal, as was its severity. Only on serial radiological examination could one appreciate some evidence of its presence.

Gordon (1961) regards rickets in premature infants as being due to low body stores of calcium and phosphorus, rapid growth, faulty absorption of fat-soluble vitamin D and prolonged inexposure to sunlight.

Much higher rates of rickets were found by Follis, Park and Jackson (1952), after the second month of life, but these were based on microscopic findings. It must also be remembered that the babies who attended the Follow-up Clinic at Stobhill Hospital were those of relatively conscientious mothers who were interested in their child's welfare and would be more likely to persevere with supplementary vitamin D than those mothers who did not take the trouble to attend the Clinic. In the latter babies it is quite possible that rickets was a more pronounced feature.

Infant Characteristics - Mental Development

In the past 25 years the survival rate of low birth-weight infants has increased, and this has been accompanied by much work on the assessment of the subsequent progress of such babies. A high incidence of handicap has been found, which is probably related to the ability now to keep the smaller babies alive. The conclusions most generally accepted are that those infants of between 2000g. and 2500 g. at birth are very similar in development to those of normal birth weight (Capon, 1957; Harper, Fischer and Rider, 1959; Grewar, Medovy and Wylie, 1962; Drillien, 1965) although they may fall on the lower side of ratings for those born at term. With decreasing birth weight there is increasing abnormality and varying degrees of mental retardation from gross deficiency and cerebral palsy to minimal cerebral damage in the form of learning and behaviour defects, as described by Knobloch and Pasamanick (1959). In addition there are now recognized two severely damaged groups, usually under 1500 g. in birth weight, one the offspring of relatively infertile, and thus older, mothers and two, the male offspring of mothers with severe complications in pregnancy (pre-eclamptic toxaemia with or without essential hypertension or ante-partum haemorrhage)(Drillien, 1965; 1967). Tarjan (1962) also noted a predominance of males with Intelligence Quotients of less than 70, associated with delay in maturation and impairment of learning and social adjustment.

It is unfortunate that emphasis is laid on birth weight in the majority of studies, as this confuses the issue of aetiology; birth

weight is secondary not only to the duration of gestation, but to all factors acting before and during the course of pregnancy. It thus seems probable that the criterion of birth weight tends to obscure antecedent factors. Its value is mainly one of prognosis. In the present study an attempt has been made to give as much attention to the duration of gestation as to the birth weight. It is unfortunate too that in some studies twin babies have been taken into consideration with singleton babies, as such pregnancies are at an inherent biological disadvantage. It is for this reason that singleton low birth-weight babies only are assessed in this part of my thesis.

Neuropsychiatric abnormality may originate at any point in development. It may be an inherent feature of the ovum or spermatozoon, or of the early conceptus. Subsequently abnormalities of the uterine environment may produce abnormal development potentials. Hazards of labour and delivery may damage the nervous system, as may difficulties in the neonatal period. Finally the environment of the child has a very great influence on the attainment of his full potential.

Developmental tests, depending on maturation of the nervous system, combined with a standard neurological examination, are considered to be adequate measures of future performance (Knobloch and Pasamanick, 1959; Drillien, 1961). Knobloch and Pasamanick (1963) consider that adaptive development in the early months is a particularly good criterion for the prediction of intellectual development. Nevertheless Wright and Tarjan (1963) and Oppenheimer and Kessler (1963) stress that no hurried prognosis should be made on the basis of one examination, having

found that in some cases repeated studies will show increasing deviation from developmental norms, whilst in others, as reported by Illingworth (1961), there may be considerable delay in general maturation during the first years of life with normal attainment at a later date. Oppenheimer and Kessler suggest as further safeguards for accurate prognosis that reports should be made in terms of general range of ability rather than in numerical terms, and that all observations should be recorded and not only those elicited by individual test items. Korsch, Cobb and Ashe (1961) compared the independent assessments made by 88 paediatricians and found a tendency to assess over-optimistically children who were subnormal and to undervalue children who were physically unwell at the time of testing. The greatest accuracy was in assessment of the normal child. Knobloch and Pasamanick (1959) stressed the need for careful search where there was a wide variation of results for one child.

A simple illustration of how developmental tests work was obtained from the present study by evaluating the developmental progress of these low birth-weight babies on the basis of their age from the actual date of birth. The tests defined with accuracy the degrees of immaturity seen in these babies. One had thus evaluated the tests and found them adequate to detect immaturity of development. When correction was made for the chronological immaturity of the babies, as is the usual practice, a number of infants was found to be within normal range, whilst a number still lagged behind. Thus the tests had picked out those infants who showed abnormal immaturity for their chronological age.

These are the infants who are prone to various degrees of neuro-psychiatric upset in future years. Knobloch and Pasamanick (1959) considered that minimal cerebral damage, as manifested by clearly defined deviation from normal neurological and behaviour developmental patterns, was usually compensated by 15 months to 18 months of age, but that signs were still present in the pre-school years if sought. Capon found motor development slow, but usually mastered by three years of age. Nevertheless even after this he found a

> "tendency to 'educational subnormality', impaired power of mental concentration and mental fatigue not expected in the general child population".

Harper et al. re-tested the children examined at 40 weeks by Knobloch and Pasamanick, by then aged five years, and found them to be still inferior. At seven years of age Drillien's group (1963) likewise still showed impairment, with frequent behaviour disturbance in school. Likewise Lubchenco, Horner, Reed, Hix, Metcalf, Cohig, Elliott and Bourg (1963) found 10-year olds of low birth weight to suffer from a high incidence of physical and mental defects, from an excess of emotional upsets, and "school failures" in 30 per cent. with normal intelligence. Finally Douglas (1960 a, b) examined school children at eight years and 11 years of age and found the low birth-weight children to be inferior. He noted however that their response to testing was poorer by 11 years of age than at eight, and concluded from this, and as a result of Health Visitors reports on the home circumstances, that it was in fact the poor environment from which these children came which determined their

retardation. Drillien (1965; 1967) also reported a higher incidence of handicap in low birth-weight babies from poorer homes, but pointed out a tendency for the handicapped male infant to come from an impoverished environment whereas as many normal as handicapped girls came from poor environments.

Some developmental processes are innate and almost reflex when the normal infant is exposed to the standard test conditions. This probably applies best of all to motor development, which can hardly fail to progress provided that the nervous system is intact and the infant is given the opportunity to hold up his head, to lift his head from a pillow, to sit unsupported or to stand. In the other three main fields of development (adaptive, language and personal-social) environment has more effect. Normal adaptive development requires an intact motor system, with the application of judgement, which improves with experience. This explains its importance in the prediction of intellectual potential. Language development is a more independent form of learning than adaptive development, although it must depend ultimately, for articulation, on an intact motor system. Finally personal-social development depends greatly on the environment of the child. Nevertheless the child's reaction to his environment must be largely dependent on his capabilities in the other fields of development.

Barnett (1961) has given an excellent discourse oh the behaviour and needs of infant mammals, which bears particularly on the effect which a poor or good mother or environment could have on the development of a low birth-weight baby. He states that all behaviour tends to maintain,

or to restore, specific bodily states. Highly simplified, the proposition is that all learning depends on the urge to get something that helps to keep the body in a steady state. Four factors at least are bound up with motivation in infancy. There is maintainance of homestasis by the stereotyped acts of sucking, head turning, crying, clinging and following. There are "drives" which build up through deprivation, and may result in later life in either inhibition or excessive practice of the deprived factor. Cutaneous stimulation is important. Handling, or "gentling" has been found in rats to produce better growth, better food utilization and an improvement in intelligence. There is an early sensitive period for handling, being at under 20 days in infant rats, and this has much less effect at 50 days to 70 days. This is an observation parallel to that of McCance (1962 a, b) who found that undernutrition at an early stage had a permanent retarding effect on growth. The time of greatest effect for both types of deprivation was early.

Barnett reports that stress is also required in the fulfilment of normal development and here those animals which had been handled suffered less adverse effect under stressful conditions and accommodated more quickly to these conditions than did the animals who had received no cutaneous stimulation. This finding is probably parallel to that of Knobloch and Pasamanick (1959) who reported that children with neurological damage were "afraid of strange things and situations". This characteristic was evident in four infants of this series where examination almost failed on this account. Whether it is due in low

birth-weight infants to lack of maternal interest, or to the inability of the low birth-weight infant, through immaturity, to interpret these external approaches, is not clear. It is quite probable that both influences are at work. Barnett found that steroid output in both handled and deprived animals was the same but that under stress the output in the handled animals was higher and developed earlier in life. Whilst cutaneous stimulation is a "need" of infant mammals it is not an essential for survival.

A later stage is reached when the animal derives stimulation for development by exploration. One would judge that this phase starts in the human infant when he inspects his own hands, and his dress and feet. As motor development progresses he is able to sit and this increases his range for exploration. This early stage Barnett calls "learning to learn". It is at first slow and inefficient, but forms a necessary stage in

> "organizing the great mass of connecting neurons in the forebrain, so that, later on, rapid responses and rapid learning can take place".

Bowlby (1958) considers that a single mother-figure not only provides this cutaneous stimulation, but also reduces "drives", resulting in the introduction of "substitute behaviour". Thus we see that progress is being made through tactile association, preferably with one person, and that behaviour is already being influenced by that person at a very early stage. As the infant's horizon increases he is more and more influenced by his environment, but only to the extent to which he is inherently capable of response.

Barnett differentiates between the "needs" of infant mammals, which he defines as the requirements for optimum performance, and the "essentials", such as food, which are requirements only for survival. These "needs" are agencies which improve intelligence, socialize the animal and induce resistance to stresses. It is of interest that Patton and Gardner (1962) have found that even with a good appetite and adequate supply of food some children can show gross failure to thrive, including delay in ossification, as a result of "maternal deprivation".

On the above basis the early facets of developmental progress in low birth-weight babies becomes more comprehensible. If in addition to deficiency of these early environmental needs there is immaturity, preconceptual or intrauterine subnormality or obstetrical hazard the outlook for these infants is poor indeed.

It is well-known that low birth-weight babies tend to be born to mothers of poor medico-socio-economic status. They are thus handicapped not only by their low birth weight but by their environment. Zellweger (1963) states that one-fifth to two-fifths of all cases of mental retardation are due to polygenic inheritance and difficult to distinguish from those due to poor socio-economic environment and cultural deprivation. It seems probable that the two overlap to a considerable extent. Barker (1966) states that low intelligence of unknown cause (but where the Intelligence Quotient is over 50) is usually related to genetic endowment and an environment "unfavourable for intellectual development". Tarjan found Intelligence Quotients of under 70 especially "in the economically and culturally deprived"

and thought that "lack of intellectual stimulation and the opportunities for exploration in early childhood might be the most important causative factors". Baird (1959) also considered that obstetrical hazards play a small part in causing physical and mental handicap compared to genetic and environmental factors. Douglas took the view that poor home background was the reason for the lack of intelligence in the 11-year olds who had been of low birth weight, blaming "lack of parental care, and low educational aspirations".

It is thus unfortunate, but a part of the complex social causes of prematurity that low birth weight is a characteristic of the type of environment which produces little intellectual stimulation. The atmosphere for a developing child may be only a little better than that of an institution, the effect of which Gesell and Amatruda describe very well (1960). There seems to be no doubt that intellectual stimulation through example or competition is essential for the individual to develop to his full potential. Barnett showed that when "bright rats" were mixed with "dull" rats, the dull rats improved in intelligence and the "bright" rats did not deteriorate. Likewise it has been shown in schoolchildren that by mixing the bright with the not-so-bright, the latter improve, whilst the former are not affected by the association.

Thus it is evident that environment has an overwhelming influence on development and that this influence is effective from a very early age. In addition, however, "low birth weight, prenatal conditions likely to cause foetal hypoxia and potentially traumatic methods of delivery may lower the resistance level (of the nervous system) to environmental

stress" (Drillien, 1963). This would be consistent with Barnett's observations on the effect of stress on his "handled" and "deprived" animals. The immature or damaged baby may either not receive or not translate properly the approaches of his mother or the influences of his environment.

Such is the general situation regarding the neuropsychological development of young mammals. From the more specific point of view of this study it has already been said that motor development seems to be the most truly reflex type of development, and is probably the field on whose normal development other types of behaviour are most dependent for their normal progress. In the present study there were more infants with retardation in the motor field than in the other three fields, viz. 28 of 83 (33.7 per cent.) compared with 18 per cent. showing adaptive abnormality, 12 per cent. showing retardation in language development and 8.3 per cent. showing slowness in personal-social development. Capon also noted slowness in the learning of motor control. The reason for this is not plain. The extreme is cerebral palsy, which is a well-known accompaniment of low birth weight. In this series only one baby suffered from cerebral palsy, despite the fact that one third of all the infants showed some retardation in motor development during the first year. Knobloch and Pasamanick (1959) state that developmental tests define the degree of clumsiness which may be normal or may represent motor retardation and cerebral palsy. The child seen in this study with cerebral palsy suggested by her appearance an inherent or genetic defect rather than damage through immaturity. She was born at 31½ weeks

gestation weighing 1614 g. (108 per cent. of expected weight), and suffered from severe cyanotic attacks during the first 36 hours of life. Motor development was obviously retarded by the age of 20 weeks, and adaptive development less obviously retarded. Language and personal-social development were within normal limits. Her appearance was rather odd with prominent ears, a small face and pointed chin. Drillien, Ingram and Russell (1962) noted a difference between normal birth-weight and low birth-weight children with cerebral palsy. The normal birth-weight cases were the result of abnormalities of labour and delivery whereas the low birth-weight cases were the result of multiple factors, largely prenatal. Polani (1958) found low birth-weight babies with cerebral palsy to be characterized by relatively good intelligence, freedom from seizures, symmetrical neurological signs and spastic paraplegia, all atypical of the diffuse brain damage of anoxia. Likewise Berenberg and Ong (1964) found infrequent mental retardation, uninvolved speech, but a particularly frequent involvement of both legs in cerebral palsied children who had been of low birth weight. These two descriptions apply very well to the child of the present study.

The frequency with which motor retardation was found in the present group of low birth-weight babies can be explained in several ways. It seems probable that the development of motor ability is the least dependent of the four fields on environment. The normal child cannot help but make progress unless he is forcibly restrained from so doing. It is the most reflex or innate of the developmental fields. It is therefore the one which can be least well compensated for if it is

defective. Or it may be that motor development is comparatively well advanced in utero by full term. Immaturity will interfere with this development either so early and severely that it will never attain a normal state, or rather later in pregnancy when normal potentials are there, and although slow to develop, eventually catch up with the norm. Thirdly, one wonders if the tests used for motor development are more sensitive or more easily observed by the relatively inexperienced examiner than are the tests in other fields. On the whole this is not felt to be the case as all the tests are so well and naturally performed by the obviously normal child. They have been so selected that they encompass the range of the infant's natural reactions and are performed with swiftness and enthusiasm when the ability is there.

In the children studied here retardation in motor development was found to be related to immaturity but not necessarily to the lowest birth weights. Maternal illness showed a high incidence in these infants but no specific illness was involved. Similarly neonatal abnormality at under and over four hours of age had no bearing on subsequent motor development. These findings suggest that immaturity was the main cause of motor retardation and therefore that maternal influences are of primary importance.

Adaptive retardation was next considered. It will be remembered that this represents motor ability modified by judgement and therefore depends to a considerable extent on satisfactory motor progress. It was found to be affected by short gestation, but not necessarily by very low birth weight. There was again an increased incidence of

maternal illness, but no specific illness was involved. This form of retardation therefore also depends on a variety of maternal illnesses which singly or together result in early termination of pregnancy. Retardation of adaptive development was also associated with a high incidence of abnormality at under four hours of age but not by any one specific abnormality. After the first four hours cyanotic attacks were damaging in this field. The latter finding indicates that some adverse factor was still present in these infants after they had recovered from the experience of birth. These infants may have been already damaged in utero, the cyanotic attacks simply representing a continuing manifestation of the damage, which at a later date appeared as retardation of adaptive development. Alternatively the damage may be the result of neonatal hypoglycaemia. A third explanation is that sudden periods of hypoxia after establishment of normal extra-uterine cellular metabolism may bring about neurological damage. Hypoxia at this time may be of more importance than that occurring immediately after birth in the apnoeic infant, where no changeover to extra-uterine conditions has taken place. It may be possible by continuous positive-pressure respiration and by attention to hypoglycaemia to prevent such attacks. McDonald (1963) reported that cyanotic attacks were present in the neonatal period in a significant number of children with cerebral palsy; these children had been of very low birth weight (less than 1800 g.) and short gestation. In Part IV of this thesis concerning twin pregnancy, it is shown that the second twin suffers most from the process of labour and delivery, but is almost recovered by the end of four hours. Transferring this finding back to

these low birth-weight babies it would seem that these cyanotic attacks, occurring after four hours of age represent not a birth difficulty but either an inherent, perhaps genetic, abnormality in the foetus, or a manifestation of gross immaturity. Retardation in adaptive development therefore appears to be due not only to immaturity but also to inherent defect in the foetus.

Language development was remarkably free from the effects of pregnancy, delivery and the neonatal period. This is also the finding of Knobloch and Pasamanick (1959) and Berenberg and Ong. It is an ability which is highly dependent on environment. This was well seen in the infant whose mother was a deaf mute. One would expect language retardation also in those infants of low birth-weight who are deaf (Fisch and Norman, 1961; Barton, Court and Walker, 1962) but the present group of infants did not show this, possibly because they were under one year of age and it is usually only at a later date that such hearing defects are identified. One would also expect to find language retardation in conjunction with gross general mental retardation but such a combination did not occur in this group of infants.

Personal-social development is considered to be the type of development which is most dependent on environment. Nevertheless the infant can only use his environment to the extent of his own mental readiness. In the present study the great majority of mothers came from the ordinary working class population of Glasgow, with few exceptions of very good or very bad homes. Little can therefore be said of this comparative aspect. Presumably however the influence is already

at work in the first year of life although the results are not clearly apparent until several years have passed. Immaturity was related to retardation in this field. Very low birth weight was not particularly related, but a high incidence of maternal illness, of no specific type, was found. The findings of immaturity and a high incidence of maternal illness associated with retardation in personal-social development are now regarded by some workers (Drillien, 1965, 1967; Douglas, 1960 b) as being inter-related through environment. This type of retardation was not associated with neonatal illness at under or over four hours of age, either in incidence or type, that is, it was independent of birth effects, and of inherent defects in the foetus.

It may be concluded that multiple pre-natal factors, resulting in immaturity in many instances, and post-natal factors are the main influences associated with retardation, and that the fundamental adversities responsible for pre-natal factors are those adversities to which the low birth-weight baby is exposed in the post-natal period when he returns to his own milieu.

Seven infants in all showed retardation in more than two fields of development. This does not include the infant with cerebral palsy, whose language and personal-social attainments were within normal range. This is a small number from which to draw conclusions but the results are fairly clear cut. Five of these retarded infants were grossly immature; the sixth was born at 35 weeks gestation after an ante-partum haemorrhage, and the last was born at 40 weeks gestation, her mother

having suffered a clinical attack of rubella at the 16th week of gestation. Immaturity thus made the biggest contribution to retardation in these low birth-weight babies. Birth weights were not all very low and neither the type nor the incidence of maternal illness showed any difference in these infants from those infants who tested normally in the four fields of development; nor was there any excess of early or late neonatal illness, nor any specific neonatal illness associated with these babies.

One must conclude therefore that immaturity from various causes was the most frequent factor associated with general retardation in this group of infants, and that, excluding immaturity, specific lesions such as ante-partum haemorrhage, which can ex sanguinate and shock the foetus, or rubella, should be expected.

In the present series the rate of intrauterine growth, as measured by the percentage of expected weight which had been attained for the period of gestation, had no influence on any of the four fields of development, nor on general developmental retardation in these infants. This was also the finding of Drillien (1967). Nevertheless one feels that there must be exceptions to this, dependent on the cause of slow growth. If it results from poor uterine environment then it is possible that, being born alive, the infant may be unscathed, but if the slow growth results from a defect in the foetus itself then it seems probable that post-natal development, physical and mental, will be sub-normal. In the series of Wallace and Mickie (1966) it is possible that

the defective foetus was the cause and not the result of the low oestriol production. It is evident that there is much to be learnt from the study of intrauterine growth retardation.

Finally a summary was made of the state of these low-weight babies by the end of the first year. It is not very encouraging. Only one third of their number had suffered no physical illness or mental retardation. Those who made the best progress were between 37 and 40 weeks maturity and in the highest weight group (2001 g. to 2500 g.). At under 32 weeks gestation and under 1500 g. the outlook is poor indeed. Thus it is seen that the main aim must be the prevention of immaturity, and it follows from this that prenatal paediatrics is a subject of the utmost importance.

SUMMARY

1. The incidence of singleton low birth-weight babies in the Stobhill Maternity Unit, from January 1959 to May 1960, was 302 of 3,093 deliveries (9.8 per cent.). One hundred of these low birth-weight babies died perinatally, 51 being stillborn and 49 dying in the first month of life.

2. The mothers tended to be over 30 years of age, to be in their fourth or subsequent pregnancy, to have a history of a previous low birth-weight baby and to suffer from more than two illnesses in their current pregnancy. Ante-partum haemorrhage, pre-eclamptic toxaemia and a group of diverse illnesses causing fairly severe constitutional upset were associated with the birth of these low-weight babies.

3. The mothers were more often in hospital prior to the onset of labour than were the mothers of normal-weight babies, on account of illness associated with pregnancy. Breech deliveries were more frequent, and the amniotic membranes ruptured for a longer interval of time prior to delivery than in the control group of babies. Breech delivery is regarded as a natural concomitant of immaturity. Delay in the onset of labour following membrane rupture may be due to subnormal uterine distension through low birth weight.

4. These babies were characterized by a high incidence of congenital defect at birth (12.6 per cent. total; 7.6 per cent. lethal).

Further defects found at follow-up examination brought the total incidence to 22.8 per cent.

5. At under four hours of age the most common characteristics of these babies were apnoea at birth, subnormal lung aeration, oedema, hypotonia and cyanosis.

6. At over four hours of age these low-weight babies were characterized by respiratory distress, cyanotic attacks, collapse and jaundice. It is suggested that the respiratory distress syndrome results from hypo-perfusion of the foetal lungs during labour and at the moment of delivery, and that immaturity, both structural and physiological, plays a large part in its effect. The difficulty may be aggravated by obstruction to air intake immediately following delivery.

7. Low birth weight occasioned considerable delay in discharge from hospital. In 20 per cent. of babies hospital care was required for over five weeks.

8. In the first year of life rapid weight gain was seen, especially in the babies showing the severest degree of intrauterine growth retardation. Normal weights were often reached by the 27th week of life. Nevertheless one third of babies remained consistently under-weight during the first year of life.

9. Anaemia was found in 16.5 per cent. of the 85 babies seen at the Follow-up Clinic. It was frequently associated with a gestation

period of under 32 weeks and was also seen with rapid post-natal growth and infection. In four infants the haemoglobin level remained subnormal despite the administration of iron.

10. An over-all increase of infection was not seen in this group of low-weight babies. There was however an increased incidence of bronchitis, and this was associated with immaturity, delay in the onset of respiration at birth, and to respiratory distress.

11. The incidence and severity of rickets in these babies who were seen at the Clinic was minimal and detectable only on serial radiological examination.

12. Mental development was most often retarded in the motor field in the first year of life; 28 of 83 infants (33.7 per cent.) were involved. The next highest incidence of retardation was in the adaptive field (18.0 per cent.), followed by field of language development (12.0 per cent.) and of personal-social development (8.3 per cent.).

13. Seven of 85 infants showed retardation in more than two fields of development. In addition one suffered from cerebral palsy.

14. Other features thought to be associated with low birth weight were convulsions, screaming and lack of concentration.

15. Over-all only one third of these 302 low birth-weight babies were considered to be within normal limits during the first year of life. One third suffered from one or more of the physical or mental

disabilities already mentioned, and one third died perinatally. (Figure 23).

16. No normal infants were derived from mothers delivered before 32 weeks gestation. Between 37 and 40 weeks 51 per cent. of low birth-weight babies were within normal limits in the first year of life, the highest rate seen at any period.

17. At birth weights of 1500 g. and less no normal infants were seen. At 2001 g. to 2500 g. 55.1 per cent. of infants were within normal physical and mental limits during the first year of life.

18. A study was made of the inter-relationships of maternal, neonatal and infant characteristics. The following points emerged:-

    a) Respiratory abnormality at birth and under four hours of age, and oedema were significantly related to immaturity but not to birth weight, nor to the total incidence of maternal illness nor to any specific illness.

    b) There was an inter-relationship between the four main clinical abnormalities occurring at under four hours of age (respiratory, oedema, hypotonia, cyanosis) and those occurring at over four hours of age (respiratory distress, cyanotic attacks, collapse, jaundice). This is due in part to the over-lapping of these signs, to the common denominator of immaturity and also to specific relationships such as that of hypoxia to glucuronyl transferase depression resulting in jaundice. It is questioned if the early administration of albumen to oedematous babies

might reduce later jaundice.

c) Retardation in motor development was associated with immaturity and with a high incidence of maternal illness.

Retardation in adaptive development was related to immaturity, to a high incidence of maternal illness, and to a high incidence of neonatal abnormality at under and over four hours of age. Cyanotic attacks after four hours of age were specifically related to retardation in adaptive development. Continuous positive-pressure respiration might tide these babies over this difficulty.

Language development was free from all the influences considered. It was noted to be related to environment where there was retardation in the infant of a deaf and dumb mother.

Personal-social development showed most evidence of the effect of immaturity, but no other marked influence was found on this field of development.

d) In seven generally-retarded infants immaturity was present in five (with a gestation period of less than 32 weeks) and the specific lesions of ante-partum haemorrhage at 35 weeks gestation, and maternal rubella were regarded as causative in the remaining two infants. No other particular maternal illnesses or neonatal abnormalities were significantly related to this group of infants and no pattern of birth-weight was seen.

e) There was no evidence that intrauterine growth retardation resulted in subsequent mental handicap.

PART III

THE SMALL, "TERM" BABY

PART III

THE SMALL "TERM" BABY

INTRODUCTION

It is now recognised that the term "premature" is not satisfactory in reference to all infants weighing 2500 g. (5 lbs. 8 ozs.) or less at birth. The World Health Organization has recommended the term "low birth-weight baby" as being more meaningful. This, however, still does not distinguish between the small immature baby and the small, mature or "term" baby. The following section was prepared to examine the differences, if any, between the small immature infant and the small mature infant.

For this purpose a small, "term" baby is defined as a baby weighing 2500 g. or less at birth and being of over 37 weeks maturity, and a small immature infant as one weighing 2500 g. or less at birth and of under 37 weeks maturity. No infant of under 28 weeks gestation has been included.

The dividing line of 2500 g. and 37 weeks is appropriate and satisfactory as, in accordance with the work of Scammon and Calkins, and of Streeter, (quoted from Potter, 1961) the average foetus reaches the weight of 2500 g. at the 37th week of gestation.

MATERIALS AND METHODS

Of 302 "premature" infants in this survey 139 (46 per cent.) were small "term" babies, and the remaining 163 (54 per cent.) were small immature babies. In the following small section the two groups are compared for sex, the duration of gestation, the range of birth weights, maternal characteristics, neonatal characteristics at birth and under four hours of age, and at over four hours of age. The perinatal mortality rates are also compared.

RESULTS

Sex

There was no significant difference in the distribution of males and females in the two groups of infants, those of 2500 g. or less at birth and of over 37 weeks maturity, and those of 2500 g. or less and under 37 weeks maturity ($p < 0.30 > 0.20$).

Duration of Gestation

Table LVIII shows the duration of gestation in 139 small "term" infants and 163 small, immature infants. By definition the former are all of more than 37 weeks maturity. The table shows, however, that 54 per cent. of the immature infants were in fact of under 34 weeks maturity, giving them an additional three weeks, at least, of immaturity to contend with in comparison with the small "term" babies.

Range of Birth Weights

Table LIX shows the range of birth weights in 139 small "term" infants and 163 small immature infants. Almost 80 per cent. of the "term" infants were in the 2001 g. to 2500 g. group, whereas only 40 per cent. of the immature babies had reached this birth-weight group. In all lower birth-weight groups the immature infants preponderate.

Maternal Characteristics

Age. Table LX shows maternal age in five-year groups in these mature and immature low birth-weight babies. Statistical evaluation at under and over 30 years of age shows no significant difference in the two groups ($p < 0.20 > 0.10$).

Parity. Table LXI shows the parity of the mothers of these 139 small

"term" infants and 163 immature infants. There is no statistically significant difference ($p < 0.20 > 0.10$).

Height. There was no statistically significant difference in the numbers of mothers of 150 cms. and less, and of over 150 cms. in these two groups of babies ($p > 0.95$).

Previous Obstetrical History. Table LXII shows the previous obstetrical histories of the mothers of these two groups of babies. There was no significant difference in the incidence of miscarriages, stillbirths, previous low birth-weight babies or illness in a previous pregnancy in the two groups. The statistical values are shown in the table.

Maternal Illness in the Current Pregnancy. Table LXIII shows the number of illnesses occurring in each mother amongst 139 with small, "term" babies and 163 with small, immature infants. The numbers are similar to each other, and the difference is not statistically significant.

Table LXIV shows the type of illness in these mothers, and their percentage incidence in each group. Ante-partum haemorrhage was the only illness occurring with significantly different frequency, being more common in the mothers of immature, low birth-weight babies.

Duration of Rupture of Amniotic Membranes Prior to Delivery

The time interval between rupture of the amniotic membranes and delivery was longer amongst the immature group of babies than amongst the mature group of low birth-weight babies (Table LXV; $p < 0.05 > 0.02$).

Type and Incidence of Common Clinical Abnormalities in Mature and Immature Low Birth-Weight Babies at Birth and Under Four Hours of Age

The small, mature babies were compared with the immature babies on six points:- congenital defect, birth injury, respiratory abnormality

oedema, hypotonia and cyanosis. The results and statistical values are shown in Table LXVI.

Congenital Defect. There was no significant difference in the incidence of congenital defects in these two groups of babies, nor were lethal defects any more common in one group than the other.

Birth Injury. There was no significant difference in the incidence of birth injury in the two groups of babies.

Respiratory Abnormality. Respiratory abnormality, comprising apnoea at birth and in the first four hours, and evidence of poor aeration was significantly more common in the immature than the mature babies.

Oedema. Oedema was seen significantly more frequently in the immature than the mature babies.

Hypotonia. Hypotonia occurred similarly in both groups of babies.

Cyanosis. Cyanosis occurred similarly in both groups of babies.

Type and Incidence of Common Clinical Abnormalities in Mature and Immature Low Birth-Weight Babies at Over Four Hours of Age

The small mature babies were compared with the immature babies on six points:- respiratory distress, cerebral irritation, cyanotic attacks, sudden collapse, jaundice and sepsis. Table LXVII shows the results and the statistical analysis.

Respiratory Distress. Respiratory distress occurred significantly more frequently in the babies of under 37 weeks gestation than in those of over 37 weeks gestation.

Cerebral Irritation. Cerebral irritation occurred with similar frequency in the two groups of babies.

Cyanotic Attacks. Cyanotic attacks were significantly more frequent in the immature than the mature babies.

Sudden Collapse. Sudden collapse occurred with similar frequency in the two groups.

Jaundice. Jaundice was seen in significantly more of the immature than the mature babies.

Sepsis. Sepsis also was seen in more of the immature than the mature babies.

Age at Discharge from Hospital

Table LXVIII shows the age at discharge from hospital of the 110 surviving, mature, low birth-weight babies, and the 92 surviving, immature, low birth-weight babies. The small mature babies were ready for discharge sooner than the immature babies ($p < 0.01$).

Perinatal Mortality

Table LXIX sums up the perinatal mortality in these two groups of low birth-weight babies. It is significantly different, being 20.9 per cent. for the mature infants, and 43.5 per cent. for the immature infants. Both are high figures in relation to the over-all perinatal mortality rate of 4.9 per cent. for all singletons born in the Stobhill Unit.

Stillbirth accounted for the loss of 18 (62.1 per cent.) of the small "term" babies, and 33 (46.5 per cent.) of the small immature babies. The ratio of stillbirths to deaths was thus slightly bigger in the mature, low birth-weight babies than in the immature, low birth-weight babies.

DISCUSSION

Of 302 low birth-weight babies born in the Maternity Unit of Stobhill Hospital 139 (46 per cent.).were of 37 weeks maturity or more. Drillien (1959) found that between 37 per cent. and 46 per cent. of low-weight infants in Edinburgh were of over 38 weeks gestation. Colman and Rienzo (1962) found a 31 per cent. and Scott and Usher (1966) a 39 per cent. incidence of low-weight babies who were of over 37 weeks maturity. The Stobhill figure is thus on the high side of that reported in other series.

More of the mature infants were in the higher weight groups, especially 2001 to 2500 g., than were the immature babies, 54 per cent. of whom were of under 34 weeks gestation, at which time even under optimal intrauterine conditions the foetal weight is only 1745 g.

The mothers of the immature babies differed from those of the small "term" babies in that they showed an increased incidence of ante-partum haemorrhage, and an increased time interval between rupture of the amniotic membranes and delivery. This early bleeding may indicate simply the termination of pregnancy from a variety of causes or may be evidence of maternal rejection of foetal tissue through a specific immunological response. The long duration of membrane rupture prior to delivery in the immature baby is well known and is accounted for not so much in terms of hours as in days and sometimes weeks. This feature is usually referred to as spontaneous premature rupture of the membranes and carries a poor prognosis from immaturity rather than from infection.

The babies differed in those characteristics which are dependent on maturity. At birth and in the first four hours of life apnoea, sub-normal aeration and oedema were characteristic of the immature babies although the mature babies were not entirely free from these difficulties. Likewise, after four hours of age established respiratory distress, cyanotic attacks and jaundice were significantly associated with the immature babies. It is apparent from these findings that the immature baby is at a considerable disadvantage compared with the small, mature baby, but that the latter is by no means exempt from trouble. North (1966) also found the small immature baby to have fewer neonatal complications than the small mature baby.

Colman and Rienzo, and Yerushalmy, van den Berg, Erhardt and Jacobziner (1965) found a high incidence of severe congenital anomalies amongst the small, "term" babies, but this was not seen in the present study where similar numbers of lethal congenital defects were present in the two groups.

The perinatal mortality amongst the mature low birth-weight babies was less than half of that seen in the immature babies (20.9 per cent. compared with 43.5 per cent.), but was still four times as high as the over-all perinatal mortality rate for all singleton deliveries in the Unit (4.9 per cent.). In addition it was found that the mode of loss for the small "term" baby was most often by stillbirth and for the immature infant by neonatal death. This preponderance of stillbirths was also noted (in Part I) in those infants lost at over 37 weeks gestation who were over 2500 g. at birth. The explanation of this is

not clear. It may be the result of gradual failure of placental function with cessation of growth of the foetus and reduction in the volume of liquor amnii so that there is no distension-stimulus for the uterus to start labour contractions, the foetus thus dying in utero. Nevertheless this does not explain why the foetus should be expelled alive at an earlier period of gestation when under normal circumstances it is very difficult to induce labour artificially.

In conclusion it can be seen that although these mature low-weight infants suffer less morbidity and mortality than the immature low-weight babies they still require special care. Whilst having the advantage of maturity they have the disadvantage of a poor uterine environment. When born alive they should, with good paediatric care, surmount this difficulty whereas the immature baby tends to suffer not only the adversity of intrauterine growth retardation but also that of undeveloped structural and functional systems.

SUMMARY

1. Infants weighing 2500 g. and less at birth and of over 37 weeks gestation were compared with those weighing 2500 g. and less but of less than 37 weeks gestation.

2. The incidence of these small, "term" babies was 139 of 302 low birth-weight babies (46.0 per cent.).

3. The mothers of these two groups of small babies were similar in that they tended to be over 30 years of age, to be in their fourth or subsequent pregnancy, and to have a history of previous low-weight babies. Their illnesses were similar with the exception of ante-partum haemorrhage which was significantly more frequent amongst mothers of the immature group of babies. The duration of membrane rupture prior to delivery was also significantly longer in the immature group of babies.

4. In the early neonatal period apnoea at birth, subnormal aeration and oedema were characteristic of the immature babies and were significantly less frequent in the mature babies.

5. After the first four hours of life respiratory distress, cyanotic attacks, collapse, jaundice and sepsis were significantly more frequent in the immature, low-weight babies than in the small, "term" babies.

6. Perinatal mortality in the small mature babies was 20.9 per cent.

and in the immature babies 43.5 per cent.. Both compare badly with the over-all rate of 4.9 per cent. for singletons in the Stobhill Maternity Unit.

7. Stillbirth was a more common mode of loss than was neonatal death in the small, mature babies.

8. It is concluded that the small "term" baby is at less of a disadvantage than the small immature baby, but that special care is nevertheless indicated. When live-born he should recover satisfactorily from intrauterine growth retardation whereas the baby of short gestation has also to contend with structural and functional immaturity.

PART IV

PERINATAL CHARACTERISTICS OF TWIN PREGNANCY ASSOCIATED WITH LOW BIRTH WEIGHT

PART IV

PERINATAL CHARACTERISTICS OF TWIN PREGNANCY ASSOCIATED WITH LOW BIRTH-WEIGHT

INTRODUCTION

Amongst all the low birth-weight babies born in the Maternity Unit at Stobhill Hospital during the period of this survey 21.1. per cent. were accounted for by the babies of twin pregnancies. The incidence of low birth-weight babies in 71 twin pregnancies was 57 per cent. compared with 9.8 per cent. in 3093 singleton pregnancies. It is seen thus that twin pregnancy makes a considerable contribution to the problem of low birth-weight. It was thought to be of interest to examine the perinatal characteristics of these babies to see what special difficulties they had to overcome. By comparing the two babies of the same mother more might be learned of factors arising during labour which have an adverse influence on the wellbeing of the newborn infant. It was hoped also to throw some light on the second twin's reputation for increased mortality and morbidity.

MATERIALS AND METHODS

In 51 of 71 twin pairs born in the Stobhill Maternity Unit between January 1959 and May 1960 one infant, or both, weighted 2500 g. or less at birth. All the babies of the remaining 21 pairs weighed over 2500 g., and all of these survived. The twin pairs with low birth-weight babies are the subject of this section. Their perinatal

characteristics have been examined under the following seven headings:-

Incidence

The duration of gestation

Birth weight

Maternal characteristics

Neonatal characteristics in relation to order and size

- at birth and under four hours of age
- at over four hours of age
- age at discharge from hospital

Perinatal morality.

RESULTS

Incidence of Twin Pregnancy.

The incidence of twin pregnancy was 71 of 3164 pregnancies (2.2 per cent.).

Incidence of Low Birth-Weight Babies

Eighty-one babies (30 pairs and 21 single babies of pairs), or 57 per cent. of all the babies of twin pregnancies weighed 2500 g. or less at birth.

The Duration of Gestation

Table LXX shows the duration of gestation of these 51 pregnancies in which one or both babies was of low birth-weight.

Two-thirds of the pairs were immature (under 37 weeks gestation) and one third were of under 34 weeks maturity.

Birth Weight

Table LXXI shows the range of birth weights of these 102 infants in which one or both weighed 2500 g. or less at birth. Very few (11.8 per cent.) were 1500 g. or less and 20.6 per cent. were over 2500 g.

Maternal Characteristics in Twin Pregnancy Associated with Low Birth Weight

The following factors concerning the maternal characteristics of twin pregnancy associated with low birth weight are considered: age, parity and illness in the current pregnancy. These factors are compared with similar factors in the mothers of 100 healthy babies of normal weight and of 302 singleton, low birth-weight babies.

Age. Table LXXII shows the ages in five-year groups of 51 mothers having twins of low birth weight compared with that of 100 mothers with singletons of normal weight. The figures show a trend only for the former mothers to be aged 30 years or more, the p value being between 0.10 and 0.05.

There was no significant difference in numbers of mothers over 30 years of age with low birth-weight twins and with low birth-weight singletons (Table LXXIII).

Parity. There was no significant difference in the parity of mothers

of low birth-weight twins compared with normal-weight singletons ($p < 0.50 > 0.30$; Table LXXIV), nor with low birth-weight singletons ($p < 0.20 > 0.10$; Table LXXV).

Type and Incidence of Illness During Pregnancy. Table LXXVI shows the type and incidence of illness in 51 mothers with twin pregnancies associated with low birth-weight babies compared with that in 100 mothers of singleton infants of normal birth weight. Pre-eclamptic toxaemia was significantly more frequent in the mothers of twins ($p < 0.01$), whilst iron-deficiency anaemia and a diagnosis of hydramnios were slightly more frequent (p 0.10 0.05). Oedema without hypertension or proteinuria, and megaloblastic anaemia were seen in two mothers with twin pregnancies but in none of the mothers of singletons.

When a similar comparison was made for the mothers with twin pregnancies and the mothers of singleton, low birth-weight babies, it is apparent that iron-deficiency anaemia is the only illness which occurred significantly more frequently in the mothers with twins ($p < 0.01$; Table LXXVII).

Neonatal Characteristics of Low Birth-Weight Twins at Birth and Under Four Hours of Age

The following section compares the clinical conditions of the babies of twin pairs according to the birth weight and birth order for the presence of congenital defect, superficial birth injury, respiratory abnormality, oedema, hypotonia and cyanosis. Table LXXVIII shows the results.

Congenital Defect. One pair of twins was conjoined. No defects were seen in any second twins, and only minor defects were seen in the remainder. There was no relation to birth size or order.

Birth Injury. No superficial birth injury was seen in smaller first twins. The difference in incidence in the other babies was not statistically significant.

Respiratory Abnormality. There was significanly more apnoea at birth, and evidence of suboptimal lung aeration in bigger second twins than in the bigger first twins *($p < 0.02 > 0.01$). The smaller twin whether first or second in order of birth also experienced respiratory difficulty.

Oedema. Oedema was seen significantly more frequently in big second twins compared with big first twins *($p < 0.05 > 0.02$) and was also seen in small twins.

Hypotonia. No smaller first twins were limp at birth. The remaining groups of babies all showed hypotonia, but there was no significant difference in incidence in the three groups.

Cyanosis. The bigger second twin showed cyanosis more frequently than did the other three groups *($p < 0.05 > 0.02$ when comparing the bigger second twin with the bigger first twin).

Neonatal Characteristics of Low Birth-Weight Twins after Four Hours of Age

The following section compares the condition of the babies of

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*Using Yates modification of the Chi-Square Test.

twin pairs according to birth-weight and birth order for the presence of respiratory distress, cerebral irritation, cyanotic attacks, collapse, jaundice and sepsis. Table LXXIX shows the results.

Respiratory Distress. The bigger first twins showed no respiratory distress. The incidence amongst the other three groups of babies was not significantly different.

Cerebral Irritation. The smaller first babies showed no cerebral irritation and there was no significant difference in incidence in the other three groups.

Cyanotic Attacks. No cyanotic attacks were seen in the bigger first twins nor in the smaller second twins. The difference in incidence in big second twins and small first babies was not significant ($p<0.70 > 0.50$).

Collapse. Sudden collapse was seen only in the bigger second twin, in two of 22 babies, (9.1 per cent.).

Jaundice. Jaundice occurred in all four groups of babies. The difference in incidence was not statistically significant ($p<0.30 >0.20$).

Sepsis. Sepsis occurred with similar frequency in all four groups of babies.

The Effect of Birth Weight and Disparity in Weight on Birth Order

Birth weight did not affect birth order in the present study, 23 heavier and 21 lighter babies than their co-twins being born first in 44 pregnancies with live-born infants. In the 23 deliveries where

the big twin was born first the mean weight difference in twin pairs was 485 g. compared with 363 g. in the 21 deliveries where the small twin was first-born.

Age at Discharge from Hospital

Table LXXX compares the duration of stay in hospital of these four groups of babies. Almost a half of the numbers of big first twins was discharged from hospital at the age of ten days or less, the usual time for healthy singletons, compared with one third of the small first twins and one sixth of the small second twins.

Perinatal Mortality in Twin Pregnancy Associated with Low Birth Weight

Incidence. From the 28th week of gestation to the 28th day of life 14 of 136 babies (10.3 per cent.) were lost, eight being stillborn and six dying neonatally. In addition two pairs of twins were born before the 28th week of gestation and two more single babies died after the 28th day of life but before discharge from hospital, making the total mortality in 71 twin pregnancies 20 of 142 babies, or 14.1 per cent.

Fourteen of these babies constituted seven pairs, and six were single babies of pairs, making a mortality of 18.3 per cent. for all twin maternities.

Over the whole period under survey 153 of 3093 singleton babies (4.9 per cent.) died between the 28th week of gestation and the 28th day of life, compared with 14 of 136 twin babies (10.3 per cent.). Thus the

perinatal morality for twins is more than double that of singletons.

The Influence of the Duration of Gestation on Mortality in Twin Pregnancy. Table LXXXI shows the duration of gestation in 20 twin babies who died. Sixteen infants (80 per cent.) were of less than 37 weeks maturity and 11 (55 per cent.) were of under 34 weeks maturity.

At under 32 weeks gestation pairs of babies were lost. At 32 to 37 weeks both pairs and single babies were lost, and after the 37th week single babies were lost. Thus the outlook for survival improves with increasing maturity up to term.

The Influence of Birth Weight, the Sum of the Birth Weights and the Percentage Difference in Birth Weights on Mortality in Twin Pregnancy. Table LXXXII shows the range of birth weights of the 20 low birth-weight babies who died. Twelve losses (60.0 per cent.) occurred in babies weighing 1500 g. or less. The percentage loss decreases as the weight increases and there were no foetal or infant deaths in babies weighing over 2500 g. at birth.

Table LXXXIII shows that the sum of the two birth weights in 51 pairs of twins amongst whom 20 babies were either stillborn or died corresponded broadly with the effect of maturity. When pairs of babies were lost the combined weight was 3000 g. or less; between 3001 g. and 4000 g. both pairs and single babies were lost; above 4000 g. single babies only were lost. Thus in low birth-weight twins the bigger the sum of the birth weights, the better is the outlook for survival.

The effect of the difference in birth weights, expressed as a percentage, on mortality when one or both babies weighed 2500 g. or less at birth was investigated. Table LXXXIV shows the results. When the disparity is less than 20 per cent. of the sum of the two birth weights the mortality is between eight per cent. and 14 per cent. Where the disparity is greater the mortality rises progressively. The difference is statistically significant at p value < 0.01.

The Influence of Birth Weight and Birth Order on Mortality. Table LXXXV shows the mortality in twin pregnancy associated with low birth weight, according to the birth weight and birth order. When macerated foetuses are excluded there is no statistically significant difference in mortality in the four groups of infants ($p < 0.30 > 0.20$).

Mortality According to the Sex of Twin Pairs. There was no significant difference in either the frequency of male, female or mixed pairs, nor in their mortality rates ($p < 0.50 > 0.30$). Nor was there any significant difference in mortality when that of all pairs of the like sex, male and female (14 of 66 infants) was compared with that of mixed pairs (6 of 36 infants), (Table LXXXVI).

There was insufficient information in the case records to determine the effect of zygosity.

DISCUSSION

MATERNAL CHARACTERISTICS

The incidence of all twin pregnancies in the present series is 71 of 3164 deliveries, 2.2 per cent. or one in 44. Dunn (1965) found the only higher incidence than this, in Birmingham, where it was one in 26. He attributes this to the selective admission of these patients to the Birmingham Maternity Hospital. Table LXXXVII shows the incidence of twin pregnancy in other series. Broadly, it varies from one to four per cent. and the rate seen in hospital is dependent on the policy of the hospital in making accommodation available for this and other complications of pregnancy and delivery.

The greatest danger in twin pregnancy is that it will terminate prematurely (Aaron, Silverman and Halperin, 1961, MacDonald, 1962, Potter, 1963). The babies of the present study are no exception to this. One-third were born at under 34 weeks gestation, one-third between 34 and 37 weeks, and one-third at over 37 weeks gestation. Unfortunately these findings may be influenced by the fact that only details of pairs of babies showing low birth-weight were collected. Nevertheless it seems unlikely that any pairs where each infant weighed over 2500 g. were of under 37 weeks gestation. Immaturity then is common, and is the greatest hazard in twin pregnancy.

The birth weight of twins reflects broadly the pattern of immaturity. However whereas 64.6 per cent. of the pairs with low birth-

weight babies were of under 37 weeks gestation, 79.4 per cent. of the individual babies were 2500 g. or less. There is restriction of growth in utero. Nevertheless the total foetal weight is ahead of that of the singleton foetus for the same length of gestation.

The mothers of twin pairs tended to be older than those of normal-weight singleton babies, but no older than the mothers of low birth-weight single babies. One would be tempted to say that the incidence of an unusual event (twin pregnancy or the birth of a low-weight singleton) would increase with the increased opportunity for it to occur. That is, that it should correspond to increasing parity. This however was not found to be the case, there being no significant difference in the parity distribution between mothers of twins and normal birth-weight singletons, nor mothers of twins and low birth-weight singletons in this study. Increasing maternal age thus appears to be a significant factor in the incidence of twin pregnancy. Danielson's study (1960) shows no difference in either age or parity of mothers with twins compared with those with single babies. Seski and Miller (1963) reported a higher incidence of twin pregnancy with both increasing age and parity. Graves, Adams and Schreier (1962) and Hendricks (1966) reported increasing parity to be related whilst the latter worker found an increased incidence between 25 and 35 years of age after which therewas a fall. Robertson (1964) found an increased incidence at 25 to 40 years, and a very high rate amongst primigravid patients. The diversity of these reports leads one to believe that the

findings are largely dependent on the types of patient admitted to each hospital. In the Stobhill Unit the mothers with twin pregnancies are given high priority. In the present series it seems that maternal age has more bearing on the form of division of the zygote than the number of ova previously fertilized, an hypothesis which would seem very reasonable.

Maternal morbidity is known to be increased in twin pregnancy. This increase is in the main due to an increased incidence of pre-eclamptic toxaemia and iron-deficiency anaemia. In MacDonald's series at the Royal Maternity Hospital, Glasgow (1962) the incidence of pre-eclamptic toxaemia was 24.2 per cent. compared with 37.3 per cent. at Stobhill Hospital during the same period. Low figures of 4.9 per cent. (Seski and Miller, Detroit) and 10.8 per cent. (Waddell and Hunter, Rochester) have been reported. Similar figures to our local ones are reported by Robertson (Edinburgh), of 32 per cent., Graves et al. (Memphis) 37.5 per cent., and Danielson (Stockholm) 25 per cent.. In the primigravid patient with twin pregnancy pre-eclamptic toxaemia is even more frequent (Danielson; Robertson, 1964) and was present in 37 per cent. of MacDonald's series. It is of interest that although this high incidence of pre-eclamptic toxaemia is present in twin pregnancy compared with that in mothers with normal-weight babies there is in fact no difference in incidence when compared with mothers of single babies of low birth weight. I think this point has not been made previously. The inferences are difficult. It seems

probable that the same mothers will suffer from pre-eclamptic toxaemia and tend to produce low birth-weight babies whether they have a singleton or multiple pregnancy.

Iron-deficiency anaemia (haemoglobin < 10.5 g. per 100 ml.) was slightly increased amongst the mothers of this series with twin pregnancy in comparison with the controls, and very much higher in incidence than in the mothers of low birth-weight singletons. One can understand the high incidence in the twin pregnancy. In the Glasgow area the incidence of nutritional anaemia is very high. It follows that when maternal iron stores are being depleted by two foetuses, whose total weight is above that of the singleton for the same gestational age, anaemia will become manifest more frequently. In MacDonald's series a haemoglobin level of less than 8.5 g. per 100 ml. was found in 17 per cent. of mothers with twins, and in Robertson's series 40 per cent. of patients showed a haemoglobin level of under 10.2 g. per 100 ml. Robertson wrote that "pre-eclamptic toxaemia at 30 to 32 weeks and anaemia which is slow to respond to iron at mid-pregnancy may indicate twin pregnancy". Megaloblastic anaemia is also found to be more frequent than in the mothers with singleton babies. In the present series two of 51 mothers with twins, one of 302 mothers of low birth-weight singletons and none of 100 mothers with normal-weight babies suffered from megaloblastic anaemia.

Hydramnios is reported to occur in some twin pregnancies, in the order of 3 per cent. in Danielson's series, 10 per cent. in that of

Graves et al., 1.6 per cent, in that of Seski and Miller and 5.9 per cent. in the present series. MacDonald considers its connection with the subsequent development of pre-eclamptic toxaemia and accidental haemorrhage, between the 26th and 31st weeks, so firm that he advocates rest in hospital (before 30 weeks gestation) for the patient with hydramnios. In the group of singleton low birth-weight babies hydramnios was also seen, but this was in association with congenital abnormalities, mainly anencephaly and multiple defects. One of the three cases of hydramnios in the twins of the Stobhill series occurred with the conjoined twins, but in the others there was no deformity. It seems therefore that the cause of hydramnios is far from clear. Seski and Miller also found the foetal outlook poor in twin pregnancy with hydramnios, as did Graves et al., despite the absence of congenital defect.

Neonatal Characteristics of Twin Babies at Birth and Under Four Hours of Age (where one baby or both weighed 2500 g. or less at birth)

One important conclusion has been reached from consideration of the next three small sections on the condition of twin babies at under four hours and at over four hours of age, and on their perinatal mortality. It seems that one must try to differentiate as carefully as possible between neonatal characteristics arising as a result of birth difficulties, and birth difficulties and neonatal abnormalities arising from inherent intra-uterine factors; abnormalities in twins

may be attributed simply to birth order or size when in fact these two may in turn be the result of some other, more basic, defect. There is much concern in medical literature for the second twin, implying that the increased hazard is the result of this baby being second in order of birth, but it seems possible in some instances that the order is determined by and not the cause of the condition of the second baby. This problem is best illustrated by two examples. Firstly, higher perinatal mortality rates have been reported for second twins (Spurway, 1962, and Donaldson & Kohl, 1960). This seemed to be the case in the present series, with a perinatal mortality of 23.1 per cent. for all second twins and 12 per cent. for all first twins. However it has been pointed out by MacDonald (1962) that a macerated foetus is invariably delivered second in order. He has seen a macerated foetus presenting late in the first stage, but the live foetus has been born first. Before comparing "birth hazards" of first and second twins one must distinguish therefore between intrauterine deaths and fresh stillbirths. When this correction is made in the present series the second twin runs no increased risk of mortality. The following authors agree that there is no increased mortality risk for the second twin: Waddell and Hunter, Aaron, Silverman and Halperin (1961), Graves et al., Thompson and Johnson (1965). It seems likely that forceful uterine contractions during the second stage of labour can obtain little purchase on a dead foetus as the muscle tone of the living foetus is necessary to

provide the amount of resilience which enables contractions to effect expulsion. This is one example of the dangers of dealing collectively with "the second twin". Secondly, a foetus whose birth weight is 2000 g. or less and is 25 per cent. below that of its co-twin (the classification of Babson, Kangas, Young and Bramhall, 1964) would be less effectively expelled than the bigger twin and would thus tend to be second in order of delivery. In the present study almost equal numbers of big twins and small twins were first-born. Nevertheless in examining the difference in weights of twin pairs a considerably bigger weight difference was noted where the big twin was first-born than where the small twin was first-born. This probably indicates that provided the weight difference is large enough and both babies are alive, the big twin tends to be delivered first.

Brown and Wallis (1963) found that severe intrauterine malnutrition predisposes to neonatal hypoglycaemia. These small twins suffer from hypoglycaemia in the neonatal period (Reisner, Forbes and Cornblath, 1965), remain subnormal physically and mentally up to at least eight and a half years of age (Babson, Kangas, Young and Bramhall, 1964) and are found more often, subsequently, in mental institutions than are first twins (Berg and Kirman, 1960). In addition these very small twins have fewer cells with less cytoplasm than their bigger co-twins (Naeye, Benirschke, Hagstrom and Marcus, 1966). Illingworth and Woods (1960) considered that the low birth-weight twin with cerebral palsy belongs to the inherently defective group, whilst the other twins were mentally

retarded on account of "prematurity". On the other hand this marked dysmaturity in one twin may be a reflection of asymmetrical distribution of placental circulation. Whatever the explanation, the cause of subnormality is inherent in the foetus and its development, and the fact that it is delivered second in order is dependent on and due to the cause of its general inferiority. This then is a danger of attributing to obstetrical hazards thos abnormalities which are in fact inherent biological disadvantages of twin pregnancies.

The circumstances under which the second twin is in danger of dying are at least four fold. Robertson (1964) says that long delay between the first and second delivery increases the risk of mortality, and this is seen particularly in undiagnosed twins where one is born at home, and the other, after much delay, in hospital. The second twin is in danger again if undiagnosed and if an oxytocic drug is given after the birth of the first baby without first palpating the uterine fundus. It is also in danger in breech delivery particularly after version (Aaron et al.). Obviously there is also danger in monochorionic twins where the placenta begins to separate before the second twin is delivered. Here expeditious delivery of the second twin is essential. Cord prolapse, although more frequent than usual, was thought by Robertson to be detected and dealt with so rapidly in twin delivery in hospital as to constitute not a very great risk.

In the present series the bigger second twin was shown to be at a disadvantage as regards morbidity at birth and under four hours of age. He suffered more frequently from respiratory abnormality, oedema

and cyanosis than the other babies. These are probably all associated with anoxia during labour and delivery. MacDonald considered that the extra risk for second twins was of asphyxia and trauma, and that these could be avoided by skilled anaesthesia and "early controlled delivery of the second twin with membrane rupture at five minutes and delivery complete within 20 minutes".

The most important point in the safe delivery of the second twin is the time interval elapsing between the delivery of the first and second twins. Danielson points out that the second twin undergoes the trauma and hypoxia not only of its own delivery but also that of the first twin. He was prepared to wait two hours before effecting delivery. Seski and Miller at the other extreme found that the average interval between the delivery of live babies was 7.6 minutes, whereas foetal death was associated with an average interval of 23 minutes. They say the mode of delivery for the first twin should be the same as for a singleton, and then the second twin should be delivered as rapidly as possible "with good judgment employed". It is evident that individual circumstances must be taken into account at each delivery, and as Robertson points out "the management of the delivery of the second twin is probably more important than the actual method of delivery". It is to be noted that the big first twins are remarkably free from early neonatal difficulties.

Neonatal Characteristics of Twin Babies at Over Four Hours of Age

After four hours of age all differences in incidence of neonatal abnormalities are reduced. The bigger second twin showed a slightly increased incidence of cerebral irritation, which probably resulted from difficulties at delivery and two of the surviving 22 bigger second twins showed sudden collapse. Thus it appears that the babies were already recovering from the effects of delivery by the end of the fourth hour of life. It is noted again that the big first twins are remarkably free from morbidity. No increased incidence of respiratory distress was seen in second twins on statistical analysis. This is not the finding of Potter (1963) who states

> "I have long felt that the main conditions responsible for the development of hyaline membranes must already exist at the time of birth. The fact that hyaline membranes occurred more than twice as often among second twins as among first twins may well indicate that conditions surrounding the birth of the second twin or transpiring in the interval between the birth of the first and second twins may predispose to the development of this condition"

This idea, that conditions do exist at the time of birth which predispose to respiratory distress is borne out in Part II of this thesis, where respiratory distress is shown to be related in a statistically significant manner to apnoea at birth and sub-optimal aeration in low birth-weight babies. Perhaps this high incidence in

second twins seen by Potter was also related to the tendency of the disproportionately low birth-weight baby to be delivered second, but it was not evident in the small series at present being considered.

As one would expect the big first twins were ready for discharge at much the same time as a healthy singleton infant, whilst the lower the birth weight the longer was the duration of nursery care. The small second twins required the longest period of special care.

I have not considered the condition of all first twins as compared with all second twins since from what has already been said it will be realized that I do not feel this is a just comparison. The second twins who are bigger than the first suffer more difficulties at birth and in the early neonatal period. These difficulties appear to pass off almost within hours, and are undoubtedly the result of the hypoxia of two labours. The second twins who are much smaller than the first constitute a quite separate group, being born second probably as a result of inferiority, either through genetic or developmental defect inherent in twin pregnancy, or through inequality of intrauterine supplies, the result of vascular communications in the placenta.

Perinatal Mortality

It is noteworthy that no infants of over 2500 g. at birth died perinatally. This was also the findings of Graves et al.. Table LXXXVIII shown the perinatal mortality in twin pregnancies in other

series. At Stobhill the mortality amongst twins was over twice as great as the mortality amongst all singleton babies. Several factors relating to the twin babies of 2500 g. and less merit discussion. These include: the duration of gestation, the birth weight, the percentage difference in birth weights, the influence of zygosity, the influence of early diagnosis and of in-patient hospital care and delivery on mortality and morbidity in twin pregnancy. The influence of birth order and of emergencies in labour have already been discussed in relation to perinatal mortality.

The duration of gestation was less than 37 weeks in 16 of 20 infants (80 percent.) who died in this series, and less than 34 weeks in 55 per cent. This degree of immaturity is the main cause of mortality. Nevertheless Dunn (1965) states that in multiple pregnancy one might reasonably regard a 40-week gestation as being in danger from placental insufficiency, and Dunnihoo and Harris (1966) consider, perhaps on a common basis, that the induction of labour at 36 weeks in monoamniotic twins might be of value in reducing mortality, since 60 per cent. of these pregnancies go beyond 36 weeks with a 21 per cent. fetal loss, cord intertwining being one of the main dangers. Timmons and Alvarez (1963) stress the importance of realizing the situation and delivering the second twin with speed. Dunnihoo and Harris offer a method of diagnosis of this important situation. Abdominal amniocentesis is carried out, followed by the injection of radio opaque

material. If only one amniotic sac is present this can usually be appreciated, and after the lapse of one hour dye will be seen in the intestines of both infants if they are enclosed in a single sac. Plainly the danger here is also of placental detachment before the second twin has been delivered. The placental end of the umbilical cord should be clamped as soon as the first baby is delivered, to prevent exsanguination of the second baby.

Much the most frequent problem in twin pregnancy is immaturity. This is said to be due mainly to the extra volume which the uterus is required to accommodate, the sum of the birth weights in twins being well above the expected for the duration of gestation in a singleton pregnancy. More attention is being given now to the importance of rest in hospital from the middle weeks of pregnancy, 28 to 31 or 32 at admission, and this seems to be effective in adding the necessary maturity to these pregnancies in order to produce infants who will survive. Rest is known to improve placental efficiency whereas physical labour may be deleterious (McClure Brown, 1962, Smith 1966); moreover rest in the early stages is as yet the main standby in the prevention of pre-eclamptic toxaemia, which occurs early and frequently in twin pregnancy. Everything possible should be done to gain three or four weeks of extra maturity for these babies. Robertson however states that after the 36th week these mothers can be allowed home again without increased risk. He does not explain why, but perhaps this is

in keeping with the hypothesis that placental insufficiency occurs earlier in twin pregnancy, and that 36 to 38 weeks might by the optimum time for delivery, and after which intrauterine deaths tend to occur.

Birth weight is a reflection of the maturity of these babies, and is a retrospective measurement of the well-being of any pregnancy. Nevertheless several generalizations are of interest. Twelve of 20 babies (60 per cent.) dying in this series weighed 1500 g. or less at birth, and the remaining eight (40 per cent.) were between 1501 and 2500 g. No infants of over 2500 g. were stillborn or died. Potter found that amongst infants weighing 1,000 to 2,500 g. at birth the mortality was 10.5 per cent., whilst in the present series taking all infants of under 2,500 g. the mortality was 19.6 per cent.. As one would expect the prognosis for survival improves with individual increasing birth weight as with total increasing birth weight. The critical level for individual foetuses is between 2,000 and 2,500 g. (Guttmacker and Schuyler, 1958; Danielson, 1960; MacDonald, 1962; Spurway, 1962; Potter, 1963; Seski and Miller, 1963; Robertson, 1964). At the other end of the scale Danielson points out that if the second baby is very big difficulties in extraction may increase mortality.

It is notable in this series that the greater the divergence

between the birth weights of the individuals of the pairs the greater is the perinatal mortality. Care was taken to be sure that this was so despite intrauterine deaths in which, naturally, the weight-disparity between the two foetuses would increase progressively. This difference in weight in monozygous twins is probably due to the sharing of a placenta, with vascular anastomoses. One foetus, furnished with a good blood supply develops at the expense of the other with the poorer supply. Whether this is entirely quantitative, or also qualitative, we do not know. This situation represents a form of the placental transfusion syndrome (Benirschke, 1961) of "chronic" type in comparison with that in which members of twin pregnancies become acutely anaemic or plethoric during labour and delivery as a result of inter-communications in the placental circulation. It is relevant here to note the increased perinatal mortality found in monozyous twins by Benirschke (1961), Potter (1963), Robertson (1964) and Gittelsohn and Milham (1965). The relative importance of the long-term effect of asymmeterical blood supply, and the acute effect of associated labour difficulties (cord obstruction due to intertwining, or placental detachment) in these babies is not known.

Potter found the increased perinatal mortality in the monozygous twins to be due to increased prematurity. This raises the possibility that the limit of placental reserve had been reached early since there were two infants dependent on one placenta. Presumably the converse

is true that dizygous twins have a lower perinatal mortality and less prematurity because each foetus will have the full benefit of it's own placenta. It would follow then that premature labour in dizygous twin pregnancies is the result of pushing maternal rather than placental reserves beyond their limit. It would be of interest to determine if in the mothers of dizygous twins the onset of pre-eclamptic toxaemia is later than in those of monozygous twins. Perhaps one could infer from this whether the site of origin of the basic abnormality in pre-eclamptic toxaemia is the maternal kidney or the single, over-worked placenta.

I feel that the matter of zygosity is probably of prime importance in relation to the survival and well-being of twins, but have no way of knowing at this stage what the situation was as regards the infants of this series, since the case notes available are inadequate in this respect. Whilst the application of *Weinberg's rule tells us how many of these pregancies were mono- and dizygous there is no way of identifying the individual pairs. This is information of utmost importance which should be universally and uniformly recorded. In a series of twin pregnancies examined by Potter 22.8 per cent. were found to be monozygous with one placenta and one chorion, and a further 20 per cent. to be probably but not definitely monozygous.

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*Weinberg's Rule, quoted from Potter states: "The total number of dizygotic twins in any population should be twice the number of different sex, and this subtracted from the total should give the number who are monozygotic".

Diagnosis prior to delivery is essential for the assured safe delivery of twin babies. The earlier the diagnosis is made, the better the outlook should be. Immaturity is the main cause of loss in twin pregnancy. In Robertson's series nine per cent. of twins were delivered before the 32nd week and accounted for 52 per cent. of his total foetal loss. One must therefore make the diagnosis even before the 28th week, on the grounds that measures can be taken which may help to avoid premature labour. The primigravid patient must receive special attention (Dunn, 1965). Barter, Hsu, Beck and Pugsley (1965) have advocated the use of electrocardiographic tracings for the certain diagnosis of twin pregnancy as early as the 18th week. A history of multiple pregnancy in the family, large size for dates, the early development of pre-eclamptic toxaemia, and anaemia should always suggest multiple pregnancy. X-ray can be used to confirm diagnosis, but should not be carried out until well after the 16th week of pregnancy. Once the diagnosis is made bed rest in hospital is advocated from the 30th to the 36th week. Robertson thinks that once the 36th week is passed there is no longer any necessity to rest a healthy mother in hospital, and that she can be discharged home to return shortly before delivery is due. Prophylactic therapy against anaemia, both iron and folic acid, should be started early.

Whenever placental adequacy is in question, as it is in the prognosis for foetal survival in twin pregnancy, the need for a reliable, quick method of estimating placental function or foetal

well-being stands out clearly, in order that pregnancy may be terminated before it is too late, always providing, of course, that the stage of hazardous immaturity has been passed. This phase certainly does exist, as shown by MacDonald's series in which perinatal mortality was 12.5 per cent. in patients with no pre-eclamptic toxaemia and only 9.9 per cent. in those with pre-eclampsia. This he considered to be due not only to the fact that these patients developed pre-eclamptic toxaemia when they were past the stage of dangerous immaturity, but they were still at less than 36 weeks gestation, when the rest necessitated by pre-eclamptic toxaemia was beneficial in other ways to the pregnancy.

Hospital delivery is essential for quick operative procedures to be carried out as the occasion demands. Expert paediatric care is then necessary to give these immature, dysmature or asphyxiated babies the best hope of survival and normal development.

SUMMARY

1. The incidence of twin pregnancy in the Stobhill Maternity Unit between January, 1959 and May, 1960 was 71 in 3,164 mothers or 2.2 per cent..

2. Sixty-six per cent. of these twin pregnancies terminated at under 37 weeks gestation.

3. Eighty-one (57 per cent.) of the babies of these pregnancies weighed 2500 g. or less at birth. Of these 60 infants were twin pairs and 21 were single babies of pairs. They accounted for one fifth of the total numbers of low birth-weight babies born in the Unit during that time.

4. A high incidence of pre-eclamptic toxaemia was the only notable maternal feature, beingpresent in 37.3 per cent. of these mothers compared with only 14 per cent. of the mothers of normal-weight singleton babies, but 26.5 per cent. of mothers with low-weight singleton infants. Age, parity, previous obstetric history and iron-deficiency anaemia were not significantly associated with twin pregnancy in this series.

5. The big first twins were remarkably free from neonatal abnormality both at birth and at under and over four hours of age. The big second twins showed the most morbidity whilst the smaller twins, whether first or second, occupied a midway position. The condition

of the big second twins improved after the first four hours of life, indicating that these difficulties were in all probability the result of trauma and anoxia during labour.

6. Perinatal mortality amounted to 10.4 per cent. of all twin babies. There were no perinatal deaths in twin pairs where both babies weighed over 2500 g. at birth. Loss was dependent on immaturity and low birth-weight. In addition perinatal deaths tended to occur where the difference in weights of the babies of pairs was more than 20 per cent. of the sum of their birth weights.

7. When allowance was made for infants dying in utero (who are almost always delivered second in order) there was no increase in mortality for the second twin whether bigger or smaller than the first.

8. It is thought that the reputation of the small second twin of inferiority is dependent on prenatal factors, e.g. asymmetrical distribution of placental circulation, and that this inferiority and small size are the cause and not the result of being born second.

9. In the human species twin pregnancy carries inherent biological disadvantages which cannot be entirely overcome. Resting the mother in hospital from at least the 32nd to the 36th week of gestation, and delivery in hospital appear to offer the best results so far. There is probably a place for the serial

estimation of maternal urinary oestriol excretion in these pregnancies as they approach full term.

PART V

RENAL-TRACT INFECTION IN PREGNANCY

PART V

RENAL-TRACT INFECTION IN PREGNANCY

INTRODUCTION

Pregnant women have been known for a long time to be especially susceptible to renal-tract infection. Weiss and Parker (1939) drew particular attention to this and to the range of disorders which constitutes pyelonephritis and its complications and sequelae. Since 1955 information has amassed on the subject of renal-tract infection, largely as a result of the work of Kass (1955, 1956, 1957, 1960, 1962) who put a quantitative meaning into the enumeration of bacteria in clean-voided urine. This placed subsequent investigations on an objective level and obviated the necessity for catheterization. This mass of information is disseminated widely through medical literature. Renal-tract infection is the business of the physician, surgeon, obstetrician, paediatrician, geriatrician. The result may be that through this lack of channelling, through this diversity of application, the main impact of these advances is lost.

The great advance which the work of Kass has produced is the opportunity to diagnose and treat renal-tract infection before it produces symptoms. Secondly these patients can be supervised bacteriologically for many months with the intention of treating relapse or re-infection at the earliest possible stage. From this it follows

that no patient once known to have urinary-tract infection should escape surveillance and thus run the risk of progressive renal infection with its sequelae of increasing azotaemia, hypertension, cardiac failure and cerebral vascular accidents.

Pregnancy is a starting point for renal-tract infection in many women. Between 40 per cent. and 70 per cent. of cases remain asymptomatic. This would seem to offer an excellent opportunity for the establishment of infection in the renal parenchyma. Thus to identify and treat all pregnant women with significant bacteriuria might produce a considerable improvement not only in immediate maternal health, but in health at a much later time in life.

During the past decade, and particularly as a result of the observations of Kass (1962), maternal bacteriuria has been suspected as being a cause of low birth weight and increased perinatal mortality. It was from the point of view of testing this finding that the present study on maternal renal-tract infection was undertaken. Many of the findings coincide with those of other workers, but points of variance arise which raise new problems and which would form starting points for further investigation.

This study is set out in small sections according to the plan shown in the Table of Contents.

A. BACTERIOLOGICAL ASPECTS

MATERIALS AND METHODS

Specimens of urine from 2,521 consecutive patients attending the antenatal clinic at Stobhill Hospital, Glasgow, were examined for infection by three methods. A pilot study was carried out using 0.1 ml. drop preparations of freshly-voided, whole-volume and uncentrifuged urine, stained with Gram's stain. Specimens showing numerous Gram-negative rods were regarded as positive (Figure 24). The triphenyl tetrazoleum chloride test (T.T.C. test, Simmons and Williams, 1962) was next used in conjunction with Gram-stained preparations (Figure 25 and 26). Clean mid-stream catch specimens were obtained under my direct supervision for these tests, and the tests themselves were carried out by me personally. At this time each positive specimen and approximately every tenth negative specimen of urine was examined also by bacterial count using the fluid dilution technique (Kass, 1955, 1957), (Figures 27, 28, 29 and 30). Ultimately bacterial count by the quantitated loop technique (McGeachy and Kennedy, 1963) became routine practice in the Department of Bacteriology at Stobhill Hospital, and this method was used alone for the large majority of specimens. This latter group of specimens were clean, mid-stream, catch specimens obtained by the patient, following written instructions. Sterile water was used for cleaning. Following the finding of bacteria in the urine the organisms was identified, and where the count was over 10,000 per ml. drug sensitivity was ascertained by standard methods in the Department of Bacteriology.

RESULTS

Numbers of Tests Performed and the Incidence of Positive Specimens

Table LXXXIX shows the numbers of specimens of urine tested and of positive specimens found by one or more of the three methods used.

Detailed Results of Bacterial Counts

Table XC shows the bacterial state of the urine of 1,934 pregnant women at their first visit to the antenatal clinic according to the bacterial count. The results are arranged according to the organism isolated. Group I comprises coliform organisms only, Group II coliform organisms with other organisms, Group III non-coliform organisms and Group IV sterile specimens. Each of the former three groups, I, II and III is subdivided to show the level of bacteriuria found; that is, over 100,000 organisms per ml. (significant bacteriuria), 10,000 to 100,000 per ml. (suspicious bacteriuria), and under 10,000 organisms per ml. (minimal bacteriuria). It is seen that the largest number of patients, some 70 per cent., produced sterile urine. The next largest number, 17.7 per cent., showed non-coliform organisms in the under-10,000 per ml. level. Thus 88 per cent. of antenatal patients have no evidence of infection at their first visit to the clinic.

The highest number of significant and suspicious bacterial counts was seen in the pure coliform group, whilst coliforms with other organisms accounted for only 1 per cent. of all the specimens.

Type of Organism

Only two patients with significant counts of pathogenic organisms showed organisms other than Gram-negative bacilli. In one the infection was due to Streptococcus faecalis, and in the other to a coagulase-positive Staphylococcus pyogenes. It is thus seen that the coliform organisms as a group occupy a place of special importance in renal-tract infection during pregnancy. Escherichia coli accounted for 80 per cent. of the Gram-negative rod infections, Bacillus proteus for 13 per cent., Bacillus paracolon for 3 per cent., and mixed Gram-negative rods for 4 per cent.

Such was the bacterial state of these 2,521 pregnant women at their first visits to the antenatal clinic. However, bacteriuria during pregnancy is far from being a static condition. The next section deals with natural development of untreated bacteriuria.

B. THE NATURAL DEVELOPMENT OF BACTERIURIA IN PREGNANCY

MATERIALS AND METHODS

One hundred and forty-two pregnant women attending the antenatal clinic at Stobhill Hospital were found to have coliform renal-tract infection. One hundred and thirty-three of these patients showed significant levels of coliform bacteriuria during the antepartum period. These patients gave an average of six specimens each prior to delivery. Patients found to be infected were allocated to two groups, one on long-term chemotherapy and one untreated. The untreated patients and those with minimal and suspicious bacteriuria are the subject of this section.

RESULTS

Incidence of Significant Bacteriuria

The over-all incidence of renal-tract infection was 8.7 per cent. of 2,521 antenatal patients. Table XCI shows the data from which this figure is derived.

Period of Gestation at which Significant Bacteriuria was Found

It is seen in Figure 31 that there is no well-defined peak incidence of infection, and that the percentage of positive specimens bears a close relation to the numbers of patients visiting the clinic for the first time at any given period.

Natural Course of Untreated Gram-negative Bacteriuria

(i) Development of Significant Bacteriuria from Minimal Levels. Of 78 patients with bacterial counts of under 10,000 organisms per ml. at the first antenatal visit, 9 (12 per cent.) subsequently showed counts of over 100,000 organisms per ml. during the antepartum period.

(ii) Development of Significant Bacteriuria from Suspicious Levels. Of 51 patients with bacterial counts of between 10,000 and 100,000 organisms per ml. at the first antenatal visit 33 (66 per cent.) subsequently showed counts of over 100,000 organisms per ml., 29 during the antenatal period, and 4 immediately post-partum.

(iii) Interval from the Detection of Suspicious and Minimal Levels of Bacteriuria to the Finding of Significant Bacteriuria. Thirty-seven patients who were observed during the course of increasing bacteriuria are included in Table XCII. It shows the interval of time elapsing from the finding of lower levels of bacteriuria to the finding of a bacterial count of over 100,000 organisms per ml. It is seen that 2 patients (5.4 per cent.) developed significant counts in less than two weeks, and in the remaining 35 (94.6 per cent.) the interval varied from 2 to over 20 weeks.

(iv) Interval from the Detection of Suspicious and Minimal Levels of Bacteriuria to the Finding of Significant Bacteriuria in Relation to the Initial Bacterial Level. Table XCIII shows the time taken for lower levels of bacteriuria to reach 100,000 organisms per ml.

or more in 36 patients. It is seen that the higher the bacterial count in the initial specimen the sooner does it reach the singificant level.

(v) The Development of Overt Renal-tract Infection. Of 65 patients with significant bacteriuria 32 (49.3 per cent.) showed clinical evidence of renal-tract infection during the antepartum period. The findings are summarized in Table XCIV. Symptoms varied from nocturia, to increased frequency of micturition day and night, dysuria, abdominal and back pain, fever, vomiting and rigors.

(vi) Interval from the Detection of Significant Bacteriuria to the Development of Overt Renal-tract Infection. In 20 patients of the untreated group the development of overt renal-tract infection was observed after the detection of bacilluria. In the 21st patient shown in Table XCIV intermittent chemotherapy interrupted the natural course of the disease. In seven patients allocated to the long-term chemotherapy group, clinical pyelo-nephritis developed before treatment was started. These patients are also included here.

Table XCV shows the interval of time elapsing between the finding of infection and the development of symptoms in these 27 patients. It shows that 5 patients (18.5 per cent.) developed symptoms within two weeks of the detection of significant bacteriuria.

In the remaining 22 patients (81.5 per cent.) the time interval was between 2 and 24 weeks.

DISCUSSION

Gram's stain gave the highest percentage of positive results. This was due to the lack of quantitative definition possible with such a method, where bacterial levels of over 50,000 per ml. are appreciable (Sweeney, 1963) and even over 10,000 per ml. (Ambrose and Hill, 1965). Switzer (1960), Rehm and Fishman (1963) and Goss, Franklin, Hunter and Skogland (1963) accepted stained smears as being reliable screening methods. Cattell and Lefford (1963) stated:

> "There is no reason to believe that research programmes previously carried out are in any way invalidated by failure to use bacterial counts."

The validity of the above explanation is confirmed by consideration of the figures obtained by bacterial count. A four per cent. incidence of positive specimens (organisms over 100,000 per ml.) was obtained from first-visit patients. At subsequent visits however a further 2.2 per cent. was added, giving a total incidence of positive specimens of 6.2 per cent. by bacterial count, a figure very similar to that given by the Gram-stained preparations of 6.4 per cent. Thirty-three of 42 specimens eventually showing significant bacteriuria were originally int the 10,000 to 100,000 organisms per ml. group. Bulger and Kirby (1963)

preferred a Gram-stained preparation to the T.T.C. test in that it is a simple direct examination of unspun urine. In the preparation of the Gram-stained droplets it was noted that where the deposit in the urine was heavy, with numerous organisms and pus cells, part of the specimen was sometimes washed off. It is claimed that this difficulty can be avoided by the use of methylene blue as a bacterial stain (Goss, Franklin, Hunter and Skogland, 1963; Schamadan, 1964).

The T.T.C. test gave an incidence of positive specimens of 4.5 per cent.. By this method, which is more accurate than the other chemical tests at present available, only bacterial levels of over 100,000 per ml. are recognised. At this level it is claimed by its designers (Simmons and Williams, 1962) to be 100 per cent. reliable for coliform organisms, and since almost all cases of renal-tract infection in pregnancy are coliform in origin it should be a suitable test for use at an antenatal clinic. However it does miss those levels of bacteriuria below 100,000 per ml.. This is of importance in the antenatal patient in whom bacterial multiplication may be very rapid, and in particular where it is impractical to obtain a urine specimen from every patient at each visit to the clinic. A test is needed which gives an indication from the first specimen of the need for careful bacteriological follow-up.

Other chemical tests available are the catalase disc flotation test (Braude and Berkowitz, 1961) and the modified nitrite test (the Greiss test) (Smith et al., 1961). These have both been found to give

correlation with positive bacterial counts in less than 50 per cent. of instances, whereas the T.T.C. test in the hands of the same workers (Kincaid-Smith, Bullen, Fussell, Mills and Huston, 1964) detected 86 per cent. ofcases. Greenberg, Stamler, Zackler and Anderman (1965) reported the finding of such irregular results from the catalase disc flotation test that they abandoned it very early in their investigation of the adequacy of methods for the diagnosis of bacteriuria. Hinton and van der Hoeven (1965) obtained a reliability rate of between 70 per cent. and 90 per cent. with the T.T.C. test whilst Seneca and Peer (1965) obtained only 66 per cent. accuracy after four hours, and 75 per cent. accuracy after 24 hours incubation.

For practical routine procedures one must establish whatever test will give the most information from one specimen, and in my experience this is the bacterial count. Greenberg et al. (1965) agree with this stating that

> "Justification for a relatively expensive detection procedure such as quantitative, non-catheterized urine culture obviously depends not only on the wide prevalence of bacteriuria in some populations, but also on its recognized deleterious effect on mother and fetus."

Bacterial counts, as originally performed by the fluid dilution technique, were somewhat time-consuming. With the development of the quantitated loop technique (McGeachy and Kennedy, 1963) and with reporting simplified to "over 100,000 organisms per ml.", as opposed to an exact count, the time taken is considerably less. This type of examination

leads with least delay also to the exact identification of the organism and its drug sensitivities. In addition those specimens with minimal and suspicious bacteriuria are identified. In order to establish any of these three methods of investigation, Gram-staining, the T.T.C. test or bacterial count, as a routine practice for all antenatal patients at their first clinic visit it is necessary to provide a technical service. It would not be worth establishing any method producing less than this information.

It is gratifying that in 88 per cent. of patients no suspicion of urinary tract infection was found. It indicated that the specimens, which were attended to by each patient herself, carrying out written instructions, were adequately clean. It is to be noted that plain sterile water or saline should be used for washing, since antiseptic solutions such as chlorhexidine markedly reduce the bacterial count (Roberts, Robinson and Beard, 1967). The collection of these specimens does not therefore add an impossible load to the work of the nursing staff. The trays used were all set up before the Clinic started, each with the patient's name and the necessary forms made out.

The incidence of renal-tract infection, symptomatic and asymptomatic, was found to be 8.7 per cent. in 2,521 antenatal patients in the present series. Other workers have reported rates varying between 4.4 per cent. (Kaitz and Hodder, 1961) and 11 per cent. (Cavanagh and Sandberg, 1966). Details of other series are shown in Table XCVI.

There thus appears to be a high degree of agreement in various parts of the world regarding the incidence of renal-tract infection in pregnancy.

Gram-negative rods are the most frequent pathogens in pyelonephritis (Kass, 1960; Whitby and Muir, 1961; McGeachy and Kennedy, 1963; Ambrose and Hill, 1965; Bush, Orkin and Winter, 1965; McCabe and Jackson, 1965). In this series of pregnant women they account for a particularly high proportion of cases.

Until now scant attention has been given to the progress of pregnant women with lower levels of bacteriuria than 100,000 organisms per ml. It is seen from the foregoing results that bacteriological follow-up of such patients is of importance. Twelve per cent. of pregnant women showing initial levels of Gram-negative rod bacilluria of under 10,000 organisms per ml., and 66 per cent. of women showing levels between 10,000 and 100,000 organisms per ml. subsequently developed significant bacilluria. The incidence of clinical pyelonephritis arising from significant bacteriuria in pregnancy varies from 40 per cent. in Kass's group (1960) to 60 per cent. in Turner's group (1961) and 50 per cent. in the present study. The time interval between the detection of significant bacteriuria and the onset of clinical pyelonephritis, as shown in Table XCV, indicates that one has the opportunity to eradicate infection before the development of symptoms in most instances. In those patients with lower levels of bacilluria there is an even earlier recognition of the patient at risk.

It would seem therefore, that by positive and prompt follow-up of all antenatal patients with any level of Gram-negative bacilluria, and the administration of chemotherapy as soon as the bacterial count reaches 100,000 organisms per ml., it should be possible to prevent almost all cases of acute clinical pyelonephritis of pregnancy, and to reduce the rate of chronic pyelonephritis in later years.

SUMMARY

The incidence rate of renal infection in pregnancy, symptomatic and asymptomatic, in a group of 2,521 patients at Stobhill Hospital, Glasgow, was 8.7 per cent.

Gram-negative bacilli preponderated as pathogens, and E. coli accounted for 80 per cent. of these infections.

Twelve per cent. of patients with "minimal", and 66 per cent. of patients with "suspicious" levels of Gram-negative bacilluria subsequently developed significant levels of infection. In 95 per cent. of patients this process took over two weeks.

Fifty per cent. of patients with significant bacteriuria developed clinical pyelonephritis. In 80 per cent. of patients this process took over two weeks.

If clean-voided, mid-stream specimens of urine are examined for infection at each patient's first antenatal visit, and all patients with

any level of Gram-negative bacilluria are followed at each visit, it should be possible to reduce considerably the rates of clinically-manifest acute pyelonephritis of pregnancy, and of subsequent chronic pyelonephritis.

Bacterial count by the quantitated-loop technique was found to be the most satisfactory method for the investigation.

C. BACTERIURIA IN PREGNANCY RELATED TO MATERNAL FACTORS

MATERIALS AND METHODS

This section relates to the same 133 pregnant women attending Stobhill Hospital, Glasgow, who were found to have * significant coliform bacteriuria during the antepartum period. Alternate patients with infection were given prolonged chemotherapy. The remainder were left untreated. When the latter developed symptoms they were given a short conventional course of chemotherapy. By the 37th week there were 58 patients with sterile urine and 75 with persistent bacteriuria; among the latter were some patients who had failed to respond to chemotherapy. For certain comparisons a control group of 500 patients was formed by using information relating to approximately every fourth patient whose urine was sterile at the first visit and in whom there was no prior history or subsequent evidence of renal tract infection.

In the postpartum period the incidence of clinical pyelonephritis in the bacteriuric and control groups was compared. Specimens of urine were examined on the third postpartum day, between the second and sixth, and at and after the sixth postpartum week. The groups decrease in numbers as bacteriological examination of the urine on the third day was not established as routine practice until the series was well under way, and is still not the practice after discharge from the wards.

It is not the purpose here to assess in detail the effects of

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* 10^5 organisms per ml.

treatment. Broadly speaking, many of the successfully treated bacteriuric patients ceased to receive chemotherapy on admission in labour. All patients with bacteriuria on the third day after delivery were given chemotherapy for at least one week.

RESULTS

Maternal Age

Table XCVII shows that there was a significantly higher incidence rate of renal tract infection in antenatal patients under the age of 20 years compared with that in patients aged between 20 and 40 years ($p < 0.01$).

Parity

Table XCVIII shows that the highest rate of renal tract infection occurred in those women who were pregnant for the fourth time or more ($p < 0.01$).

Outcome of Previous Pregnancies

Tables XCIX and C are concerned with the outcome of previous pregnancies in the 89 patients with bacteriuria and 320 parous patients with no bacteriuria. Table XCIX shows that there were significantly more mothers who had experienced foetal loss in a previous pregnancy amongst the currently bacteriuric patients than amongst the non-bacteriuric patients. On the other hand the number of infants lost to

each mother was very similar, being 1.42 and 1.48 respectively. Table C shows that significantly more low-birth-weight babies had been previously born to the currently bacteriuric patients, than to the non-bacteriuric women ($p < 0.01$ for both considerations).

Previous Instrumental Delivery.

Nineteen of 89 parous mothers (21.4 per cent.) with bacteriura in their current pregnancy had previously undergone instrumental delivery, compared with only 45 out of 320 (14.0 per cent.) in the non-bacteriuric group. Further, it was amongst those mothers who had Caesarean sections that the increased incidence rate was found. In the bacteriuric group of patients 17 of 89 (19.1 per cent.) had previously undergone Caesarean section, compared with 29 of 320 women (9.0 per cent.) in the non-bacteriuric group. The numbers are statistically significant ($p < 0.02$; > 0.01). Caesarean section therefore appears to be related to subsequent urinary tract infection.

History of Previous Renal-Tract Infection.

Clinical renal-tract infection had occurred previously in 26 out of 133 mothers (19.5 per cent.) found to have infection in their current pregnancy, compared with 18 out of 500 (3.6 per cent.) with no current renal infection. The numbers are statistically significant ($p < 0.01$). In addition to the "patient rate" being higher, the "attack rate" was also higher in the currently affected mothers. These 26 mothers had suffered at least 32 attacks of clinical infection, with 5 patients "never really free" from symptoms. In the control group

the 18 patients each gave a history of only one clinical attack. In the 26 bacteriuric mothers having a history of previous renal-tract infection, 75 per cent. of their attacks had been related to pregnancy (50 per cent. antepartum; 25 per cent. postpartum). In the 18 currently non-bacteriuric mothers with previous clinical infection 90 per cent. of their attacks were associated with pregnancy (40 per cent. antepartum; 50 per cent. postpartum). It appears therefore, that those mothers found to have bacilluria at the time of this study represented those with a tendency to recurrent urinary-tract infection.

Incidence of the Common Complications of Pregnancy.

Clinical evidence of renal tract infection occurred in 32 of 65 (49.3 per cent.) untreated bacteriuric patients. The incidence rates of the other common complications in the bacteriuric and non-bacteriuric patients are compared in Table CI. Pre-eclamptic toxaemia was the only illness showing a highly significant difference, being more frequent in the non-bacteriuric mothers. Iron-deficiency anaemia, and uterine haemorrhage after the 28th week of gestation were rather more frequent in the baoteriuric than the non-bacteriuric mothers.

Renal Tract Infection after Delivery

(i) Incidence of Clinical Pyelonephritis within Seven Days of Delivery.

The patients with clinical pyelonephritis shown in Table CII comprise all those with local or generalized symptoms or signs

which would have led to bacteriological diagnosis of renal-tract infection, had bacterial counts not been routine practice on the third postpartum day.

Table CII shows that the incidence of clinical pyelonephritis was three times greater in mothers who were persistently bacteriuric during the antenatal period than in those mothers from whom bacteriuria was eradicated by the 37th week, and ten times greater than in the non-bacteriuric mothers. All the differences are statistically significant. A more detailed assessment reveals that of those mothers with untreated bacteriuria at the 37th week, 14 received chemotherapy for a variety of reasons between that time and the third postpartum day. This number would otherwise have contributed to the high rate of clinical pyelonephritis in the postpartum period.

(ii) Incidence of Asymptomatic Bacteriuria on the Third Day after Delivery. Table CIII illustrates that over 60 per cent. of patients who were bacteriuric beyond the 37th week of gestation were still significantly infected on the third postpartum day. This figure is ten times higher than that for the patients whose bacteriuria was cleared by the 37th week, and twenty times higher than for those patients who were non-bacteriuric antenatally. All differences are statistically significant. Here again a more detailed assessment shows that of those mothers with untreated

bacteriuria at the 37th week, all 10 patients with sterile urine postpartum had received chemotherapy, for various reasons, between that time and the third postpartum day. This means that the urine did not spontaneously become sterile in any of the patients followed, at least in the early puerperium.

(iii) Incidence of Bacteriuria Two to Six Weeks after Delivery. Table CIV shows the incidence of persistence of bacteriuria between the second and sixth week after delivery in 35 patients who were bacteriuric beyond the 37th week, and 35 patients who were clear by the 37th week of pregnancy. It shows that over twice as many patients showed significant and suspicious levels of bacteriuria in the former group as in the latter.

(IV) Incidence of Bacteriuria at and after the Sixth Postpartum Week. Table CV illustrates the incidence of persistence of bacteriuria at or after the sixth postpartum week in 20 patients who were bacteriuric beyond the 37th week, and 22 patients who were clear by the 37th week of pregnancy. Two-thirds of the former group were still infected, compared with one-third of the latter.

(V) Type of Organism found on Third Postpartum Day. Thirty of 82 bacteriuric mothers who had specimens examined on the third postpartum day had significant bacteriuria. Of these 29 were coliform infections. The urine of the remaining patient showed

a Streptococcus faecalis. Twelve of 336 non-bacteriuric mothers of the control group had significant bacteriuria on the third postpartum day. Only eight of these specimens showed coliform organisms. The remaining patients showed S. faecalis (2) and haemolytic streptococci (2).

DISCUSSION

The age of maximal incidence of renal-tract infection in pregnancy in this series was under 20 years. This group was small and included one patient who had undergone a previous Caesarean section with catheterization, and another who was multigravid. These factors, unexpected in this age group, influenced the results. Most writers agree that pregnant women have a relatively high rate of bacteriuria, and that this high rate persists or increases towards middle age (Kass, 1962; Fry, Dillane, Joiner and Williams, 1962; Jackson, Arana-Sialer, Andersen, Grieble and McCabe, 1962; Carleton, Baker and Richards, 1965). In the present series the incidence rate of bacteriuria increased with the fourth pregnancy. Turck, Goffe and Petersdorf (1962) and Carleton et al. also found an increased rate with multiparity. Since increasing parity tends to run parallel to increasing age these findings are probably dependent on inter-related

factors. Factors predisposing to renal-tract infection in the pregnant woman include hydroureter and hydronephrosis, vesicoureteral reflux (Hutch, Ayres and Noll, 1963), a tendency to incomplete emptying of the bladder in the postpartum period, which may be aggravated in the older parous patient by decreased tone of the pelvic floor, cystocoele and procidentia. This is at a time when the antibacterial activity of the urine is at its lowest (Roberts and Beard, 1965). The nature of this activity is not entirely understood. It is known, however, that urea is bactericidal and bacteriostatic (Schlegel, 1961) and it seems possible that when urinary secretion increases after delivery (Roberts and Beard, 1965) the urea concentration may be sufficiently reduced to allow free bacterial multiplication.

Looking at the previous obstetric behaviour of the bacteriuric patients, compared with the control group, one finds that there were significantly more mothers with foetal and infant loss in the currently bacteriuric group of patients than in the non-bacteriuric group. On the other hand the number of infants lost per mother was not significantly different. Schamadan (1964) also noted this. Kincaid-Smith and Bullen (1965) found that bacteriuric and treated bacteriuric patients produced similar high rates of perinatal loss and prematurity, and thought that the essential disadvantage of these mothers was some basic renal impairment, which predisposed them to bacteriuria, and that the disadvantage was not the infection itself. On the other hand, in

the present series there appeared to be factors producing recurrent loss in individual non-bacteriuric patients, one mother having seven pregnancies and one having five terminating in foetal loss.

It is generally accepted that catheterization brings with it a risk of bladder infection. In this series a history of previous Caesarian section was found to be twice as common in the bacteriuric patients as in the non-bacteriuric patients. This is in all probability because catheterization is more frequent or prolonged than is usual in the patient who is delivered vaginally. In addition there may be more congestion and trauma to the urethra from the same cause as that for which the Caesarian section was necessary, and this has been shown by Cox and Hinman (1965) to predispose to infection. Hunt and Bradley (1966) reported postpartum bacteriuria to be more common in primigravid than multiparous patients, and in patients delivered by forceps, probably on account of the more prolonged and difficult labours in such cases. They also noted an increased incidence in patients who were catheterized on one occasion only. It would seem that the indications for catheterization require review, as does the subsequent management of the patient. Prophylactic chemotherapy or chlorhexidine bladder lavage following catheterization has been recommended (Clarke and Joress, 1960; Slade and Linton, 1960; Martin and Bookrajian, 1962; Gillespie, Lennon, Linton and Slade, 1962; Turck and Petersdorf, 1962; Hannah, 1963). Bacteriological follow-up is mandatory.

The high coincidence of previous clinical attacks of infection of the urinary tract and of bacteriuria during pregnancy indicates that discovery of bacteriuria in pregnancy delineates a fairly clear-cut group of women who are predisposed to recurrent attacks of renal-tract infection, which may progress to chronic pyelonephritis and its sequelae.

The development of clinical evidence of renal-tract infection in relation to bacteriuria has already been discussed. The striking feature in this study is the absence of pre-eclamptic toxaemia and hypertension in the bacteriuric patients. This is not in accordance with the findings of either Peters, Laviettes and Zimmerman (1936), Finnerty, Massaro, Kakaviatos and Chupkovich (1961), or Kincaid-Smith and Bullen. Dixon and Brant (1967) however found no increased incidence of essential or terminal hypertension or of pre-eclamptic toxaemia in their bacteriuric patients.

Iron-deficiency anaemia was twice as common in the bacteriuric group of mothers as in the non-bacteriuric mothers. Giles and Brown (1962) reported a high rate of infection of the renal-tract in anaemic patients who failed to respond to routine administration of iron and folic acid, but found that these patients improved after the eradication of bacteriuria. The mechanism of the anaemia associated with renal infection in pregnancy is obscure. Uterine haemorrhage after the 28th week of gestation was also rather more frequent in the bacteriuric than

non-bacteriuric mothers, and this may be related to increased uterine irritability of either reflex nature from the inflammatory process in the adjacent kidney and ureter (Mitchell and Benson, 1957) or from endotoxin stimulation of the myometrium (Wiederman, Stone and Pataki, 1962). Cavanagh and McLeod (1966) were nevertheless unable to demonstrate any oxytocic effect of lipopolysaccharide E. coli 026.B6 on isolated strips of human myometrium, pregnant or non-pregnant.

Bacteriuria may resolve spontaneously or with minimal chemotherapy after delivery (Low, Johnston, McBride and Tuffnell, 1964). On the other hand the trauma of labour or the need for catheterization often precipitate a patient with previously asymptomatic bacteriuria into a severe clinical attack of pyelonephritis. Other patients continue with asymptomatic bacteriuria, and if no routine bacteriological check is carried out and no appropriate treatment is instituted, may proceed into the future with pyelonephritis. Table CVI shows the high rate of persistent infection following delivery found by other workers. In the present series the same pattern was seen with the frequent occurrence of clinical pyelonephritis in the untreated bacteriuric group during the early puerperium, and, with even greater frequency, asymptomatic bacteriuria. Bacteriuria persisted in one-third to two-thirds of patients. The highest rate was found in thosepatients who were not treated, or were unsuccessfully treated in the prenatal period and given a short course of chemotherapy postnatally. The picture, however, was

significantly improved in those patients who received prolonged chemotherapy during the antenatal period and whose urine was sterile by the 37th week. This emphasizes the importance of diagnosing bacteriuria as early as possible in pregnancy and eradicating it then. Furthermore, there is a strong case for continuing prophylactic chemotherapy through the danger period of labour and the puerperium. If bacteriuria persists despite these measures full investigation of the renal tract is indicated. If investigations show no surgicallyremediable lesion, prolonged chemotherapy may be the only help that can be offered to these patients. It would also be wise to recommend the postponement of further pregnancies until the urine has been sterile for a considerable period of time.

SUMMARY

The incidence rate of urinary tract infection in a group of antenatal patients studied at Stobhill General Hospital, Glasgow, was highest in patients under 20 years of age. The incidence rate of infection increased with the fourth pregnancy.

There were more mothers in the currently bacteriuric group of ante-natal patients who had foetal loss or surviving low-birthweight babies in previous pregnancies than amongst the non-bacteriuric group.

The incidence of foetal loss per mother was the same for the two groups. Previous Caesarian section was twice as common in the bacteriuric group of patients as in the non-bacteriuric group.

There had been previous clinical renal-tract infection in 20 per cent. of bacteriuric patients and in 4 per cent. of non-bacteriuric patients. It was most often related to pregnancy.

The incidence of clinical pyelonephritis was 50 per cent. in bacteriuric mothers. Non-bacteriuric mothers showed pre-eclamptic toxaemia and hypertension more frequently than did the bacteriuric patients. Iron-deficiency anaemia and uterine haemorrhage after the 28th week of gestation were more common in the bacteriuric mothers.

In the immediate postpartum period clinical pyelonephritis occurred ten times more frequently in the bacteriuric than the non-bacteriuric mothers, and spontaneous reversal from infected to sterile urine was not seen. Following discharge from hospital after delivery bacteriuria was again found in 30 per cent. of patients whose urine had been rendered sterile by the 37th week and in 65 per cent. of patients whose urine had remained infected beyond the 37th week of gestation. Long-term chemotherapy in the antenatal period reduced the incidence of bacteriuria in the later puerperium more effectively than a short postpartum course of treatment.

D. DETAILS OF TREATMENT

MATERIALS AND METHODS

A therapeutic study was carried out on the same 133 pregnant women attending the antenatal clinic at Stobhill Hospital, Glasgow, who were found to have urinary-tract infection during the antepartum period. As already described alternate patients with infection were allocated to a long-term treatment group and the remainder left untreated unless they developed symptoms, when they received a short course of chemotherapy. The patients in the long-term treatment group were given an intensive course of the drug being used, followed by a prophylactic dose. In two patients there was resolution of infection without treatment.

In all patients receiving treatment drugs to which the organism was found sensitive in vitro were used. When the urine was not sterile after 14 days of treatment this drug was changed. When bacteriuria recurred after clearing and the organism was reported sensitive to the drug already in use a repeat intensive course was given. If reported insensitive the drug was changed.

Four drugs were used regularly in all but four patients who are not considered further. The drugs used regularly were the short-acting sulphonamides, ampicillin, nitrofurantoin and nalidixic acid. The following dosage was used:-

Sulphadiazine and Sulphadimidine:

Intensive Course: One gram, six hourly for six days, with an alkali mixture and at least four pints of fluid daily.

Prophylactic dose: One gram b.d. up to the time of delivery.

Ampicillin:

Intensive course: 500 mg., eight hourly for 10 days.

Prophylactic dose: 250 mg. b.d. up to the time of delivery.

Nitrofurantoin:

Intensive course: 50 mg. six hourly for 10 days.

Prophylactic dose: 50 mg. b.d. up to the time of delivery.

Nalidixic Acid:

Intensive course: One gram, six hourly for seven days.

Prophylactic dose: Not used.

RESULTS

The Ultimate Course of 127 Patients

Figure 32 shows the ultimate course of these 127 patients following the finding of significant bacteriuria. It is seen that by the time of delivery 83 had received some chemotherapy for urinary-tract infection. In 52 of these (63 per cent.) the urine became sterile and remained so up to the time of delivery. In the remaining one third of treated patients bacteriuria persisted or recurred.

Comparison of the Efficacy of Four Drugs in Eradicating Bacteria from the Urine

Table CVII shows the success rate of eradication of bacteria with each drug. One hundred and seven courses were prescribed for 83 patients. The table shows that the success rate for each drug was very close to 70 per cent., and that no one drug was superior to the other three.

Number of Patients Treated and the Duration of Treatment

Table CVIII shows the number of patients receiving each of the four drugs, the average and the total number of weeks for which each was given, and the longest period over which each drug was administered to one patient. Short-acting sulphonamides, ampicillin and nitrofurantoin were all administered over long periods, whilst negram was used only as a seven-day course in seven patients. No adverse reactions were seen with any of the drugs in the mother or infant.

Apparent Reasons for Failure of Eradication of Bacteria from the Urine

Table CIX summarizes the apparent reasons for failure of these four drugs. The development of resistance, demonstrated in vitro, is the only absolute cause, and was seen in five instances, four with sulphonamide and one with ampicillin. Inadequate dosage or inadequate duration of therapy was blamed in 21 instances. This arose from a variety of causes including failure to impress on the patient the importance of continuing treatment and with the prescribed dose;

inaccessibility of patients who changed their addresses, changed their general practitioners or defaulted from the clinic (or all three); shared medical supervision where no one took the ultimate responsibility for treatment; irresponsibility of the patients themselves. Few assays were done for urinary drug levels and the assessment of unreliability was based on default from the clinic, failure to visit the general practitioner and difficulty of the Health Visitor in making home contact with the patient. In addition some patients were known to have behaved similarly in previous pregnancies, and to have left hospital on their own responsibility. Finally, in two patients thought to be reliable six courses of drugs were used without success.

DISCUSSION

Bacteriological examination of the urine of pregnant women should be carried out as routine practice. All patients with bacterial counts of more than 10^5 per millilitre should receive treatment, and in this way one can avert, in most instances, the development of clinical illness during the antepartum period (Kass, 1960: Little, 1965, 1966; Kincaid-Smith and Bullen, 1965; Patrick 1966).

Success in eradicating bacteria from the urine however is not so frequent. In the present series of patients the urine was rendered sterile and remained so until the time of delivery in only 52 of 83

patients (62.7 per cent.). In the remaining one-third bacteriuria either persisted, or recurred before delivery.

There was little to choose in the efficacy of the four drugs used. This was also the finding of Hibbard, Thrupp, Summeril, Smale and Adams (1967) in pregnant women admitted to hospital because of overt renal-tract infection. They used sulfisoxazole, chloramphenicol, nitrofurantoin and ampicillin. Little (1966) found a 100 mg. dose of nitrofurantoin at night-time effective in clearing bacteriuria in 82 per cent. of infected pregnant women, but noted that relapse occurred when treatment was stopped. Schamaden (1964) found methenamine mandelate with methionine, and methenamine mandelate alone ineffective in treating bacteriuria in pregnancy. Klotz (1965) notes that methenamine mandelate is not effective in dealing with urea-splitting organisms. There is undoubtedly much more to the eradication of bacteriuria than the mere prescribing of a chemotherapeutic agent.

In the present study short-acting sulphonamides, ampicillin and nitrofurantoin were all used over long periods without ill effect on the mother or foetus. Sulphadiazine or sulphadimidine was used as a first choice since this is the agent in the use of which we have the longest experience. Nitrofurantoin was employed in only half as many patients, but again over long periods and without ill effect. The dose of 50 mg. six hourly is lower than that recommended by the makers (Smith, Kline and French) and was prescribed to avoid the risk of the patient stopping the drug on account of nausea and vomiting. Ampicillin is more expensive than either of these. It induced no allergic reactions

and much the same rate of success was obtained. Nalidixic acidhad just been introduced. There was little information regarding its long-term use, particularly in pregnant women, and it was therefore not prescribed as prolonged therapy. No adverse reactions were seen in those patients who received a one-week course.

In Table CIX the apparent reasons for failure of eradication of bacteria from the urine are given. In only five of 32 unsuccessful courses could absolute blame be ascribed to the relationship of the drug and the organism. Sulphonamide resistance developed in four patients and ampicillin resistance in one. Six failures, in two patients, were ascribed to a "difficult lesion". The explanation for the lack of response is not known but it was felt that the infective lesion was probably well established, in that both patients had suffered from overt pyelonephritis in recent pregnancies, and that the lesions were therefore "difficult" ones to treat. Fairley, Bond, Adey, Habersberger and McCredie (1966) noted that ureteric urine was infected in 44 per cent. of women with asymptomatic bacteriuria in pregnancy, and concluded that the kidney was the site of origin of infection. Regardless of whether the kidney was the original or terminal site of infection, it is reasonable to assume that where the upper urinary tract is involved treatment will be more difficult. This is especially so where vesico-ureteric reflux has developed.

In 21 of 32 (66 per cent.) unsuccessful courses of chemotherapy it would appear that failure was due toneither drug nor to the nature of

the lesion, but to human limitations. Essentially these should be preventable. More care in supervision, more receptive and conscientious patients, and a better understanding of the mode of development of renal-tract infection in pregnancy might have reduced their number appreciably.

It has been noted that there is much more to the eradication of bacteria from the urine than the mere prescription of a therapeutic agent. In a later section (F) a review of recent observations on non-obstructive renal-tract infection is made, particularly in relation to uro-dynamics and physical factors rather than to therapeutic agents. These factors have the possibility of clinical application and might enhance the effectiveness of therapeutic agents.

However, in order to complete the findings of the present study without further interruption this section has been held over, and the next section deals with the influence of renal-tract infection on the foetus and infant in these 133 mothers attending the Antenatal Clinic at Stobhill Hospital.

SUMMARY

In the treatment of renal-tract infection in the present series of antenatal patients the four drugs used, the short-acting sulphonamides, ampicillin, nitrofurantoin and nalidixic acid, were of equal value in eradicating bacteria from the urine. The initial over-all success rate

for the four drugs was 70.2 per cent., whilst only 62.7 per cent. of patients showed maintainence of sterile urine up to the time of delivery. No adverse effects were seen. Failure due apparently to human limitations was more frequent than that due to drug resistance or difficult lesions.

E. THE INFLUENCE OF MATERNAL RENAL INFECTION ON THE FOETUS AND INFANT

MATERIALS AND METHODS

Of 133 antenatal patients with coliform bacteriuria of over 100,000 organisms per ml., 75 were known to be infected for periods of from 2 to 28 weeks, with an average of 13 weeks. These patients were still bacteriuric at the 37th week, or at the time of delivery where this occurred earlier. In the remaining 58 mothers bacteriuria was successfully eradicated by prolonged chemotherapy. The urine was sterile by the 37th week and had been so for periods of from 4 to 22 weeks, with an average of 12 weeks. The first part of this Section deals with the incidence rates of abortions, stillbirths, and neonatal deaths in these two groups of patients and in a control group of 500 mothers with no urinary infection in the antepartum period. Prematurity rates are compared for the three maternal groups in respect of infants weighing 2500 g. and less and of under 37 weeks' gestation, 2500 g. and less and over 37 weeks' gestation, and more than 2500 g. but under 37 weeks' gestation.

The second part deals with the possibility of transfer of infection from the mother to the baby. Urine specimens were collected from the babies after careful local washing of the infant with sterile water, thorough drying, and the application of a Chironseal bag (Down Bros. and Mayer and Phelps Ltd.). Bacterial counts by the quantitated loop

technique were carried out by the Bacteriology department, Stobhill Hospital. Counts over 100,000 organisms per ml. were regarded as constituting significant infection. Amniotic fluid was obtained by Drew-Smythe catheter in 16 cases, by abdominal amniocentesis in two and at the time of spontaneous membrane rupture in one. Gram-stained smears were prepared and the remaining fluid was cultured. Umbilical cord blood was obtained by needle puncture of the vein and injection into standard blood culture media. Sections of placentae and cords were prepared by the Pathology Department, Stobhill Hospital, by routine methods. The numbers of specimens examined are shown in Table CXIV.

RESULTS

Foetal and Infant Loss

Table CX shows the numbers of abortions, stillbirths, and neonatal deaths in the three groups of patients: 75 essentially-bacteriuric patients, 58 successfully-treated patients, and 500 mothers with sterile urine in the antepartum period. It shows that there was no significant difference in the abortion or stillbirth rates in the three groups of mothers. Neonatal deaths, however, were significantly more frequent in both the bacteriuric and treated bacteriuric mothers than in the control group ($p < 0.01$ for both comparisons). There was no significant difference in the number of neonatal deaths amongst the bacteriuric and the sucessfully-treated mothers.

Low Birth-Weight and Short Gestation Babies

Table CXI illustrates the incidence rates of low birth-weight and/or short gestation babies in the same three groups of mothers. Statistical analysis shows that there is no significant difference in incidence rates of babies at a disadvantage in mothers with bacteriuria, with successfully-treated bacteriuria, and in non-bacteriuric mothers. Further, by lightening the groups by removal of babies of low birth-weight associated with pre-eclamptic toxaemia, there is still no significant difference.

Congenital Defects.

Table CXII shows an analysis of the type of congenital defect present in this series of cases. Since the developmental processes concerned were already complete by the time these patients were first seen, it is reasonable and convenient to consider all the bacteriuric mothers together.

It is seen in this table that congenital defects were more frequent amongst the infants of bacteriuric than non-bacteriuric mothers, and further, that while the nature of the defect was varied in the latter group, five of seven infants in the former group showed abnormalities of dorsal mid-line fusion. Four defects (3 per cent.) in the infants of the infected mothers were lethal, compared with three (0.6 per cent.) in the non-infected mothers ($p < 0.01$).

Evidence of Transfer of Infection from Mother to Baby

Neonatal Bacteriuria and Clinical Pyelonephritis. Table CXIII shows the incidence of significant coliform bacteriuria on at least one occasion in the infants of 41 mothers of the bacteriuric group, 28 mothers of the successfully-treated bacteriuric group, and 29 non-bacteriuric mothers. The infants of non-bacteriuric (control) mothers showed no significant coliform bacteriuria, whereas those of both the persistently bacteriuric and the successfully-treated mothers showed significant levels of bacteria in their urine and there was no significant difference in its incidence in these two groups (p 0.70 0.50).

Clinical pyelonephritis was seen in four (3 per cent.) of the above infants of 133 bacteriuric mothers, and in one (0.2 per cent.) of 500 infants of the non-bacteriuric mothers. Three of the four cases occurred in infants of the 58 mothers whose bacteriuria was eradicated by the 37th week of gestation, and the remaining case occurred in a mother who was bacteriuric at least during the last 12 weeks of pregnancy and into the puerperium.

Amniotic Fluid Infection Eight specimens of amniotic fluid were obtained from mothers who were bacteriuric beyond the 37th week of gestation. In four of these specimens coliform bacilli were found on examination of Gram-stained smears (Figure 33). E. coli was grown on culture in three, and in the fourth the receptacle for collection of amniotic fluid was accidentally contaminated with chlorhexidine cream,

and no growth occurred. Three specimens of amniotic fluid were obtained from bacteriuric mothers whose urine was sterile by the 37th week of pregnancy, and eight specimens from non-bacteriuric mothers. They showed no organisms in Gram-stained smears, and no growth on culture.

Umbilical Cord Blood Infection. Umbilical cord blood was cultured from 19 mothers with bacteriuria beyond the 37th week of pregnancy. Six of these produced a growth of E. coli, and in four of these the growth was described as heavy. Twelve specimens were cultured from mothers whose bacteriuria was eradicated by the 37th week. Of these, two specimens showed a growth of Esch. coli, and both were described as heavy. Twenty specimens of cord blood were obtained from non-bacteriuric mothers and all were sterile.

Infection in Placentae and Umbilical Cords. Seventeen placentae and cords were examined for evidence of infection in the form of leucocytic infiltration. Five of these belonged to the mothers whose bacteriuria persisted after the 37th week of gestation. One cord showed leucocytic infiltration outwith the normal limits (Figures 34 and 35) and one showed scanty leucocytes not considered to be significant. The remaining speciments were of normal appearance. Twelve placentae and cords were obtained from the group of mothers whose bacteriuria was eradicated by the 37th week. One placenta showed scanty leucocytes in one area only, and one showed an abscess (Figures 36, 37, 38 and 39). Three umbilical cords showed areas of haemorrhage, and in one this was accompanied by

leucocytic infiltration. The remaining specimens appeared normal. Placentae and cords from 12 non-bacteriuric mothers were examined: 11 showed no abnormality, but in the 12th there were small areas of polymorph infiltration in the placenta. In none of these mothers were the membranes ruptured for more than eight hours before delivery. Table CXIV summarizes the results of examination of the above specimens of amniotic fluid, umbilical cord blood, placentae, and cords for infection.

DISCUSSION

Prematurity is taken by most authors to mean infants of 2500 g. or less at birth. Kass (1962) reduced the high rate of 25 per cent. to 10 per cent. by eradication of bacteriuria with prolonged chemotherapy. Henderson, Entwisle, and Tayback (1962) and Kincaid-Smith and Bullen have confirmed the finding of an increased prematurity rate, but the latter workers were unable to reduce this by eradication of bacteriuria. Neither Kaitz and Hodder (1961), Turck, Goffe, and Petersdorf (1962), Monzon, Armstrong, Pion, Deigh, and Hewitt (1963), Schamadan (1964), Bryant, Windom, Vineyard and Sanford (1964), Hipple and Schulman (1965) Little (1966), Wilson, Hewitt and Monzon (1966) nor Dixon and Brant (1967) have been able to demonstrate an increased prematurity rate. It

is probable that prematurity differs in both aetiology and frequency in various parts of the world, and in Glasgow acute renal infection appears to play no significant part in its incidence; nor was there any evidence of progressive hypertensive renal disease in this group of patients.

Little has been said of renal-tract infection as a cause of spontaneous abortion in human beings. Dixon and Brant found no increased incidence. Experimentally it has been shown that coliform endotoxin can produce widespread necrosis, which, in pregnant rabbits includes the placenta (Lansing, 1963). In this study the incidence rate of abortions in bacteriuric patients was no greater than in the non-bacteriuric patients. It is felt, however, that this is not a suitable group for such a study. The assessment of the rate of renal-tract infection in a group of aborting women would give a more reliable picture.

In the present study the notable feature is the increased neonatal death rate. Kass (1962) noted an increase in perinatal mortality in his bacteriuric mothers and stated that this was due to such conditions as prematurity and hyaline membrane disease.

This pattern was not seen in the present study. The increased neonatal death rate was accounted for by defects of dorsal mid-line fusion, which were found in 3.8 per cent. of the infants of the bacteriuric women. Kalter (1963) quotes the highest combined rate for anencephaly, spina bifida and hydrocephaly as 1.27 per cent. The incidence in other series is shown in Table XXIV of Part I. Such

defects occur between the second and eleventh weeks of gestation, before antenatal care is sought, and while one cannot say that these mothers were bacteriuric at this time one cannot be sure they were not, especially in view of Kass's finding (1960) of bacteriuria in the first two months of pregnancy. These defects were not the result of chemotherapy for urinary-tract infection. It is possible that in anencephaly associated with maternal renal infection the damage is done by the effect of endotoxin on the chorionic villi, or by direct action on the foetal cells themselves. Direct bacterial action is possible but seems less likely. Anencephaly and spina bifida are associated with birth order, possibly with a little increase in first-borns, and a definite increase after the sixth-born (Kalter, 1963); this would be in keeping with the finding in the present study of an increased incidence rate of bacteriuria in the multiparous mothers. In addition, it is well known that anencephaly tends to repeat itself in subsequent pregnancies, as does urinary-tract infection. A prospective study looking for maternal bacteriuria, bacteraemia, and circulating endotoxin during the first 8 weeks of pregnancy would be of great interest in this respect, and there is room for much work in the field of experimental teratology.

In 1930 Kobak suggested that foetal bacteraemia, without ill effect, could arise from infection in the maternal blood. In 1958 Osborne reported the finding of E. coli in the alveoli of stillborn infants with intra-uterine bronchopneumonia. He said "it is quite

certain that rupture of the membranes is not necessary" but suggested that the sequence of events might be pyelitis in the mother with transplacental transfer of organisms into the liquor, and subsequent infection of the foetus. Robinson, Krause, Johnston, and Zwicker (1965) described one case of foetal involvement as a result of maternal bacteraemia, and they said 'the placenta was no barrier', and Krafft, Haberman, and Montgomery in 1963 regarded maternal genito-urinary infection 'including vaginitis, cystitis, and/or pyelonephritis' as a possible cause of sepsis in the newborn. Kunin, Zacha, and Paquin (1962) described clustering of urinary infections in families, and it is possible that the common source may have been the mother. Mou and Feldman (1962) reported persistent significant bacteriuria in more than one member in eight of 107 families. On the other hand, Sweet and Wolinsky (1964) described an outbreak of urinary-tract and other infections in a premature nursery, stressing the infectious nature of E. coli. That intermittent bacteraemia occurs in the course of pyelonephritis is an established fact, and that this can involve the foetal circulation seems quite possible. Coliform organisms appear to have a special predilection for renal tissue, and may either be excreted from here into the amniotic fluid, from which they can reinfect the foetus, or initiate an intrauterine pyelonephritis.

The incidence of asymptomatic urinary-tract infections in the newborn is still uncertain. Special considerations regarding bacterial counts appear to be required in newborn infants. It is felt

by the author that a high bacterial count in a small infant, unlike that in a pregnant woman, is open to considerable suspicion of contamination. This is so particularly in boys when the preputial skin cannot be retracted, where there is delay of over an hour between the cleaning of the mucosa and passing of urine, and where the volume of the specimen is small. It is possible that a Gram-stained drop preparation of fresh urine might be invaluable in infants. While most of the urine specimens for this study were collected with the above factors in mind, one must admit that the control group was collected towards the end of the series, and that the technique used may have improved. This is the only doubt as to the reliability of the findings regarding bacteriuria in the babies of this study.

Having found bacteriuria one must consider its significance in the newborn infant. It is possible that significant bacteriuria can exist without the kidneys becoming involved. Thrupp, Cotran, and Kass (1964) have described an adult with persistent bacteriuria, who came to necropsy for other reasons, and in whom no renal lesion could be made out. In 1963 Cotran, Strupp, Hajj, Zanguill, Vivaldi and Kass reported experimental work in rats as showing that

> "In retrograde urinary infections pyelonephritis of a wide range of severity may be produced by varying the infective organism, and in infections with a relatively avirulent organism persistence of bacteria in the urinary tract may not be necessarily associated with significant renal lesions"

They consider it possible that a similar situation exists in man where there is persistent bacteriuria in the absence of a demonstrable renal lesion. It is known that infants can have asymptomatic bacteriuria, and that some of these develop clinical pyelonephritis within weeks or months (Lincoln and Winberg, 1964). Lich, Howerton, Goode, and David (1964) have examined 26 normal newborns and found no evidence of vesico-ureteral reflux, but, in two infants with infection reflux was demonstrated. It is known that in dogs infection alone can cause reflux (Schoenberg, Beisswanger, Howard, Klingenmaier, Walter and Murphy, 1964), and it may be that while many infants with asymptomatic bacteriuria can clear their infection quickly, a smaller number develop vesico-ureteral reflux and thence clinical pyelonephritis.

Stroup (1962) was unable to demonstrate any convincing evidence of amniotic fluid infection in 52 patients from whom specimens were obtained by amniocentesis or by Drew-Smythe catheter. In the present series the results were felt to be reliable, especially in that Gram-stained smears were positive as well as cultures. Both series are small. In the present study cases were selected in that they were known to have renal-tract infection, whereas Stroup's group were unselected and may by chance have included no case of maternal bacteraemia.

Emig, Napier, and Brazie (1961) found inflammation in 13.3 per cent. of a series of placentae and umbilical cords. This they associated

with membrane rupture of over 12 hours before delivery, and found inflammation of the birth canal in 50 per cent. of these patients. In the present study none of the patients had membrane-rupture of over eight hours before delivery, and yet leucocytic infiltration and an abscess was found. Robinson et al. found a 14 per cent. incidence rate of inflammation of cord and placentae, and in two cases they were able to demonstrate bacteria by Gram-staining. In these patients, however, infection was considered to originate in the vagina.

From what has been said it appears that there is a growing feeling that foetal bacteraemia can result from maternal bacteraemia, and that the placenta should be regarded perhaps not so much as a barrier as a transfer system. The matter of acquisition of coliform infections is of importance particularly in the infant. Neumann and Pryles (1962) state that a much higher index of suspicion is required in infants since in 1999 autopsies only 17 per cent. of pyelonephritic lesions were diagnosed antemortem. In the remainder under 16 years of age only one-third were diagnosed. Spark, Travis, Dodge, Daeschner and Hopps (1962) reported a 2.6 per cent. incidence of histologically significant pyelonephritis in 335 autopsies in patients aged between one day and 10 years.

The results of childhood infection can vary from complete clearance to death from uraemia within a few years. Innes, Williams and Sturdy (1961) state that in girls

"With each attack of pyelonephritis destruction and scarring of renal parenchyma becomes more extensive, and although symptoms of urinary infection disappear, loss of renal substance may be severe and precipitate renal failure much later in life - particularly if infection is reactivated as often occurs in pregnancy."

Steel, Leadbetter and Crawford (1963) reported on a follow-up study of 133 children with urinary tract infections between 1940 and 1950. Their results are impressive. They report 18 per cent. dead, 22 per cent. with persistent infection, and 8 per cent. with progressive renal insufficiency. Fifty-two per cent. only were found to be well. They found that "the severity of symptomatology in childhood is poorly correlated with the ultimate course", and the mortality to be inversely related to age at the time of onset. At under two years of age the outlook was especially grave. Further they found that the "incidence of toxemia and urinary-tract infection in surviving females was usually high in pregnancy".

If the mother passes on coliform infection to the foetus, as would seem to be the case, then there is the opportunity at this time to reduce foetal and neonatal urinary-tract infections, which are thought to have such a hazardous prognosis. Plainly this investigation should be extended both in numbers and design.

SUMMARY

Abortion, stillbirth, and prematurity rates were not increased in bacteriuric patients, whether or not this persisted throughout pregnancy or was eradicated by prolonged chemotherapy, when compared with a group of non-bacteriuric antenatal patients at Stobhill General Hospital, Glasgow.

The neonatal death rate was significantly increased in the bacteriuric mothers as a whole, and this was mainly due to defects of dorsal mid-line fusion.

Asymptomatic bacteriuria and clinical pyelonephritis were significantly more frequent in the infants of bacteriuric mothers as a whole, compared with those of non-bacteriuric mothers.

Evidence of infection, to suggest that maternal bacteraemia can involve the foetus, was found in amniotic fluid, umbilical cord blood, placentae, and cords.

F. Review of Recent Observations on Non-obstructive Renal-tract Infection with Special Reference to their Relevance to Treatment

It is know that chemotherapy will eradicate bacteria from the urine in from 60 per cent. to 90 per cent. of patients over a short period of time (De Luca and Fisher, 1963; Murdoch, 1964; Mond, Percival, Williams and Brumfitt, 1965; McCabe and Jackson, 1965). The long-term success rate is considerably smaller, being between 10 per cent. and 50 per cent. (Kass, 1955; McCabe, Jackson and Grieble, 1959; McCabe and Jackson, 1965; Turck, Anderson and Petersdorf, 1966). In the series of pregnant women described in this thesis the rate of eradication of bacteriuria from the start of treatment to the time of delivery was 62.7 per cent. This illustrates the limitations of what can be achieved by prescribing a drug for an out-patient. It seems probable that by administering a drug in hospital one would achieve better results, as illustrated by the study of Hibbard, Thrupp, Summeril, Smale and Adams (1967) who report a success rate of approximately 90 per cent. This leads one to consider how much more effective chemotherapy could be if one appraised and applied correctly the observations relating to urinary-tract infection appearing in medical literature in recent years. These observations have therefore been collected together here, and some conclusions reached which may be of value as adjuncts to chemotherapy.

The view now gaining increasing weight is that pyelonephritis in the non-obstructed urinary tract is most often associated with

ascending infection from the urethra (Hodson and Edwards, 1960; Kass, 1960, 1962; Rosenheim, 1963; Hanley, 1965; Williams, 1965; Klotz, 1965; Hinman, 1966). The situation could be represented like this:-

urethra ⇋ bladder ⇋ vesico-ureteral valve ⇋ ureters ⇋ renal pelvis ⇋ parenchyma

That is, there can be free flow of urine both down and up the renal tract under certain conditions. Maintenance of infection in the kidney is probably the result of re-seeding of the renal pelvis from infected urine (Jackson, Arana-Sialer, Anderson, Grieble and McCabe, 1962; Zangwill, Porter, Kaitz, Cotran, Bodel and Kass, 1962). On the other hand blood-borne infection may arise from pyelonephritis and re-infect the kidney.

Hinman states that the organisms are the normal urethral flora. Access to the bladder is gained in the following way: the patient, for one of several reasons may be unable to relax the external urethral sphincter through upset of the vesico-trigone-urethra mechanism. This may result from congenital abnormality in the urethra or bladder, of bruising or congestion as a result of sexual intercourse, normal or prolonged labour or delivery by forceps. These are all capable of producing difficulty in voiding, leading to turbulent flow or regurgitation of urine which results in the entry of considerable numbers of organisms into the bladder. It is noteworthy that Cox and Hinman (1961, 1965) showed a normal bladder to

be capable of satisfactory clearance of E. coli in from six to nine hours of retrograde injection, and complete clearance by 72 hours. Catheterization results in the introduction of urethral organisms into the bladder and since it is most often carried out to relieve difficulty in voiding, as in the postpartum woman, large numbers of organisms are pooled in the bladder.

The bladder depends on three main mechanisms for defense against infection. The most important of these is the frequency of voiding (Hinman and Cox, 1966) in that this reduces the bacterial population before there is time for gross multiplication. Whalley (1967) states that the doubling time for E. coli is one half hour only. Other factors of importance in the elimination of bacteria from the bladder are the urinary volume and the volume of residual urine. The larger the urinary volume the greater is the dilution of bacteria, and a large urinary volume can thus counterbalance to some extent the adverse effect of residual urine. Kass (1955) and Roberts, Robinson and Beard (1967) reported that a high urinary flow markedly decreases the bacterial count. The latter workers say the degree of forced diuresis necessary to achieve an appreciable reduction is achieved by the drinking of 1 litre of water. Kass (1955) stated that bacteriostasis is achieved with a urinary dilution of 1.003 and a pH of less than 5.5, or more than 8.5. It is interesting to note that in one patient of my series in whom there was resolution of infection without chemotherapy the daily intake of milk alone for

the last six weeks of pregnancy was four pints, during which time the urine became sterile. It would seem perhaps that 2400 ml. of milk is just as effective as 1000 ml. of water. In addition the large urinary volume will increase the frequency of voiding. Residual urine acts as a continuous inoculum for the perpetuation of infection. Hinman and Cox have shown that the "normal" residual urine in the bladder amounts to 0.5 ml., and that 4.8 ml. will "just maintain the bacterial population in a subject voiding 300 ml. every three hours". Further, residual urine detracts from therapy by retarding attainment of optimal drug levels and decreasing elimination of bacteria arrested in multiplication. More than this, it allows the "selective propagation of drug-resistant mutants" (McCabe and Jackson, 1965). The experimental introduction into the bladder of foreign bodies such as glass beads (Cotran, Thrupp, Hajj, Zangwill, Vivaldi and Kass, 1963) and paraffin wax bodies (Sommer and Roberts, 1966) helps to maintain infection and this probably applies to the presence of stones or fibrinous exudate in the infected human bladder. Both tend to perpetuate the infection which induced their development (Prat, Benesova and Cervinka, 1961; Fairley, Bond, Brown and Habersberger, 1967).

The establishment of infection in the bladder is also dependent on the virulence of the infecting organism and its response to treatment. Cotran et al. state that retrograde infection with E. coli is mild, whereas with B. proteus it is more severe.

Kleeman, Hewitt and Guze (1960) and Shubin and Weil (1963) also noted that proteus infections are more severe than those due to E. coli. McHenry, Martin and Wellman (1962) and Watt and Okubadejo (1967) note that pseudomonas infections have the highest mortality rate from endotoxin shock. Brumfitt and Percival (1964) consider that there may be "pyelopathic" strains of E. coli, and Sweet and Wolinsky (1964) that some strains are more infectious than others. Fairbrother and Garrett (1960) and Bush, Orkin and Winter (1965) found proteus infections particularly refractory to treatment, and the former workers also found Pseudomonas pyocyanea refractory. Kleeman et al. stated that proteus and pseudomonas infections are related to instrumentation, surgery or previous drug treatment. Bush et al. consider the persistent rise of increasingly refractory proteus infections to be due to "excessive use of antibiotics and the persistent hospital reserve of infection". Transferable "R factors" are described as a character of enteric bacilli by Smith and Armour (1966), being the episomes on which are carried genes which mediate resistance to various antibacterial drugs. These can be transferred to other bacteria by conjugation, producing the infectious transfer of drug resistance and thus refractoriness to chemotherapy.

The development of vesico-ureteral reflux in the presence of bladder infection alone has been demonstrated in dogs by Schoenberg, Beisswanger, Howard, Klingenmaier, Walter and Murphy (1964).

It is characteristic of proteus infections in this animal that reflux is more likely to develop than in infections with E. coli, and tends to clear up when bacteriuria is eradicated with drugs (Sommer and Roberts). In newborn infants Lich, Howerton, Goode and Davis (1964) have shown reflux in two infants with urinary-tract infection but none in 26 healthy infants. In pregnant women Hutch, Ayres and Noll (1963) have demonstrated reflux and subscribe to the idea that "the dilated upper urinary tract in the pregnant woman becomes infected by reflux of infected urine from the bladder". Further, Sunshine (1964) demonstrated in guinea pigs that it was only with chronic infection in the bladder that reflux developed, and concluded that "the intact uretero-vesical valve protects the upper urinary tract from a localized bladder infection". Hydronephrosis could not be induced in dogs by increased hydrostatic pressure alone, produced by gravity-fill, in the experiments of Ross and Thompson (1963). However with a primary incompetent valve as described by Hutch, Miller and Hinman (1963), or with a valve rendered incompetent by inflammation, vesico-ureteral reflux occurs. Reflux in the upward direction from the bladder to ureter is important in that the upper urinary tract is thus contaminated with infected bladder urine. The return flow of this refluxed urine from ureter to bladder after the end of micturition is of equal or more importance in that, at the time when the bladder should be empty of urine and clear of organisms, it receives this heavily infected urine which is then in effect residual urine. The situation is as bad as, if not

worse than, that in obstructive uropathy.

Williams (1962) has found that in patients with complete duplication of the ureters pyelonephritic changes are confined to the lower pole which is always served by a ureter with a short intramural course in the bladder, resulting in incompetence and reflux. Ambrose and Nicolson (1964) also noted the distribution of pyelonephritis in 29 patients with duplicated ureters to be "sharply confined" to the renal parenchyma served by the refluxing ureter, strongly supporting the ascending infection theory.

Originally it was thought that progressive renal parenchymal damage resulted from reflux alone or that reflux resulted only from lower urinary tract obstruction. Nicolai (1964) however has shown much more rapid progression of hydronephrosis in partially obstructed rabbit kidneys in the presence of infection than in non-infected controls, and Williams and Fowler (1963), using renal biopsy material, have shown that infection and not reflux alone is necessary for progressive renal damage in children. Ross and Thompson state that the combination of reflux and infection remains a "continuing hazard to the kidney". Ekman, Jacobsson, Kock and Sundin (1966) have added a useful observation to the problem of reflux in that they demonstrated the abolition of, or significant decrease in, reflux in 15 of 29 patients in whom high diuresis was induced by intravenous mannitol infusion.

The renal pelvis lends itself to infection by the state of

relative stasis of urine in this area. Localized pyelitis seldom exists. Infection is invariably disseminated to the renal parenchyma (Weiss and Parker, 1939; Hutt, Chalmers, MacDonald and de Wardener, 1961) being at first in the area adjacent to the most severely affected part of the pelvis. Subsequently suppuration occurs, in unpredictable distribution and amount (Robbins, 1967). It is known that bacterial multiplication occurs freely in the renal medulla. It is thought this may be due to diminution of complement activity through destruction of the fourth component of complement by ammonia (Beeson and Rowley, 1959). The cortex is more resistant to invasion with bacteria, probably as a result of its more liberal blood supply. Once this state of affairs has been reached it seems probable that infection is perpetuated by spread of organisms locally, and from the urine and the blood.

The mode of <u>transition to chronic pyelonephritis</u> raises problems. It has been claimed that chronic pyelonephritis can be well-advanced without any history of acute urinary-tract infection (Kimmelstiel, Kim, Beres and Wellman, 1961). This view is losing ground in face of the increasing frequency with which lower urinary-tract symptoms are found to have been present in such patients (Smellie, Hodson, Edwards and Normand, 1964; Hanley, 1965). Weiss and Parker (1939) and Kass (1960) maintain that continuing bacterial multiplication in renal tissue is necessary for the development of destruction and scarring which are associated with

hypertension and increasing renal insufficiency. On the other hand Kimmelstiel et al. and Jacobson and Newman (1962) postulate abacterial progression of the lesion, perhaps in the form of auto-immunity. To find an explanation of increasing renal insufficiency one perhaps need only postulate renal infection causing hypertension, leading in turn to progressive renal vascular damage, reduction in effective nephrons and decreasing functional flexibility. It is known however that the superimposition of an attack of acute pyelonephritis in a patient with recognized chronic pyelonephritis can produce disastrous results (Williams and Sturdy, 1961; Bulkley, 1961; Hanley, 1965). In such patients with uraemia, fatal Gram-negative bacteraemia is likely to occur. Dysplasia of renal tissue has been postulated as a cause of the changes found in chronic pyelonephritis and seems likely to apply to children. Persky (1965) says "it is possible when one sees the pyelonephritis scarred kidney in childhood one is observing the effects of dysplasia and maldevelopment, rather than the ravages of pyogenic infection". Porter and Giles (1956), Kleeman et al. and Lincoln and Winberg (1964) also incline to this view. In the renal biopsy study of Willams and Fowler (1963) however, evidence of dysplasia and maldevelopment was found to be "inconspicious" in childhood cases.

Lasting <u>immunity</u> from renal tract infection in the human being does not appear to develop as a result of an attack.

Rather, the reverse is true, in that once a kidney has been infected it is more likely to suffer further attacks of infection. Antibody has been shown to develop in children during infection of the renal parenchyma (Winberg, Anderson, Hanson, and Lincoln, 1963). In lower urinary-tract infection the development of antibody was not seen. Sanford and Barnett (1965) succeeded in producing protection, in rats, by pre-immunization prior to the induction of pyelonephritis with Gram-negative organisms. They state that immunity is not of importance in recovery, but may help to determine the organisms involved in re-infection. McCabe and Jackson state that the more time that passes from the date of a renal infection the less is there likely to be recurrence, implying that this "propensity to acquire new infections may be reversible".

Before leaving the subject of the kidney and recurrence of infection the possible existence of cell-wall-deficient bacteria, known as "protoplasts" (Kalmanson and Guze, 1964) "L-forms" (Gutman Schaller and Wedgwood, 1967), "variants" or "spheroblasts" must be mentioned. These forms are said to have been isolated from the kidneys and urine of patients with chronic infection, by use of special culture media. The bacteria become spherical, "often filterable, by the action of lysozymes, leucocyte granules, colicine, antibody and antibiotics". They change their antibiotic sensitivity pattern in that they become resistant to those drugs which act by interference with the bacterial cell wall (Guze and Kalmanson, 1964).

They remain, for instance, erythromycin-sensitive since this drug acts by inhibition of protein synthesis. They are able, it is thought, to revert to their original bacterial form. The high osmolarity of the urine in the renal medulla, where there is known to be phagocyte inhibition, is claimed to protect these forms (Andriole and Epstein, 1965). Nevertheless, Gutman, Turck, Petersdorf and Wedgwood (1965) state that L-forms should not be considered as a cause of chronic disease unless more obvious causes have been excluded.

Various other host factors influence the establishment of infection in the renal tract. Most of these relate to inherent properties of the urine or the bladder. Hinman and Cox noted in their experiments that bacterial levels in vivo were lower than in vitro, "suggesting an intrinsic defence mechanism". Kleeman, et al. also consider that there are antibacterial properties in the urine, and that these are sometimes reduced in diseased states. It has been observed by Roberts and Beard (1965) that the urine of pregnant women supports bacterial multiplication much better than that of the non-pregnant woman and that this property is especially marked immediately after delivery, and returns to normal at the sixth post partum week. At the time when it supports bacterial multiplication best the urinary secretion is increased by one third over antepartum levels and should have the effect of diluting the bacteria. On the other hand the volume of residual urine has been shown by Roberts and Beard(1965) to be greatest on the second day, which detracts from the effect of

bacterial dilution. All this occurs when the upper urinary tract is atonic.

Even in the non-pregnant woman the urinary pH and osmolality is more often at optimum levels for multiplication of E. coli than in the male and it is the early morning specimen which is the least inhibitory (Assober, Sussman, Waters, Davis and Chick, 1966). Kass (1955) and Roberts, Robinson and Beard (1967) have found the highest bacterial counts in the early morning specimen. It has been shown that the amount of urea in "normal concentrated urine" is bacteriocidal to most Gram-negative organisms (Schlegel, Cuellar and O'Dell, 1961) and it seems possible that the reverse situation is seen where there is polyuria as in diabetes mellitus, or in patients with renal decompensation, who are known to be at special risk of recurrent renal infection. Plainly the polyuria of these two conditions does not reduce the bacterial count as does that of forced diuresis. This predisposition to recurrent and refractory renal-tract infection is also associated with the inability of the kidney to concentrate drugs to effective urinary levels. Campanacci, Bonomini and Zucchelli (1963) noted this tendency to resist treatment where the creatinine clearance was more than a little reduced. In 1961 Schlegel noted that instrumentation and catheterization in the patient with already diseased kidneys or kidneys which had already been infected, were more likely to produce infection than in the patient with healthy kidneys. Shapiro (1963) thinks that the relationship between pyelonephritis and hypertension may be an increased susceptibility to pyelonephritis in the

hypertensive subject rather than the reverse. In support of this McCabe and Jackson found more re-infection in their hypertensive than in their normotensive patients. Smythe (1961) wrote "patients with resistant organisms, advanced chronic renal disease and many complicating factors are less likely to respond (to treatment) than younger individuals who have no urologic lesion, good renal function, and no complicating factors". Thus there is a good deal of evidence to suggest that the primarily diseased kidney is easily infected, contrary to the theory that infective process comes first. Nevertheless there is increasing evidence that superimposed infection in the damaged kidney is the factor which determines progressive renal decompensation.

Principles of Treatment

In non-obstructive urinary-tract infection of ascending type the first aim should be prevention, and where this is not possible steps should be taken to avert or arrest the danger where it is known to lie.

Routine bacteriological examination of the urine should be carried out in groups especially at risk of infection, such as pregnant women, hypertensive patients, women who have undergone prolonged or instrumental delivery or Caesarian section, patients who have been catheterized either "routinely" or on account of retained urine, and in addition neonates, girls and diabetics with any obscure illness or with symptoms directly referable to the urinary tract. Early, adequate treatment is of importance in eradicating bacteria. Delay in diagnosis and chronicity increases the difficulty (Kass, 1959; Arana-Sialer, Anderson, Grieble and McCabe, 1962; De Luca and Fisher, 1963, McCabe and Jackson, 1965).

Prevention of infection from catheterization can be achieved better by local bladder antiseptics than by systemic antibiotics. Kass (1955) stated that a systemic antibiotic only changed the organism. Martin and Bookrajian (1962) found chloramphenicol unhelpful. Turck and Petersdorf (1962) however found their postpartum patients were helped by sulphamethoxypyridazine. Polybactrin spraying was used by McLeod, Mason, and Pilley (1963) and by Paterson (1960) for single catheterizations, but Gillespie, Lennon, Linton and Slade (1962) found installation

of chlorhexidine solution in the bladder more effective than antiseptic lubricants. Martin and Bookrajian and Hodari and Hodkinson (1966) used neomycin and polymixin solutions for lavage, whilst Hannah (1963) used chlorhexidine di-acetate 1:20,000 as a bladder-lavage solution for patients with catheters in situ, and on closed drainage with a two-way catheter, lavage being carried out several times daily. With a single catheterization or with multiple catherizations terminal chlorhexidine or neomycin (2 per cent.) lavage appears to be satisfactory.

In 1895 Fenwick wrote that "if pus appears (in the urine) as a result of a simple catarrh, it will probably subside after rest in bed, and the free exhibition of bland diluents, to which some form of alkali is added". These measures obviously succeeded because they made the urine inhibitory to bacterial multiplication to a greater or less degree depending on the pH achieved. They increased the frequency of voiding, thus cutting down bacterial multiplication, diluting the bacteria and reducing the effect of any residual urine. Nevertheless some patients, we now know, were left with progressive renal-tract infection, some asymptomatic, some suffering intermittent overt illness.

With the use of a chemotherapeutic agent it should be possible to eradicate bacteria from the urine. All such agents are about equally effective (McCabe and Jackson, 1965) and my own experience confirms this. Their great variety indicates their limitations in producing a permanent

cure. The first requirement for drug-treatment is recognition of the drug-sensitivity of the organism and the second that of the optimal pH for that drug to act on the particular organism. These are in vitro laboratory tests, and ideally should be carried out for each specimen of urine. Brumfitt and Percival (1962) have given a table of optimal pH ranges for various drugs which can be used where the determination of individual optimal pH is not practicable. They found that where the urinary pH is uncorrected eradication of bacteria from the urine occurred in 67 per cent. of patients, whereas it occurred in 87 per cent. in whom the pH was adjusted to suit the drug in use. Without nitrofurantoin, which at that time was said to act independently of pH, the figures were 64 per cent. and 91 per cent., respectively. However, it has since been reported that nitrofurantoin is most active in an acid urine, pH 5.0 to 6.0 (Klotz, 1965). The urinary pH can be adjusted with harmless drugs, using methionine, ascorbic acid or ammonium chloride for acidification, and sodium bicarbonate or disodium acid phosphate for alkalinization. Achievement of the desired pH should be checked with papers of appropriate range.

Thirdly the dose should be adequate, that is, the drug should appear in the urine at bactericidal level. The fluid intake should be just sufficiently free as to allow the attainment of this level. Kunin and Finland (1959) report that "the more rapidly a drug is cleared by the kidney, the liklier it is to appear in the urine at therapeutic levels (despite renal failure) when the blood levels are at the usually

desired concentration". McCabe and Jackson have pointed out that bacteriostatic drugs become bactericidal if given in high enough dosage, and therefore this property of the drug is not of first importance. High urinary levels are all-important for the treatment of lower urinary-tract infections, whilst high serum levels are necessary in the treatment of renal tissue infection.

It would seem reasonable in addition to give each dose following as complete emptying of the bladder as possible so that the bacterial population and the volume of urine in the bladder are at their lowest when the drug is approaching its peak level. The frequency of administration of the drug will depend on its rate of elimination by the kidney, being sufficiently often as to maintain at least bacteriostatic levels.

The duration of intensive chemotherapy must also be adequate. Brumfitt, Percival and Carter (1962) and McCabe and Jackson consider that the urine will be abacterial in 48 hours if the drug is going to be of value. Turck, Browder, Lindemeyer, Brown, Anderson and Petersdorf (1962) say it is useless to persist with the same drug if the urine is not sterile after 14 days of therapy. The writer has examined Gram-stained preparations of urine infected with E. Coli after seven days of treatment with sulphadiazine and alkali. The bacterial flora had changed to a preponderance of Gram-positive rods. Nevertheless several small groups of Gram-negative rods were still present

(Figures 40, 41, 42 and 43). It would seem that to stop treatment at this stage is no better or perhaps worse than no treatment at all since these bacteria may be resistant and pass this property to other organisms. Plainly, close bacteriological follow-up is necessary to judge the necessary duration of chemotherapy. Ideally the urine should be re-cultured at 48 hours, again at the end of the first and second weeks. Further examination should be carried out two or three days after the termination of chemotherapy and at least monthly thereafter for six months. Any count of over 10,000 organisms per ml. of a pathogenic organism in a patient with a recent urinary-tract infection should be regarded with suspicion and a further examination made on an early morning specimen. It seems pointless to wait in such patients for the level of 100,000 per ml. since each exacerbation of infection, not necessarily clinical, will, if the kidney is involved, damage further nephrons, thus reducing the kidney's reserve capacity.

Drug combinations are not helpful. They require in vitro testing for synergy and antagonism in the presence of the infecting organism, and have not been found to give any better results than the use of one drug. They are more liable to cause adverse reactions (McCabe, Jackson and Grieble, 1959; McCabe and Jackson, 1965). Further, in treating a disease which will probably require a large range of drugs through time, it would seem unwise to risk the development of resistance to groups of drugs rather than single drugs.

Sulphonamides merit a special word. They have been the longest

in use, are probably the drug most commonly used and are the cheapest of the chemotherapeutic agents. They come in numerous forms from the short-acting to the longest acting, which is sulphormethoxine (Fanasil) (Gruneberg and Brumfitt, 1967), with a half-life in the body of 100 to 150 hours. This is designed to overcome the difficulty of the out-patient who stops treatment too soon. On the other hand for the patient with sulphonamide-allergy it would seem a poor choice. The short-acting sulphonamides give high urine and lower blood levels, and are thus particularly suitable for acute lower urinary-tract infections, whilst the long-acting sulphonamides give lower blood levels, and are probably more suitable for long-term treatment against smaller numbers of organisms (Klotz, 1965). McCabe, Jackson and Grieble (1959) obtained a success rate of 68 per cent. with short-acting sulphonamides in acute infections, but of only 30 per cent. in chronic pyelonephritis (McCabe and Jackson, 1965). These workers noted that sulphonamides were associated with the highest number of relapses. The long-acting sulphonamides and sulfisoxazole (gantrisin) are contraindicated in pregnancy and in neonates on account of their albumen-binding capacity, which results in shortageof albumen for bilirubin-binding, and can thus produce jaundice and kernicterus (Brown, 1962; Hardyment, 1962, Wilson, 1963 and Diamond, 1966). The long-acting sulphonamides are also contraindicated in all patients where renal function is impaired.

From what has been noted in the previous section it would seem that once the intensive course of chemotherapy is over the fluid intake

should be pushed up, at least in the day-time. The danger period of night and early morning should probably be covered either by an inhibitory pH of 5.0 or less, or 7.0 or more, or by a prophylactic dose of a chemotherapeutic agent. This dose should be a full single therapeutic dose to produce peak antibacterial activity at the peak danger time. This would seem better than spreading a reduced "prophylactic" dose over the whole 24 hours. Further this nightly drug should be taken after voiding, so that its effect is not mitigated by dilution in a large quantity of urine containing overwhelming numbers of bacteria.

If infection persists after 14 days of therapy, or relapses, further investigation is needed. Gutman, Turck, Petersdorf and Wedgwood consider failure to be due to an ineffective antibiotic, failure to take the drug, insufficient dosage, insufficient duration of therapy or abnormalities in the renal tract. From what has already been said regarding aetiology it is apparent that abnormalities of uro-dynamics can be as important as structural abnormalities in producing difficulties in treatment. In the pregnant woman there is stasis, which militates against successful chemotherapy. The presence of vesico-ureteric-vesical reflux produces an even more difficult situation.

Fairley, Bond, Brown and Habersberger have found bladder lavage with neomycin and Elase, which removes fibrinous exudate, to be very

effective in clearing an already infected bladder. This might be resorted to as an adjunct to further chemotherapy if the urine were not sterile after the initial 14-day course of treatment.

With the persistence of infection, or with relapses, further investigations are needed. It is worth noting here that the two procedures for diagnosing abnormalities of structure or urodynamics should be carried out under opposite conditions of hydration. Intravenous pyelography should be carried out under forced diuresis from free fluid intake so that any dilatations of the renal pelves or ureters will be well distended with dye. On the other hand micturating cystograms should be done after with-holding fluids since it is known that vesico-ureteral reflux can be abolished by a good forward flow of urine, and may thus be missed.

With the development of reflux additional therapeutic measures must be added to chemotherapy. Double and triple micturition is the most important of these measures, to rid the bladder of infected urine refluxed into it from the ureter after the end of micturition. This would be especially important at night-time, when refluxed urine may remain in the bladder for six, eight or even 12 hours in children. Gentle micturition should also be practiced, to avoid high intra-vesical pressures. Instruction in children should probably be given in hospital, by a conscientious nurse, who establishes the routine of double voiding as a habit before the child is dismissed home. Straffon and Engel (1960) and Garrett, Rhamy and Newman (1963) report

good results with this technique combined with antibiotic cover. Knappenberger (1963), Garrett, Rhamy and Newman (1963) and Mitchell and Hamilton (1964) would add urethral dilatation to these measures, and where this fails reconstruction of the bladder neck, or re-implantation of the ureter to give it a longer intra-mural course and thus more resistance to regurgitation. Fluids should be given freely to these patients to abolish reflux and to dilute the bacterial population. Chemotherapy might be confined to intermittent intensive courses, followed by maintenance of the urine at inhibitory pH levels overnight, or a single full dose of a chemotherapeutic agent at night-time. Holland and West (1963) reported good results in young girls with the long-term use of mandelamine, with an acidifying agent to keep the urinary pH to less than 5.5. On the other hand Schamadan (1964) found mandelamine with methionine inadequate for the eradication of bacteriuria in pregnant women.

Drugs producing high tissue levels should be used when the renal parenchyma or pelvis is infected. Care must be taken however in that some of these drugs (Kanamycin, colomycin, cycloserine, cephaloridine, streptomycin) are toxic, especially in the presence of renal impairment. Intramuscular ampicillin is safe and very effective against proteus infections. In addition care must be taken not to damage the foetus of the pregnant woman. Where renal parenchymal infection is present the best plan would seem to be to intermit an intensive course of a tissue-penetrating drug with a long-term course of a urine-sterilizing

drug. It has been said by Jawetz, Hopper and Smith (1957), Zangwill, Porter, Kaitz, Cotran, Bodel and Kass (1962) and by Jackson, Arana-Sialer, Anderson, Grieble and McCabe (1962) that most infections persist because of the cycle of continuous re-infection of the kidney by infected urine, the kidney then re-seeding the urine with bacteria and the urine then re-infecting the kidneys. If such a cycle is broken by rendering the urine sterile the kidneys may often rid themselves of bacteria, but this process frequently requires weeks or months. Jackson, Arana-Sialer, Anderson, Grieble and McCabe, state that there is experimental evidence to show that

> "the bacterial component of interstitial pyelonephritis can be resolved primarily by humoral and cellular defense mechanisms and may heal quite independently of antimicrobials once the continuous proliferation of bacteria in the living structures of the kidney ceases. Any agent that can eradicate bacteriuria will in all probability result in healing of the intestitial lesion"

Treatment therefore should aim at prolonged maintainance of freedom from bacteriuria. Smythe (1961) states that there is a place for chronic antibiotics in the treatment of chronic pyelonephritis. Turck, Anderson and Petersdorf (1966) tried to define the situation more clearly, recommending long-term chemotherapy for relapsing infections, but intermittent chemotherapy for re-infections. This

approach obviously requires fairly intensive bacteriological follow-up. McCabe and Jackson note that relapses with the original organism are twice as frequent as re-infection with a new organism, and that adults are prone to relapse and children to re-infection. In any case, since the kidney which is already diseased or has once had an infection is known to be prone to further infections it would seem that long-term treatment might be of prophylactic value. Finally, Bulkley (1961) has found it necessary on occasions to drain the renal pelvis with a catheter two or three times during the course of severe pyelitis.

In the pregnant woman with renal-tract infection, following an intensive course of chemotherapy to eradicate bacteria from the urine, it would seem best to adopt prophylactic measures throughout the antepartum period and until the sixth post-partum week. Structurally and physiologically the upper renal tract is in an optimum state for the firm establishment of infection at this time. Urinary pH could be made inhibitory, a prophylactic dose of a well-tested and harmless chemotherapeutic agent could be used and it seems probable that free fluid intake and double voiding would also be of value. After this bacteriological follow-up should be continued for at least six months. Further pregnancies should probably be delayed for two or three years, with the idea that the kidneys will lose their susceptibility to infection in this time. Catheterization in such patients should be done only under the greatest need, and chlorhexidine or other

antibacterial lavage carried out at the end of the procedure. In the pregnant patient with an exacerbation of acute pyelonephritis superimposed on chronic renal damage, and in the face of intractable uraemia, pregnancy should be terminated (Bulkley, 1961). This has been done following haemodialysis, and a live child obtained (Herwig, Merril, Jackson and Oken, 1965) but MacKay (1963) has found that where the maternal serum urea is above 60 mg. per cent. for any length of time the foetus does not survive. The amniotic-fluid urea nitrogen concentration was found to be higher than that of the maternal serum.

In conclusion it should be said that it is always worth treating urinary-tract infection as thoroughly as possible, whatever the stage of involvement that has been reached. The first acute attack of lower urinary-tract infection is the time for utmost attention to the eradication of bacteria from the urine, and the time at which one can hope for the best results. The longer infection persists after this the more difficult will satisfactory treatment become as the infective process progresses in extent. Nevertheless all efforts are worthwhile. The ultimate situation is summed up by McGregor (1965) who writes:

> "There is no other type of nephropathy in which fluctuation in renal function occurs so frequently; patients may approach and recede from renal failure in a most variable manner, according to the state of activity of the inflammatory

process. The residual renal units, though reduced in number, function normally; the consequence is decreasing regulatory flexibility with increasing azotaemia".

That the cure of pyelonephritis will not be achieved by antibiotics alone has been recognized by Kass (1955), Klotz (1965) and McCabe and Jackson. New work is revealing more of the physiological and dynamic characters of the urine and the urinary tract. The application of this new knowledge may supply some of the links which chemotherapy cannot furnish.

FINAL SUMMARY ON RENAL-TRACT INFECTION IN PREGNANCY

It has been shown in this study that renal-tract infection in pregnancy is frequent and is detectable in most instances in time for eradication before symptoms develop. This in itself makes routine bacteriological examination of the urine of pregnant women worthwhile. In addition there is ample evidence to suggest that pregnancy tends to result in recurrent infection. This, it is known, may have serious consequences.

Pre-eclamptic toxaemia was found to be uncommon in patients with acute urinary tract infection, and evidence of chronic renal impairment was not seen at this stage.

Bacteriuria, untreated or successfully eradicated, was not shown to have any effect on the incidence of abortion or stillbirth nor on the duration of gestation or birth weight of the live-born infant. Neonatal deaths, however, were significantly increased in the bacteriuric mothers as a whole, and this was due to defects of dorsal mid-line fusion.

There was evidence that infants of bacteriuric mothers, whether treated successfully or untreated, acquire infection from their mothers in utero and that this may be restricted to temporary bacteriuria or may progress to pyelonephritis.

It was felt that the success of chemotherapy in pregnant women is related to the quality of medical supervision and the reliability of the patient as well as to the drug itself. Even when these conditions are optimal success is not certain and this is probably due to physical

properties of the urine and alterations in uro-dynamics which are not yet properly understood but on which subjects considerable progress is being made.

STUDIES IN PERINATAL PAEDIATRICS

SUMMARY

Part I. Perinatal Influences Resulting in the Death of the Singleton Foetus or Infant

Part I of this thesis comprises a study of perinatal mortality in the Maternity Unit of Stobhill General Hospital, Glasgow, over a 17-month period from January 1959 to May 1960. The mortality rate was 4.9 per cent. of 3093 singleton deliveries.

Two groups of babies were distinguishable: viz.

Group I in whom there were well-recognized abnormalities (congenital defect, accidents of labour, haemolytic disease of the newborn, placenta praevia and intrapartum sepsis) which accounted for 45.8 per cent. of the total perinatal mortality;

Group II in whom no gross structural or mechanical abnormality was present, and which accounted for 54.2 per cent. of the total perinatal mortality.

The perinatal factors relating to these pregnancies are presented and discussed. The importance of congenital defects, and particularly of defects of dorsal mid-line fusion, of antepartum haemorrhage, pre-eclamptic toxaemia, postmaturity and the male sex of the foetus in contributing to perinatal mortality are all stressed.

Part II. Perinatal Influences Relating to Low Birth-Weight Babies and to their Development in the First Year of Life

Part II comprises a study of perinatal influences relating to 302 low birth-weight babies born in the Maternity Unit at Stobhill Hospital, and to the physical and mental development of 85 of these babies during the first year of life. Maternal, neonatal and infant characteristics are described and their inter-relationships discussed.

One third of the infants died perinatally. One third were found to be within normal limits at follow-up examination, and the remaining one third were defective on account of non-lethal congenital defects, developmental retardation, convulsions, cerebral palsy, anaemi and bronchitis.

Immaturity was the main factor on which perinatal mortality and infant morbidity depended. This was, in turn, dependent on a high incidence of maternal illness, comprising antepartum haemorrhage, pre-eclamptic toxaemia and a group of diverse illnesses of fairly severe nature. In addition specific conditions damaging to the foetus were seen, e.g. maternal rubella at 16 weeks and antepartum haemorrhage at 35 weeks gestation.

Bronchitis in the first year of life was significantly related to apnoea at birth and subnormal aeration in the first four hours of life, and to established respiratory distress after the first four hour of life.

Adaptive retardation was significantly related to cyanotic attacks occurring after the first four hours of life.

Retardation of intrauterine growth was not related to retardati of developmental progress in the infants of this series.

Part III. The Small, "Term" Baby

In Part III the baby weighing 2500 g. or less but of over 37 weeks maturity is compared with the baby of 2500 g. or less and of unde 37 weeks maturity. The incidence of these small, "term" babies was 139 of 302 low-weight babies (46.0 per cent.).

Maternal and neonatal characteristics were compared. The mothers of the mature babies showed a lower incidence of antepartum haemorrhage, and a shorter interval of membrane rupture prior to delivery than did the mothers of the immature infants.

The mature infants showed fewer neonatal complications.

The perinatal mortality rate in the small, "term" babies was 20.9 per cent. compared with 43.5 per cent. in the small, immature babies and 4.9 per cent. for all singletons born in the Unit during the same period.

It is concluded that the small, "term" baby is at less of a disadvantage than the small immature baby, but that special care is nevertheless indicated.

Part IV. Perinatal Characteristics of Twin Pregnancy Associated with Low Birth Weight

Seventy-one twin pregnancies occurred in 3164 mothers delivered in the Stobhill Maternity Unit during the period under survey, an incidence of 2.2 per cent..

Sixty-one per cent. of these pregnancies terminated at under 37 weeks gestation, and 57 per cent. of the babies weighed 2500 g. or less at birth.

Pre-eclamptic toxaemia was the only illness which occurred significantly more frequently in these mothers than in the mothers of healthy singletons. Its incidence in the mothers of low-weight singletons was similar to that seen in mothers with twins.

The big first twins were remarkably free from neonatal abnormalities, whilst the big second twins showed the highest incidence of illness.

The perinatal mortality rate was 10.4 per cent. of all twin babies, loss depending on the duration of gestation and the birth weigh There were no losses at over 2500 g.. When correction was made for intrauterine deaths there was no increased mortality amongst second twins.

Twin pregnancy engenders inherent biological disadvantages. Early rest in hospital and hospital delivery offer the best results at present.

Part V. Renal-Tract Infection in Pregnancy

Part V of this thesis is concerned with renal-tract infection i pregnancy, and with its effect on the foetus and infant.

The incidence of renal-tract infection in pregnancy, symptomati and asymptomatic, in a group of 2521 patients at Stobhill Hospital, was 8.7 per cent.

Gram-negative bacilli preponderated as pathogens, and Escherici

coli accounted for 80 per cent. of these infections.

Twelve per cent. of patients with an initial level of under 10,000 organisms per ml., and 66 per cent. of patients with an initial level of between 10,000 and 100,000 organisms per ml. of urine subsequently developed significant bacteriuria. Fifty per cent. of these patients developed clinical evidence of renal tract infection. In the majority of patients the time taken was sufficient to allow treatment to be instituted before symptoms developed.

Bacterial count by the quantitated loop technique was found to b a more suitable method of determining the presence of urinary-tract infection in antenatal patients than Gram-staining or the triphenyl tetrazoleum chloride (T.T.C.) test.

Maternal characteristics during pregnancy are assessed in comparison with a group of patients with no renal tract infection, and details of response to treatment described.

There was no increase in abortion, stillbirth or prematurity rates in the bacteriuric patients. The neonatal death rate was increased and this was due to defects of dorsal midline fusion.

Evidence is presented which suggests that maternal renal-tract infection can result in infection in the foetus.

Finally a review is made of recent observations on non-obstructive renal-tract infection with special reference to their releva to treatment.

STUDIES IN PERINATAL PAEDIATRICS

Volume II

PART I

PERINATAL INFLUENCES RESULTING IN THE DEATH OF THE SINGLETON FOETUS OR INFANT

TABLE I

NUMBERS OF INFANTS DYING PERINATALLY, GROUPED ACCORDING TO THE DURATION OF GESTATION

Gestation Period (in weeks)	All Perinatal Deaths No.	%	Stillbirths No.	Neonatal Deaths No.
28 to 32	34	22.3	12	22
32 and 33	15	9.8	9	6
34, 35 and 36	26	17.0	14	12
37, 38 and 39	51	33.3	34	17
40 and over	27	17.6	18	9
Total Infants	153	100.0	87	66

TABLE II

NUMBERS OF INFANTS DYING PERINATALLY, GROUPED ACCORDING TO THEIR BIRTH WEIGHTS

Birth Weight (in grams)	All Perinatal Deaths No.	%	Stillbirths No.	Neonatal Deaths No.
500 and less	2	1.3	2	0
501 to 1000	10	6.5	8	2
1001 to 1500	25	16.4	12	13
1501 to 2000	33	21.6	17	16
2001 to 2500	30	19.6	12	18
2501 to 3000	17	11.1	10	7
3001 to 3500	23	15.0	17	6
3501 and over	13	8.5	9	4
Total Infants	153	100.0	87	66

TABLE III

NUMBERS OF LIVEBORN INFANTS GROUPED ACCORDING TO THE TIME OF DEATH

Time of Death	Infants Dying Neonatally		
	No.		%
Under 4 hours	8		
4 to 12 hours	13	57.5	
12 to 48 hours	17		86.4
48 to 72 hours	9		
3 to 7 days	10		
8 to 28 days	9		13.6
Total Infants	66		100.0

TABLE IV

NUMBERS OF INFANTS OF GROUP I DYING PERINATALLY, CLASSIFIED ACCORDING TO THE CAUSE OF DEATH

Cause of Death	No. of Infants	% of Total Perinatal Mortality	No. of Stillbirths	No. of Neonatal Deaths
Congenital Defect	40	26.1	17	23*†
Accidents of Labour	13	8.5	11	2
Haemolytic Disease of the Newborn	8	5.2	6	2
Placenta Praevia	6	4.0	2	4°
Sepsis (Intra-Partum)	3	2.0	1	2
Total Infants	70	45.8	37	33

* Includes one infant of a diabetic mother

† Includes one infant with Rhesus haemolytic disease of the newborn who died primarily of congenital heart disease

o Includes one infant of a diabetic mother

TABLE V

TYPE AND INCIDENCE OF CONGENITAL DEFECT IN 40 INFANTS OF GROUP I DYING PERINATALLY

Type of Defect	Infants Affected No.	%	Stillbirths No.	Neonatal Deaths No.
Dorsal Midline Fusion	20	50.0	15	5
Anencephaly	9			
Anencephaly with meningocoele	1			
Hydrocephaly with meningocoele	3			
Hydrocephaly	2			
Meningocoele	4			
*Encephalocoele	1			
Genetic	8	20.0	1	7
Down's syndrome	4			
Achondroplasia	2			
Fibrocystic disease of the pancreas	1			
Hypophosphatasia	1			
Miscellaneous	12	30.0	1	11
ǂo Congenital heart disease	4			
+ Oesophageal atresia	3			
Multiple deformity	4			
Renal agenesis	1			
Total Infants	40	100.0	17	23

* Accompanied by suprarenal hypoplasia.
ǂ One with Rhesus haemolytic disease.
o One with a diabetic mother.
\+ One with anterior thoracic spina bifida and patent foramen ovale, not included in midline fusion defects or congenital heart disease.

TABLE VI

TYPE OF ACCIDENT OF LABOUR IN 13 MOTHERS OF GROUP I INFANTS DYING PERINATALLY

Type of Accident	No. of Mothers	No. of Stillbirths	No. of Neonatal Deaths
Abnormal Presentation	5	5	0
Prolapsed Cord	3	1	2
Prolonged Labour	3	3	0
Rupture of Uterus	2	2	0
Total Mothers	13	11	2

TABLE VII

NUMBERS OF INFANTS OF GROUP II DYING PERINATALLY AND CLASSIFIED ACCORDING TO THE DURATION OF GESTATION

Gestation Period (in weeks)	All Perinatal Deaths No.	%		Stillbirths No.	Neonatal Deaths No.
28 to 32	29	35.0	66.3	12	17
33 to 36	26	31.3		14	12
37 to 39	18	21.7	33.7	15	3
40 and over	10	12.0		9	1
Total Infants	83	100.0		50	33

TABLE VIII

NUMBERS OF INFANTS OF GROUP II DYING PERINATALLY AND CLASSIFIED ACCORDING TO THEIR BIRTH WEIGHTS

Birth Weight (in grams)	All Perinatal Deaths No.	%		Stillbirths No.	Neonatal Deaths No.
1500 and less	*30	36.1		18	12
1501 to 2000	18	21.7	77.1	8	10
2001 to 2500	16	19.3		9	7
2501 to 3000	6	7.2		4	2
3001 to 3500	9	10.9	22.9	7	2
3501 to 4000	3	1.2		3	0
4001 and over	1	3.6		1	0
Total Infants	83	100.0		50	33

* One foetus not weighed but known to be less than 1500 g.

TABLE IX

NUMBERS OF GROUP II INFANTS DYING PERINATALLY AND OF HEALTHY INFANTS CLASSIFIED ACCORDING TO SEX

Sex	Class of Infant			
	Dying Perinatally		Healthy	
	No.	%	No.	%
Male	56	67.5	49	49.0
Female	27	32.5	51	51.0
Total Infants	83	100.0	100	100.0

TABLE X

NUMBERS OF INFANTS DYING PERINATALLY (GROUPS I AND II) CLASSIFIED ACCORDING TO SEX AND COMPARED WITH THE OVER-ALL SEX DISTRIBUTION FOR BIRTHS IN ENGLAND, SCOTLAND AND WALES

Sex	Infants Dying Perinatally						*Over-all % Distribution
	Group I		Group II		Total		
	No.	%	No.	%	No.	%	
Male	30	42.9	56	67.5	86	55.5	51.7
Female	40	57.1	27	32.5	67	44.5	48.3
Total Infants	70	100.0	83	100.0	153	100.0	100.0

* Taken from the First Report of the 1958 Perinatal Mortality Survey (Butler and Bonham, 1963)

TABLE XI

NUMBERS OF MOTHERS OF GROUP II INFANTS DYING PERINATALLY AND OF HEALTHY INFANTS CLASSIFIED ACCORDING TO MATERNAL AGE

Maternal Age (in years)	Class of Mothers				Stillbirths	Neonatal Deaths
	With Perinatal Loss		With Healthy Infants			
	No.	%	No.	%	No.	No.
Under 20	3	3.6	8	8.0	2	1
20 to 24	23	27.7 (61.4)	34	34.0 (76.0)	13	10
25 to 29	25	30.1	34	34.0	15	10
30 to 34	17	20.5	10	10.0	8	9
35 to 39	9	10.9 (38.6)	11	11.0 (24.0)	8	1
40 and over	6	7.2	3	3.0	4	2
Total Mothers	83	100.0	100	100.0	50	33

TABLE XII

NUMBERS OF MOTHERS OF GROUP II INFANTS DYING PERINATALLY AND OF HEALTHY INFANTS CLASSIFIED ACCORDING TO PARITY

Parity	Class of Mother			
	With Perinatal Loss		With Healthy Infants	
	No.	%	No.	%
0	27	32.5	44	44.0
1 and 2	27	32.5	42	42.0
3 and more	29	35.0	14	14.0
Total Mothers	83	100.0	100	100.0

TABLE XIII

PREVIOUS OBSTETRICAL HISTORY OF 57 MOTHERS OF GROUP II INFANTS DYING PERINATALLY AND 56 MOTHERS OF HEALTHY INFANTS

Type of Abnormality in Previous Pregnancy	Class of Mothers				p value
	With Perinatal Loss		With Healthy Infants		
	No.	%	No.	%	
Miscarriage	20	35.1	17	30.4	<0.70 >0.50
Stillbirth	8	14.0	8	14.3	>0.99
*Premature Live Birth	19	33.3	6	10.7	<0.01
Maternal Illness	26	45.6	20	35.7	<0.30 >0.20

* Birth weight of 2500 g. or less

TABLE XIV

NUMBERS OF ILLNESSES IN EACH OF 83 MOTHERS OF GROUP II INFANTS DYING PERINATALLY AND 100 MOTHERS OF HEALTHY INFANTS

Numbers of Illnesses	Class of Mothers			
	With Perinatal Loss		With Healthy Infants	
	No.	%	No.	%
None	16	19.3	35	35.0
One	26	31.3	43	43.0
Two	27	32.5	20	20.0
Three	11	13.3	2	2.0
Four	3	3.6	0	0
Total Mothers	83	100.0	100	100.0

TABLE XV

TYPE AND INCIDENCE OF ILLNESS IN 83 MOTHERS OF GROUP II INFANTS DYING PERINATALLY AND 100 MOTHERS OF HEALTHY INFANTS

Type of Illness	Class of Mothers: With Perinatal Loss No.	%	With Healthy Infants No.	%	p value
Antepartum Haemorrhage	42	50.6	13	13.0	<0.01
Before 16 weeks	4		3		
16 to 27	7		5		
28 to 33	13		4		<0.20 >0.10
34 to 36	10		0		
37 and after	8		1		
Pre-eclamptic Toxaemia	28	33.7	14	14.0	<0.01
Before 34 weeks	15		1		
34 to 37	9		10		<0.01
38 and after	4		3		
Oedema	0	0	0	0	-
Hypertension	7	8.4	8	8.0	-
Albuminuria	0	0	2	2.0	-
Overt Renal Tract Infection	16	19.2	9	9.0	<0.05 >0.02
Iron-deficiency Anaemia (Hb. <10.5 g./100 ml.)	*17	20.5	+35	35.3	<0.05 >0.02
Megaloblastic Anaemia	1	1.2	0	0	-
Hydramnios	3	3.6	1	1.0	-
Miscellaneous	11	-	7	-	-
Total Illnesses	125	-	89	-	-

* 77 cases only

\+ 99 cases only

TABLE XVI

NUMBERS AND PERCENTAGE INCIDENCE OF INDIVIDUAL MATERNAL ILLNESSES TO SHOW THEIR CONTRIBUTION TO TOTAL MATERNAL MORBIDITY

Type of Illness	No. of Mothers	% Contribution to Total Maternal Morbidity
*Antepartum Haemorrhage	42	33.6
Pre-eclamptic Toxaemia	28	22.4
+Anaemia (Haemoglobin 10.5 g/100 ml.)	18	14.4
Overt Renal Tract Infection	16	12.8
Miscellaneous	11	8.8
Hypertension	7	5.6
Hydramnios	3	2.4
Total Illnesses	125	100.0

* Excluding that due to placenta praevia and local cervical lesions.

\+ Including one patient with megaloblastic anaemia.

TABLE XVII

NUMBERS OF MOTHERS OF GROUP II INFANTS DYING PERINATALLY AND OF HEALTHY INFANTS CLASSIFIED ACCORDING TO THE SEVERITY OF MATERNAL ILLNESS

Degree of Illness	Class of Mothers			
	With Perinatal Loss		With Healthy Infants	
	No.	%	No.	%
Severe	18	26.8	3	4.2
Moderate	23	34.3	17	26.2
Mild	26	38.9	45	69.2
Total Mothers	67	100.0	65	100.0

TABLE XVIII

NUMBERS OF MOTHERS OF GROUP II INFANTS UNDER AND OVER 30 YEARS OF AGE, CLASSIFIED ACCORDING TO THE SEVERITY OF ILLNESS

Degree of Illness	Maternal Age in Years			
	Under 30		Over 30	
	No.	%	No.	%
Severe and moderate	22	43.1	19	59.4
Mild and none	29	56.9	13	40.6
Total Mothers	51	100.0	32	100.0

TABLE XIX

NUMBERS OF MOTHERS OF GROUP II INFANTS CLASSIFIED ACCORDING TO PARITY AND THE SEVERITY OF ILLNESS

Degree of Illness	Parity					
	0		1 and 2		3 and more	
	No.	%	No.	%	No.	%
Severe and Moderate	15	55.6	8	29.6	18	62.0
Mild and None	12	44.4	19	70.4	11	38.0
Total Mothers	27	100.0	27	100.0	29	100.0

TABLE XX

NUMBERS OF MOTHERS OF GROUP II INFANTS CLASSIFIED ACCORDING TO THE DURATION OF GESTATION AND THE SEVERITY OF ILLNESS

Degree of Illness	Gestation Period (in weeks)					
	28 to 33		34 to 41		42 and over	
	No.	%	No.	%	No.	%
Severe and moderate	15	41.7	26	63.4	0	0
Mild and none	21	58.3	15	36.6	6	100.0
Total Mothers	36	100.0	41	100.0	6	100.0

TABLE XXI

MODE OF DELIVERY IN 83 GROUP II INFANTS DYING PERINATALLY AND 100 HEALTHY INFANTS

Mode of Delivery	Class of Infant				p value
	Dying Perinatally		Healthy		
	No.	%	No.	%	
Spontaneous Vertex	64	77.1	86	86.0	<0.20 >0.10
Caesarian Section	8	9.7	10	10.0	<0.50 >0.30
Other	11	13.2	4	4.0	-
Breech	8		0		
Forceps to Vertex	2		4		
Face to Pubis	1		0		
Total Deliveries	83	100.0	100	100.0	

TABLE XXII

NUMBERS OF GROUP II INFANTS DYING PERINATALLY AND OF HEALTHY INFANTS CLASSIFIED ACCORDING TO THE DURATION OF GESTATION AT THE TIME OF CAESARIAN SECTION

Gestation Period (in weeks)	Class of Infant			
	Dying Perinatally		Healthy	
	No.	%	No.	%
28 to 33	1	12.5	0	0
34 to 36	5	62.5	0	0
37 and over	2	25.0	10	100.0
Total Infants	8	100.0	10	100.0

TABLE XXIII

PERCENTAGE INCIDENCE OF FOETAL ABNORMALITY AFTER MATERNAL RUBELLA ACCORDING TO THE DURATION OF GESTATION AT THE TIME OF INFECTION

Series	Percentage Incidence of Foetal Malformation Gestation Period (in weeks)			
	Conception to 4th	5th to 8th	9th to 12th	13th to 16th
Lock et al. (1961)	50		15	
Campbell (1961)	30 to 70	25 to 55	20 to 40	10 to 25
Michaels and Mellin (1960)	47	22	7	-

TABLE XXIV

PERCENTAGE INCIDENCE OF MIDLINE FUSION DEFECTS IN THIS AND OTHER SERIES

Defect	Present	*British Perinatal Mortality Survey	Series ‡Dublin	Liverpool	Birmingham	Rhode Island	Zurich
Anencephaly	0.29	0.23	0.50	0.32	0.23	0.19	0.05
Spina bifida	°0.29	0.08	0.42	0.28	0.27	0.25	0.11
Hydrocephalus	0.07	0.03	0.35	0.42	0.18	0.09	0.07
Total Percentage of Defects	0.65	0.34	1.27	1.02	0.68	0.53	0.23

* Butler and Bonham (1963)

‡ Kalter (1963)

o Includes one case of anencephaly with spina bifida
one case of encephalocoele and
three cases of hydrocephaly with spina bifida

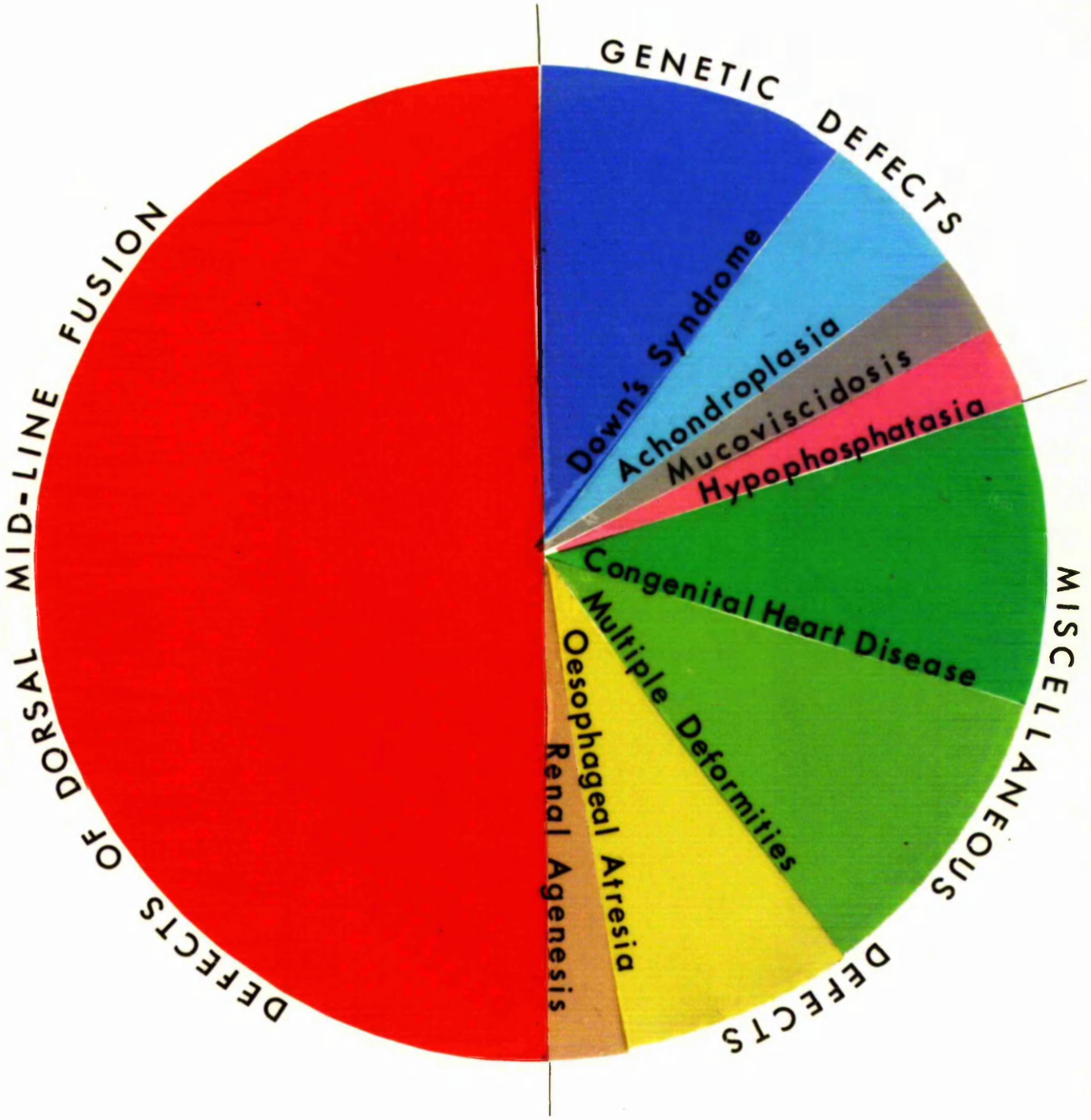

Figure 1.

Summary of the types and incidence of lethal congenital defect present in 40 infants of Group I, dying perinatally.

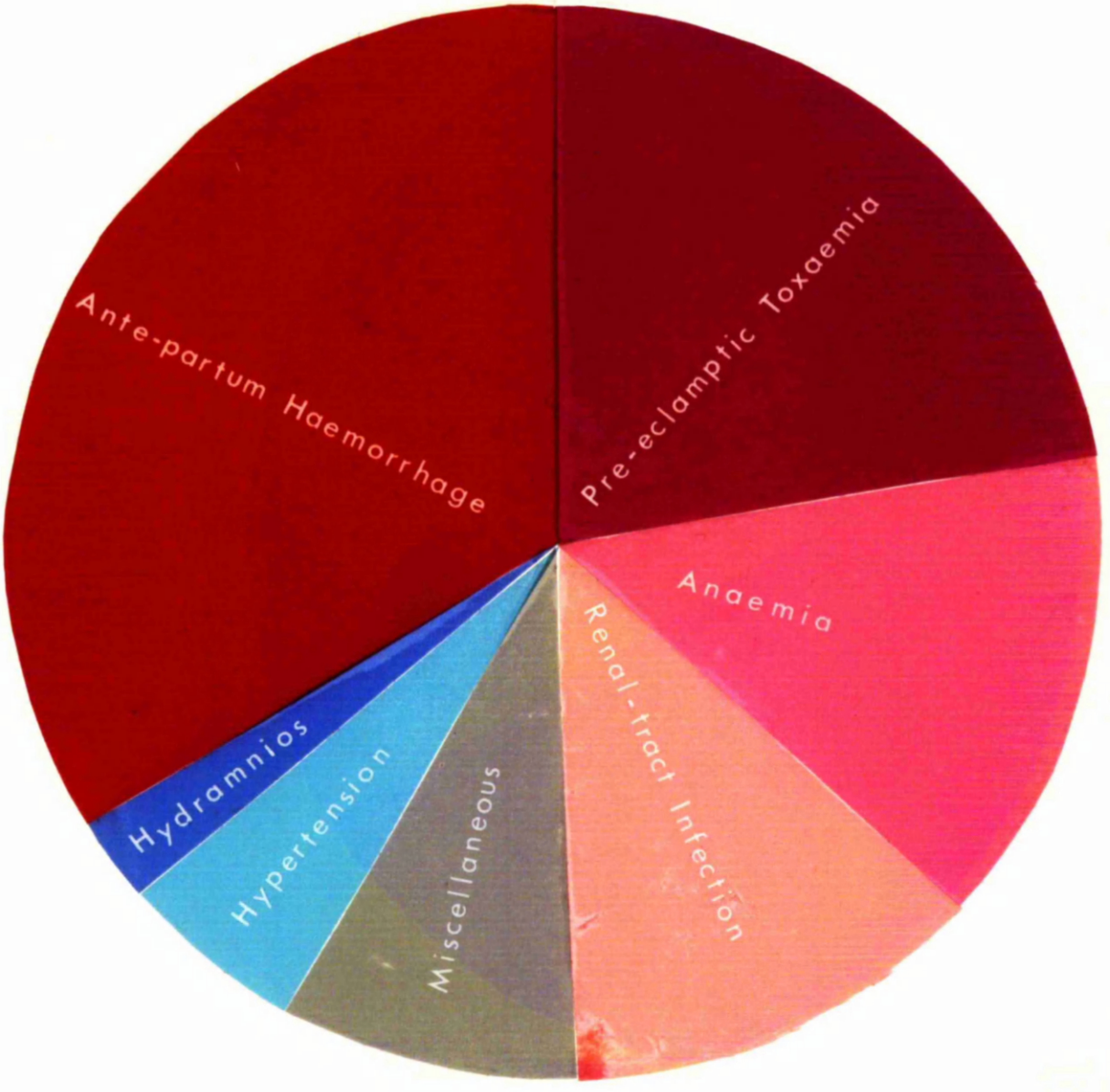

Figure 2.

Percentage contribution of the main maternal illnesses to total maternal morbidity amongst infants of Group II dying perinatally.

PART II

PERINATAL INFLUENCES RELATING TO LOW BIRTH-WEIGHT BABIES AND TO THEIR DEVELOPMENT IN THE FIRST YEAR OF LIFE

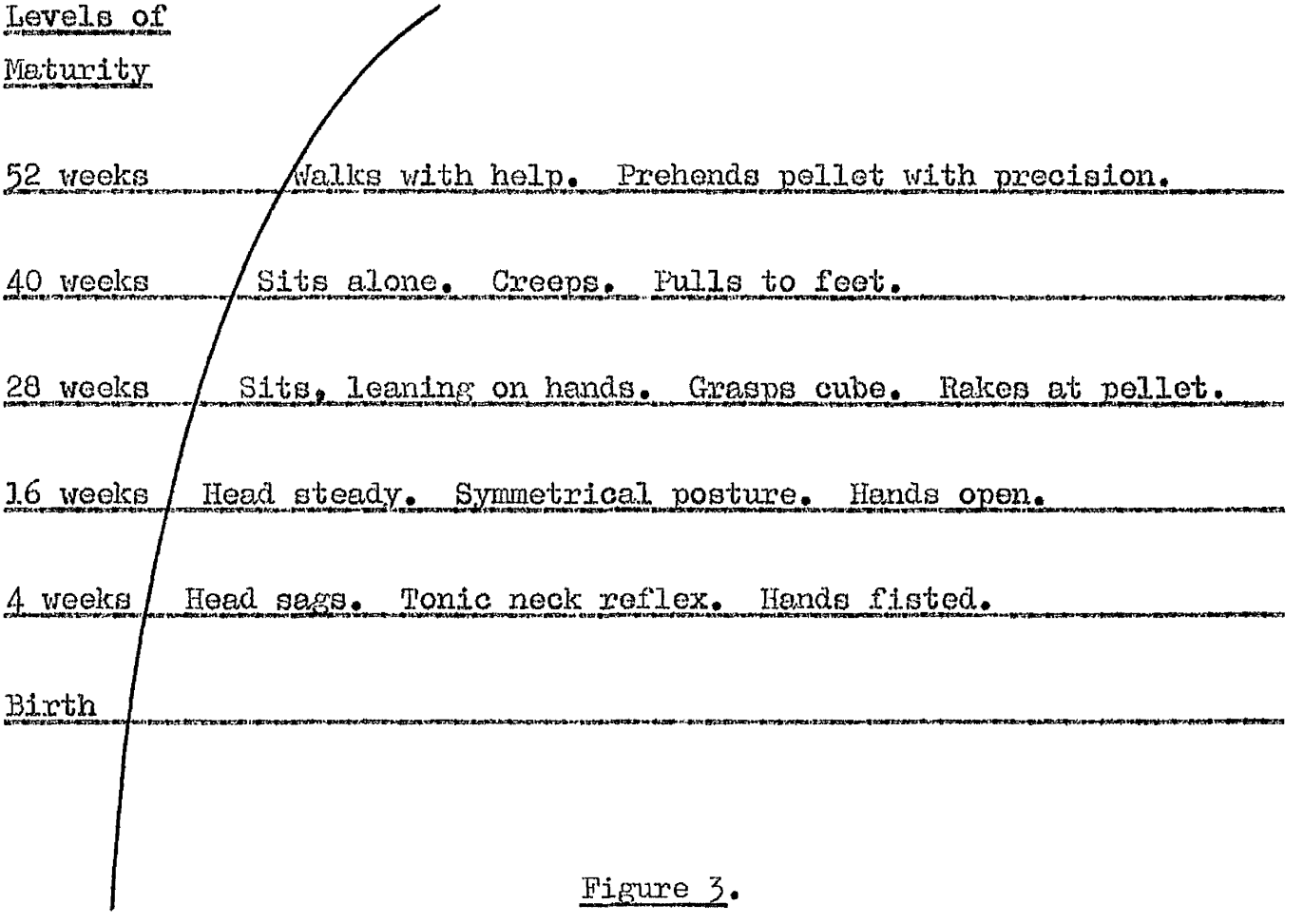

Figure 3.

DEVELOPMENTAL SEQUENCES OF MOTOR BEHAVIOUR

(Gesell and Amatruda, 1960)

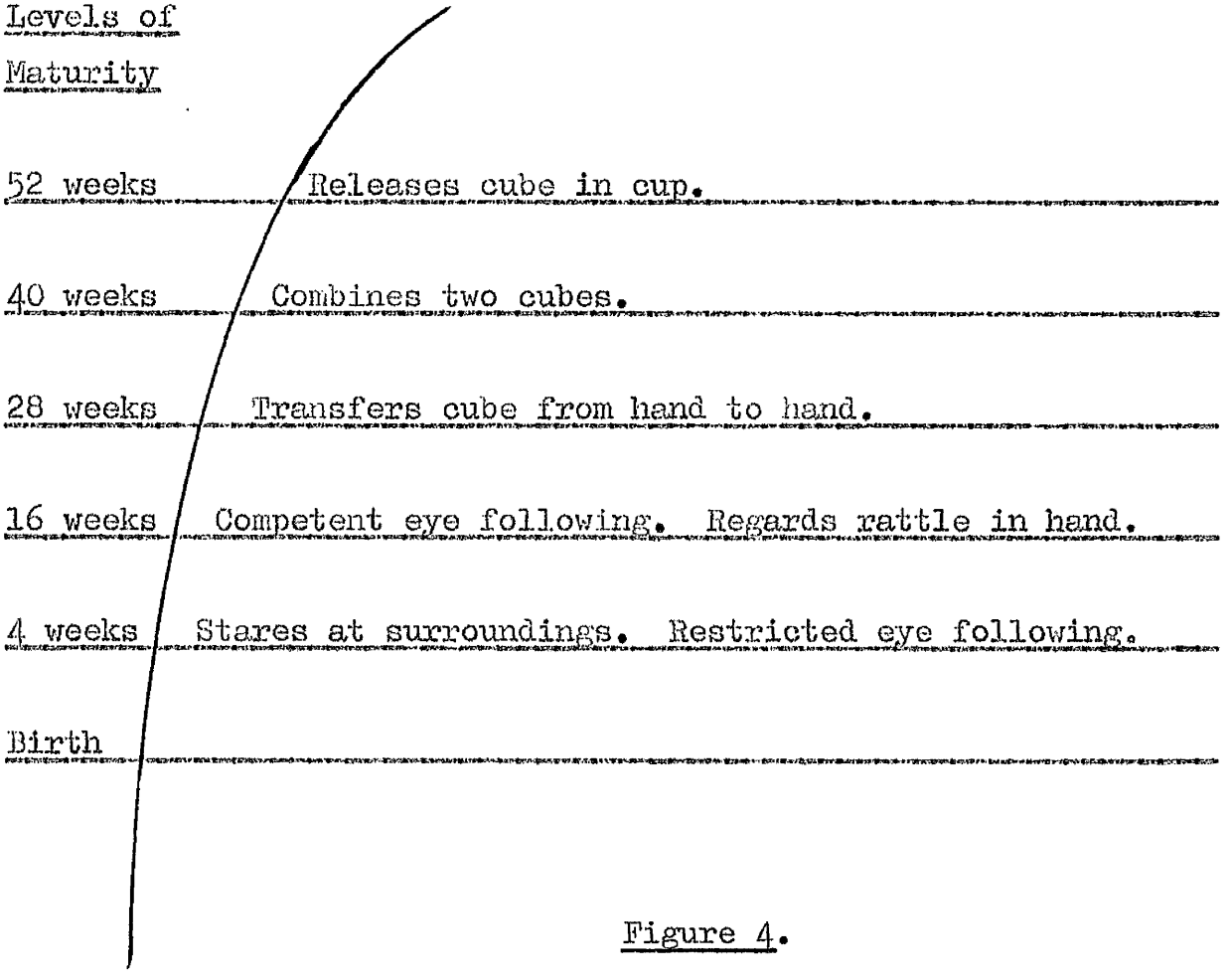

Figure 4.

DEVELOPMENTAL SEQUENCES OF ADAPTIVE BEHAVIOUR

"Adaptive behaviour ---- is motor
coordination combined with judgment"
(Gesell and Amatruda, 1960)

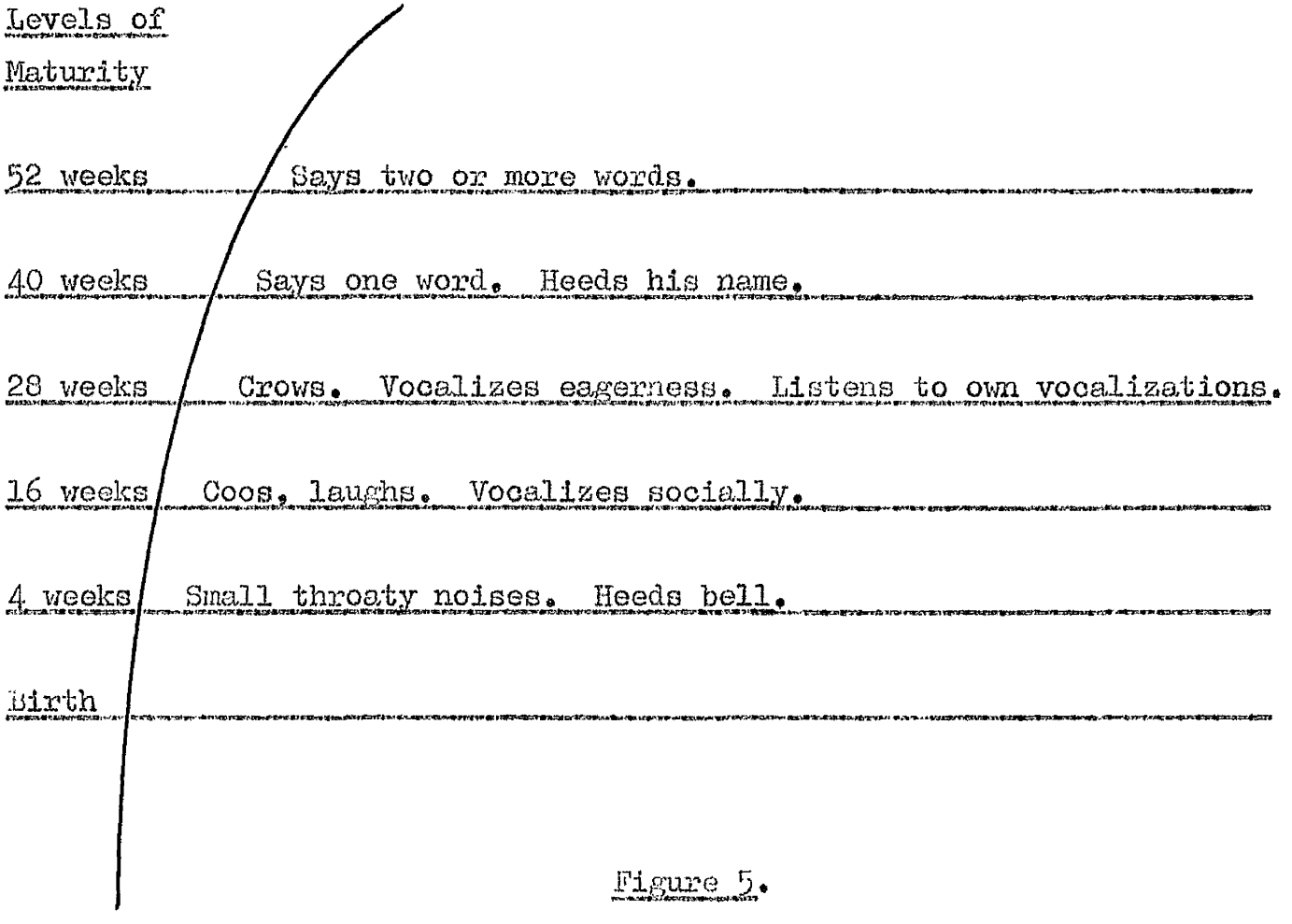

Figure 5.

DEVELOPMENTAL SEQUENCES OF LANGUAGE BEHAVIOUR

"Language maturity is estimated in terms of articulation, vocabulary, adaptive use and comprehension"

(Gesell and Amatruda, 1960)

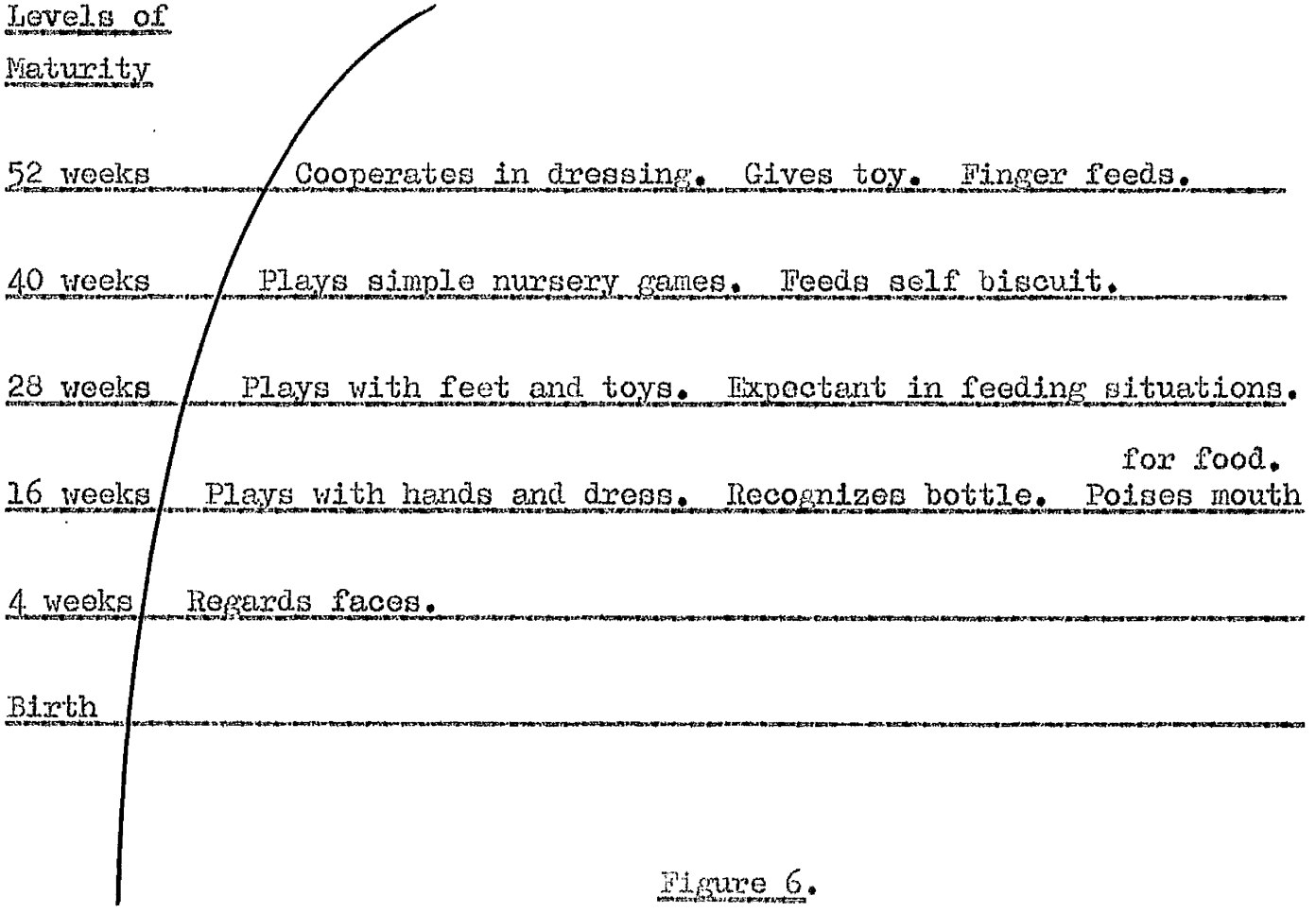

Figure 6.

DEVELOPMENTAL SEQUENCES OF PERSONAL-SOCIAL BEHAVIOUR

"Personal-social behaviour is greatly affected by the temperament of the child and by the kind of home in which he is reared. Nevertheless maturity factors play a primary role in the socialization of the child". ——— This type of behaviour depends on "the interaction of environmental influences and developmental readiness".

(Gesell and Amatruda, 1960)

TABLE XXV

ADAPTED SCORING LIST AS USED IN THE ASSESSMENT OF THE DEVELOPMENTAL PROGRESS OF 85 LOW BIRTH-WEIGHT BABIES IN THE FIRST YEAR OF LIFE

Age in Weeks	Type of Behaviour	Observation
16	Motor	Head control.
	Adaptive	Competent eye following. Regards rattle.
	Language	Coos, laughs, vocalizes.
	Personal-Social	Looks at hands. Knows bottle. Plays with dress. Poises mouth for food.
28	Motor	Sits, leaning on hands.
	Adaptive	Transfers cube. Puts objects to mouth
	Language	Listens to self. Vocalizes eagerness. Talks to toys.
	Personal-Social	"Strange". Notices own feet. Expectant in feeding situations. Takes mixed-feeding well.
40	Motor	Sits alone.
	Adaptive	Puts two cubes together. Picks up small objects.
	Language	Knows own name. Understands a few words. Says mama or dada.
	Personal-Social	Drinks from cup. Holds own bottle. Feeds self biscuit. Waves good-bye. Claps hands.
44	Motor	Stands with support
52	Motor	Stands alone. Walks with help.
	Adaptive	Releases cube in cup.
	Language	Says two words and mama and dada. Understands many words.
	Personal-Social	Helps with dressing - holds out arms. Tries to feed self with spoon and cup

TABLE XXVI

NUMBERS OF MOTHERS OF LOW BIRTH-WEIGHT BABIES AND OF NORMAL BIRTH-WEIGHT BABIES GROUPED ACCORDING TO AGE

Maternal Age in Years	Group of Mothers					
	With Low Birth-Weight Babies			With Normal Birth-Weight Babies		
	No.	%		No.	%	
Under 20	17	5.6		8	8.0	
20 to 24	94	31.1	62.9	34	34.0	76.0
25 to 29	79	26.2		34	34.0	
30 to 34	56	18.5		10	10.0	
35 to 39	40	13.3	37.1	11	11.0	24.0
40 and over	16	5.3		3	3.0	
Total Mothers	302	100.0		100	100.0	

TABLE XXVII

NUMBERS OF MOTHERS OF LOW BIRTH-WEIGHT BABIES AND OF NORMAL BIRTH-WEIGHT BABIES GROUPED ACCORDING TO PARITY

Parity	Group of Mothers			
	With Low Birth-Weight Babies		With Normal Birth-Weight Babies	
	No.	%	No.	%
0	126	41.7	44	44.0
1 and 2	92	30.5	42	42.0
3 and more	84	27.8	14	14.0
Total Mothers	302	100.0	100	100.0

TABLE XXVIII

PREVIOUS OBSTETRICAL HISTORY OF 176 MOTHERS WITH LOW BIRTH-WEIGHT BABIES AND 56 MOTHERS WITH NORMAL BIRTH-WEIGHT BABIES

Abnormality	Group of Mothers With Low Birth-Weight Babies		With Normal Birth-Weight Babies		p value
	No.	%	No.	%	
Miscarriage	69	39.2	17	30.3	<0.30 >0.20
Stillbirth	23	13.1	8	14.3	<0.90 >0.80
Premature Live Birth	67	38.0	6	10.7	<0.01
Illness	65	36.9	20	35.7	<0.80 >0.70

TABLE XXIX

NUMBER OF ILLNESSES IN EACH MOTHER OF 302 INFANTS OF LOW BIRTH WEIGHT AND 100 INFANTS OF NORMAL BIRTH WEIGHT

No. of Illnesses	Group of Mothers With Low Birth-Weight Babies		With Normal Birth-Weight Babies	
	No.	%	No.	%
None	80	26.5	35	35.0
1	121	40.1	43	43.0
2	77	25.5	20	20.0
3	19	6.3	2	2.0
4	5	1.6	0	0
Total Mothers	302	100.0	100	100.0
	Total Illnesses in 222 Mothers	352	Total Illnesses in 65 Mothers	89

TABLE XXX

NUMBER OF MOTHERS WITH MORE THAN TWO ILLNESSES, OF 302 LOW BIRTH-WEIGHT BABIES, AND 100 NORMAL BIRTH-WEIGHT BABIES

No. of Illnesses	Group of Mothers With Low Birth-Weight Babies		With Normal Birth-Weight Babies	
	No.	%	No.	%
2 or less	278	92.1	98	98.0
More than 2	24	7.9	2	2.0
Total mothers	302	100.0	100	100.0

TABLE XXXI

TYPE AND INCIDENCE OF ILLNESS IN 302 MOTHERS OF LOW BIRTH-WEIGHT BABIES AND 100 MOTHERS OF NORMAL BIRTH-WEIGHT BABIES

Type of Illness	Group of Mothers With Low Birth-Weight Babies		With Normal Birth-Weight Babies		p value
	No.	%	No.	%	
*Antepartum Haemorrhage					
Before 16 weeks	18	24.0	3	23.1	
16 to 27 weeks	15	20.0	5	38.5	<0.20
28 to 35	22	29.4	4	30.8	>0.10
34 to 36	13	17.3	0	0	
37 and after	7	9.3	1	7.7	
Total	75	24.8	13	13.0	<0.02 >0.01
Pre-eclamptic Toxaemia					
Before 34 weeks	47	58.9	1	7.1	
34 to 38	22	27.4	10	71.4	<0.01
Over 38	11	13.7	3	21.5	
Total	80	26.5	14	14.0	<0.02 >0.01
Oedema	1	0.33	0	0	-
Hypertension	22*[1]	7.3	8	8.0	<0.50 >0.30
Albuminuria	0	0	2	2.0	-
Overt Urinary Infection	39	12.9	9	9.0	<0.30 >0.20
Iron Deficiency Anaemia (Haemoglobin<10.5 g./100 ml.)	74*[2]	24.5	35*[3]	35.3	<0.20 >0.10
Megaloblastic Anaemia	3	0.9	0	0	-
Hydramnios	14	4.0	1	1.0	<0.10 >0.05
Other	44	-	7	-	-
Total Illnesses	352	-	89	-	-

* Excluding that due to placenta praevia and local cervical lesions.
*1 Includes three patients developing pre-eclamptic toxaemia.
*2 263 Results.
*3 99 Results.

TABLE XXXII

DETAILS OF LABOUR IN 302 LOW BIRTH-WEIGHT BABIES AND 100 HEALTHY NORMAL-WEIGHT BABIES

Labour Detail	Infant Group				p value
	Low Birth Weight		Normal		
	No.	%	No.	%	
Admitted in Labour	151	50.0	64	64.0	<0.02 >0.01
Admitted for other reasons	151	50.0	36	36.0	
Mode of Delivery					
Spontaneous Vertex	205	67.9	86	86.0	<0.01
Caesarian section	48	15.9	10	10.0	<0.20 >0.10
Other	49	16.2	4	4.0	-
Breech 24			-		
Forceps to vertex 11			4		
Other 8			-		
Face 6			-		
Sedation within 12 hours of delivery	152	51.3	56	56.0	†
Anaesthesia within 12 hours of delivery	58	19.2	14	14.0	†
Duration of Labour					
Normal	274	90.7	88	88.0	†
*Prolonged or precipitate	28	9.3	12	12.0	

* Prolonged labour is defined as lasting more than 36 hours in primiparae, and more than 24 hours in multiparae.

† Not statistically significant.

TABLE XXXIII

NUMBERS OF LOW BIRTH-WEIGHT AND NORMAL BIRTH-WEIGHT BABIES IN RELATION TO THE DURATION OF MEMBRANE RUPTURE PRIOR TO DELIVERY

Duration of Membrane Rupture	Baby Group			
	Low Birth Weight		Normal Birth Weight	
	No.	%	No.	%
Under 12 hours	161	65.7	74	83.1
12 to 47 hours	54	22.0	9	10.1
48 hours to 7 days	21	8.6	6	6.8
8 days and over	9	3.7	0	0
Total Infants	245	100.0	89	100.0

Note: No Caesarian sections have been included.

TABLE XXXIV

NUMBERS OF LOW BIRTH-WEIGHT BABIES GROUPED ACCORDING TO THE DURATION OF GESTATION

Duration of Gestation in Weeks	No. of Infants	% of Total	
28 and 29	13	4.3	
30 and 31	44	14.5	
32 and 33	31	10.3	
34, 35 and 36	75	24.8	
37, 38 and 39	98	32.5	46.1
40 and over	41	13.6	
Total Infants	302	100.0	

TABLE XXXV

NUMBERS OF LOW BIRTH-WEIGHT BABIES DYING PERINATALLY, GROUPED ACCORDING TO THE DURATION OF GESTATION

Gestation Period (in weeks)	Total Infants	Perinatal Deaths No.	%
28 and 29	13	8	61.5
30 and 31	44	26	59.1
32 and 33	31	14	45.1
34, 35 and 36	75	23	30.7
37, 38 and 39	98	22	22.4
40 and over	41	7	17.1
Total Infants	302	100	-

TABLE XXXVI

NUMBERS OF LOW BIRTH-WEIGHT BABIES GROUPED ACCORDING TO BIRTH WEIGHT

Birth Weight in Grams	No. of Infants	% of Total
500 and less	*2	0.7
501 to 1000	10	3.3
1001 to 1500	36	11.9
1501 to 2000	78	25.8
2001 to 2500	176	58.3
Total Infants	302	100.0

* Including one foetus whose weight was not recorded.

TABLE XXXVII

NUMBERS OF LOW BIRTH-WEIGHT BABIES DYING PERINATALLY, GROUPED ACCORDING TO BIRTH WEIGHT

Birth Weight (in grams)	Total Infants	Perinatal Deaths No.	Perinatal Deaths %
500 and less	2	2	100.0
501 to 1000	10	10	100.0
1001 to 1500	36	25	69.4
1501 to 2000	78	33	42.3
2001 to 2500	176	30	17.0
Total Infants	302	100	-

TABLE XXXVIII

NUMBERS OF BABIES GROUPED ACCORDING TO *INTRAUTERINE GROWTH STATUS TO SHOW PERINATAL MORTALITY

Intrauterine Growth Status (as %)	Total Infants	Perinatal Deaths No.	%
Less than 60	20	15	75.0
60 to 79	108	34	31.5
80 to 99	95	27	28.4
100 to 119	53	15	28.3
120 to 139	19	6	31.6
140 and over	6	2	33.3
Total Infants	°301	°99	-

* Intrauterine growth status is the birth weight expressed as a percentage of the expected weight for the duration of gestation.

° One foetus not weighed at birth, but estimated as less than 500 g., is excluded from this table.

TABLE XXXIX

NUMBERS OF LOW BIRTH-WEIGHT BABIES WITH DEVIATIONS FROM THE NORMAL INTRAUTERINE GROWTH RATE IN 55 MOTHERS WITH PRE-ECLAMPTIC TOXAEMIA AND 55 MOTHERS WITH NO PRE-ECLAMPTIC TOXAEMIA

Intrauterine Growth Status (as %)	Group of Mothers			
	With Pre-eclamptic Toxaemia		No Pre-eclamptic Toxaemia	
	No.	%	No.	%
Under 75	17	30.9 } 60.0	11	20.0 } 43.7
75 to 89	16	29.1	13	23.7
90 to 99	9	16.3 } 27.2	9	16.3 } 27.2
100 to 109	6	10.9	6	10.9
110 to 124	3	5.5 } 12.8	11	20.0 } 29.1
125 and over	4	7.3	5	9.1
Total Mothers	55	100.0	55	100.0

* Intrauterine growth status is the birth weight expressed as a percentage of the expected weight for the duration of gestation.

TABLE XI

SEX DISTRIBUTION IN 302 LOW BIRTH-WEIGHT BABIES AND 100 NORMAL BIRTH-WEIGHT BABIES

Sex	Baby Group			
	Low Birth Weight		Normal Birth Weight	
	No.	%	No.	%
Male	150	49.7	51	51.0
Female	152	50.3	49	49.0
Total Infants	302	100.0	100	100.0

TABLE XII

TYPE AND INCIDENCE OF CONGENITAL DEFECT IN 302 LOW BIRTH-WEIGHT BABIES GROUPED ACCORDING TO THE LETHAL OR NON-LETHAL NATURE OF THE DEFECT

Nature of Defect			
Lethal or Potentially Lethal		Non-Lethal	
Anencephaly	9	Craniosynostosis	1
Anencephaly with meningocoele	1	Achondroplasia	1
Encephalocoele with suprarenal hypoplasia	1	Congenital heart disease	2
		Hypotonia	1
Oesophageal atresia (one with duodenal atresia)	3	Microphthalmia and coloboma	1
Mongol with duodenal atresia	1	Wedge vertebrae	1
Hypophosphatasia	1	Talipes equino varus	2
Osteogenesis imperfecta	1	Talipes calcaneo valgus	1
Renal agenesis	1	Syndactily	1
Multiple deformity	4	Hydrocoele of testis	1
Congenital heart disease with Rhesus haemolytic disease	1	Skin tags	2
		Pectus excavatum	1
Total Infants	23 (7.6%)		15 (5.0%)

TABLE XLII

TYPE AND INCIDENCE OF ABNORMALITIES IN 251 LIVE-BORN, LOW BIRTH-WEIGHT BABIES AT UNDER FOUR HOURS OF AGE

Abnormality	Infants Affected	
	No.	%
*Respiratory	66	26.3
Oedema	60	23.9
Hypotonia	40	15.9
Cyanosis	38	15.1

* Respiratory abnormality comprises apnoea and subnormal aeration.

TABLE XLIII

TYPE AND INCIDENCE OF ABNORMALITY IN 245 LOW BIRTH-WEIGHT BABIES AND 100 HEALTHY NORMAL-WEIGHT BABIES AT OVER FOUR HOURS OF AGE

Abnormality	Infant Group				p value
	Low Birth Weight		Normal Birth Weight		
	No.	%	No.	%	
Respiratory Distress	23	9.4	0	0	-
*Cerebral Irritation	15	6.1	2	2.0	<0.20 >0.10
Cyanotic Attacks	26	10.6	0	0	-
Collapse	10	4.1	0	0	-
Jaundice	49	20.0	1	1.0	<0.01
Sepsis	30	12.2	12	12.0	>0.95

* Cerebral irritation comprises irritability, tremor, twitching and abnormal cry.

TABLE XLIV

NUMBERS OF LOW BIRTH-WEIGHT BABIES AND NORMAL BIRTH-WEIGHT BABIES GROUPED ACCORDING TO AGE AT DISCHARGE FROM HOSPITAL

Age in Days	Baby Group			
	Low Birth Weight		Normal Birth Weight	
	No.	%	No.	%
10 and less	76	37.6	89	89.0
11 to 20	51	25.2	10	10.0
21 to 35	36	17.8	0	0
36 to 49	21	10.8	*1	1.0
50 and over	18	9.0	0	0
Total Infants	202	100.0	100	100.0

* Retained in hospital on account of maternal illness.

TABLE XLV

NUMBERS OF BABIES GROUPED ACCORDING TO INTRAUTERINE GROWTH STATUS TO SHOW WEIGHT PROGRESS IN THE FIRST YEAR OF LIFE

% of Expected Weight	Time of Weighing			
	At Birth		At Follow-up	
	No.	%	No.	%
Under 100	59	69.4	29	34.5
100 and over	26	30.6	11	13.1
Variable	-	-	44	52.4
Total Infants	85	100.0	*84	100.0

* One baby not re-weighed.

TABLE XLVI

NUMBERS OF BABIES GROUPED ACCORDING TO THE SEVERITY OF INTRAUTERINE GROWTH RETARDATION TO SHOW WEIGHT PROGRESS IN THE FIRST YEAR OF LIFE

Severity of Retardation as %	No. of Infants	% of Expected Weight at Follow-up			
		100 and Over		Less than 100	
		No.	%	No.	%
Severe (under 75)	25	14	56.0	11	44.0
Moderate (75 to 89)	21	11	52.4	10	47.6
Mild (90 to 99)	12	4	33.3	8	66.7
Total Infants	58	29	50.0	29	100.0

TABLE XLVII

NUMBERS OF BABIES GROUPED ACCORDING TO THE SEVERITY OF INTRAUTERINE GROWTH RETARDATION TO SHOW THE AGE AT WHICH THIS WAS CORRECTED

Severity of Retardation as %	No. of Infants	Age by which 100% was Reached (in weeks)			
		Under 16	16 to 27	28 to 39	40 to 52
Severe (under 75)	14	1	9	3	1
Moderate (75 to 89)	11	1	8	2	0
Mild (90 to 99)	4	0	3	1	0
Total Infants	29	2	20	6	1

TABLE XLVIII

TYPE AND INCIDENCE OF INFECTION IN 85 LOW BIRTH-WEIGHT BABIES AND 39 NORMAL BIRTH-WEIGHT BABIES IN THE FIRST YEAR OF LIFE

Type of Infection	Infant Group: Low Birth Weight		Infant Group: Normal Birth Weight		p value
	No.	%	No.	%	
Respiratory System	47	55.3	16	41.0	<0.20 >0.10
Colds	25		12		
Bronchitis	17		0		
Pneumonia	2		2		
Otitis Media	3		2		
Gastrointestinal System	12	14.1	4	10.3	<0.30 >0.20
Gastroenteritis	5		1		
Vomiting	0		0		
Diarrhoea	7		3		
Miscellaneous	15	17.6	7	17.9	-
Infectious diseases of childhood	9		5		
Eye	5		0		
Other	1		2		

TABLE XLIX

NUMBERS OF LOW BIRTH-WEIGHT BABIES GROUPED ACCORDING TO THE DURATION OF GESTATION AND SHOWING THE INCIDENCE OF INFECTION IN THE FIRST YEAR OF LIFE

Duration of Gestation (in weeks)	Infant Group			
	With Infection		No Infection	
	No.	%	No.	%
Under 32	10	19.2	3	9.1
32 and 33	8	15.4	10	30.3
34, 35 and 36	6	11.5	7	21.2
37, 38 and 39	20	38.4	9	27.3
40 and over	8	15.4	4	12.1
Total Infants	52	100.0	33	100.0

TABLE L

NUMBERS OF LOW BIRTH-WEIGHT BABIES GROUPED ACCORDING TO BIRTH WEIGHT AND SHOWING THE INCIDENCE OF INFECTION IN THE FIRST YEAR OF LIFE

Birth Weight (in grams)	Infant Group			
	With Infection		No Infection	
	No.	%	No.	%
1001 to 1500	6	11.5	2	6.1
1501 to 2000	15	28.9	10	30.3
2001 to 2500	31	59.6	21	63.6
Total Infants	52	100.0	33	100.0

TABLE LI

NUMBERS OF LOW BIRTH-WEIGHT BABIES GROUPED ACCORDING TO THE DURATION OF GESTATION AND SHOWING THE INCIDENCE OF BRONCHITIS IN THE FIRST YEAR OF LIFE

Duration of Gestation (in weeks)	Infant Group			
	With Bronchitis		No Bronchitis	
	No.	%	No.	%
Under 32	6	35.3	7	10.3
32 and 33	2	11.8	16	23.5
34, 35 and 36	1	5.9	12	17.7
37, 38 and 39	5	29.4	24	35.3
40 and over	3	17.6	9	13.2
Total Infants	17	100.0	68	100.0

TABLE LII

NUMBERS OF BABIES GROUPED ACCORDING TO THEIR BIRTH WEIGHT TO SHOW THE INCIDENCE OF BRONCHITIS IN THE FIRST YEAR OF LIFE

Birth Weight in grams	Infant Group			
	With Bronchitis		No Bronchitis	
	No.	%	No.	%
1001 to 1500	3	17.7	6	8.8
1501 to 2000	8	47.0	16	23.5
2001 to 2500	6	35.3	46	67.7
Total Infants	17	100.0	68	100.0

TABLE LIII

INCIDENCE OF *RESPIRATORY ABNORMALITY AT BIRTH AND OF RESPIRATORY DISTRESS IN 17 LOW BIRTH-WEIGHT BABIES WITH BRONCHITIS AND 68 WITH NO BRONCHITIS IN THE FIRST YEAR OF LIFE

Neonatal Illness	Infant Group With Bronchitis		Infant Group No Bronchitis		p value
	No.	%	No.	%	
*Respiratory Abnormality	8	47.0	11	16.2	<0.01
Respiratory Distress	4	23.5	3	4.4	<0.02 >0.01

* Respiratory abnormality comprises apnoea and subnormal aeration.

Figure 7
Aged 20 weeks

Figure 8
Aged 32 weeks

Figure 9
Aged 50 weeks

Serial X-rays of the wrist of a low birth-weight baby showing mild rickets. In Figure 7 there is a little irregularity of the lower ends of the radius and ulna with minimal evidence of splaying, and some cupping of the ulna. In Figures 8 and 9 there is increasing density at the epiphyseal line and decreasing irregularity and cupping.

TABLE LIV

SUMMARY OF PERINATAL MORTALITY AND INFANT MORBIDITY IN THE FIRST YEAR OF LIFE IN 302 LOW BIRTH-WEIGHT BABIES GROUPED ACCORDING TO THE DURATION OF GESTATION

Duration of Gestation (in weeks)	Total Infants No.	PERINATAL PERIOD				FOLLOW-UP PERIOD					TYPE OF ABNORMALITY				
		Perinatal Mortality No.	Infants With Non-lethal Congenital Defects No.	Remainder Discharged Home No.	%	Infants Seen at Follow-up Clinic No.	Infant Group: Normal No.	%	Abnormal No.	%	Retarded Development No.	Convulsions No.	Additional Congenital Defect No.	Anaemia No.	Bronchitis No.
28 and 29	13	8	0	5	38.4	2	0	0	2	100.0	1	1	0	2	2
30 and 31	44	26	2	16	36.4	11	0	0	11	100.0	5*	0	2	6	4
32, 33 and 34	56	22	3	31	55.3	18	11	61.1	7	38.9	0	0	4	0	2
35 and 36	50	15	1	34	68.0	13	7	53.8	6	46.2	1	1	1	2	1
37, 38 and 39	98	22	4	72	73.5	29	20	68.9	9	31.1	0	0	3	2	5
40 and over	41	7	4	30	73.1	12	5	41.7	7	58.3	1	2	4	2	3
Total Infants	302	100	14	188	62.2	85	43	50.6	42	49.4	8*	4	14	14	17

* Including one case of cerebral palsy.

TABLE LV

SUMMARY OF PERINATAL MORTALITY AND INFANT MORBIDITY IN THE FIRST YEAR OF LIFE IN 302 LOW BIRTH-WEIGHT BABIES GROUPED ACCORDING TO BIRTH WEIGHT

Birth Weight (in Grams)	PERINATAL PERIOD					FOLLOW-UP PERIOD					TYPE OF ABNORMALITY				
	Total Infants No.	Perinatal Mortality No.	Infants With Non-lethal Congenital Defects No.	Remainder Discharged Home No.	%	Infants Seen at Follow-up Clinic No.	Infant Group: Normal No.	Normal %	Infant Group: Abnormal No.	Abnormal %	Retarded Development No.	Convulsions No.	Additional Congenital Defects No.	Anaemia No.	Bronchitis No.
Under 1000	12	12	0	0	0	-	-	-	-	-	-	-	-	-	-
1001 to 1500	36	25	0	11	30.6	8	1	12.5	7	87.5	1	1	1	6	3
1501 to 2000	78	33	4	41	52.6	25	11	44.0	14	56.0	5*	0	2	7	8
2001 to 2500	176	30	10	136	77.3	52	31	59.6	21	40.4	2	3	11	1	6
Total Infants	302	100	14	188	62.2	85	43	50.6	42	49.4	8*	4	14	14	17

* Including one case of cerebral palsy.

TABLE LVI

PERINANTAL MORTALITY AND INFANT MORBIDITY RATE IN 302 LOW BIRTH-WEIGHT BABIES ACCORDING TO THE DURATION OF GESTATION

Gestation Period (in weeks)	Perinatal Mortality and Infant Morbidity, expressed as a Percentage
28 and 29	100.0
30 and 31	100.0
32, 33 and 34	69.0
35 and 36	68.0
37, 38 and 39	49.0
40 and over	63.3
Over-all perinatal mortality and infant morbidity rate	69.9

TABLE LVII

PERINATAL MORTALITY AND INFANT MORBIDITY RATE IN 302 LOW BIRTH-WEIGHT BABIES ACCORDING TO THEIR WEIGHT AT BIRTH

Weight at Birth (in grams)	Perinatal Mortality and Infant Morbidity, expressed as a percentage
1000 and under	100.0
1001 to 1500	100.0
1501 to 2000	76.9
2001 to 2500	55.1
Over-all perinatal mortality and infant morbidity rate	69.9

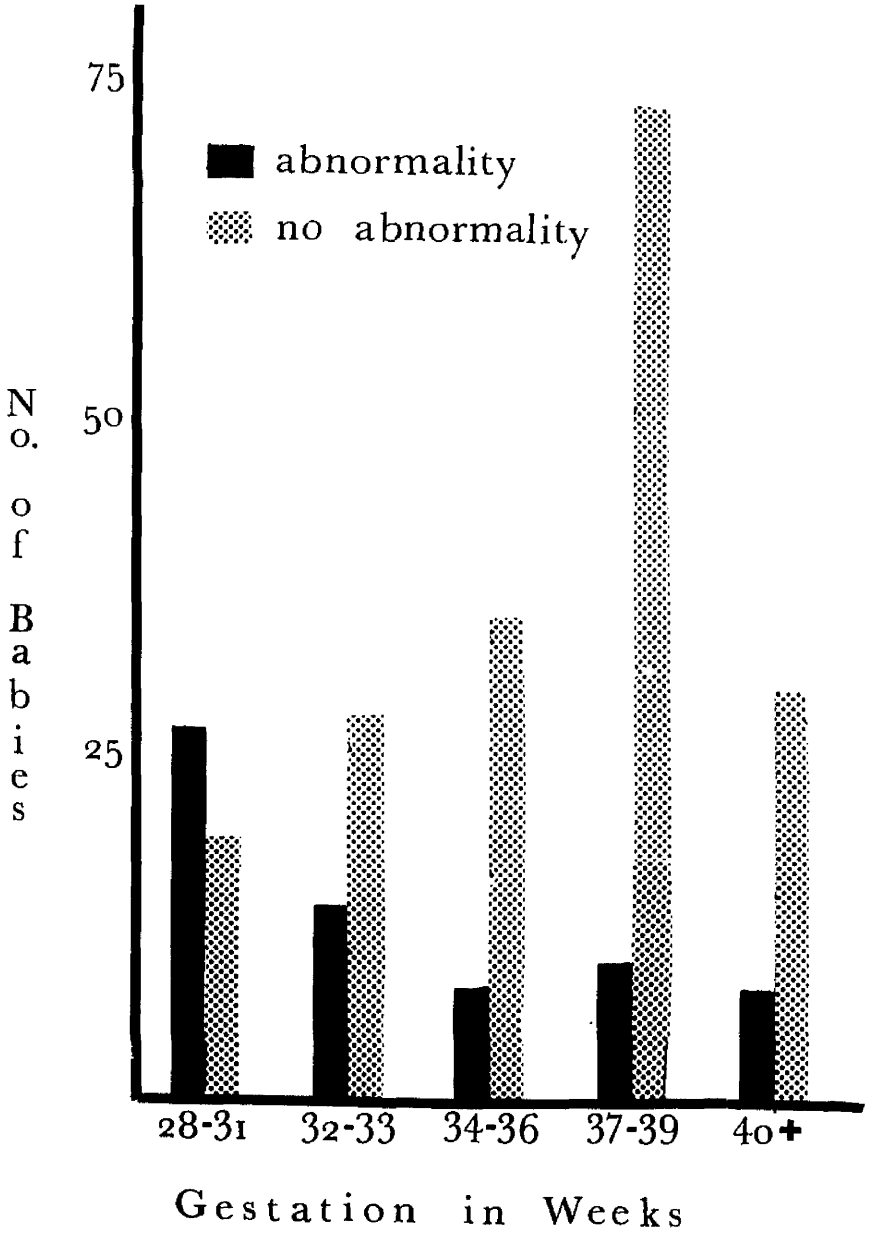

Figure 10a.

The duration of gestation in 66 low-weight babies with respiratory abnormality and 185 without respiratory abnormality at birth and in the first four hours.

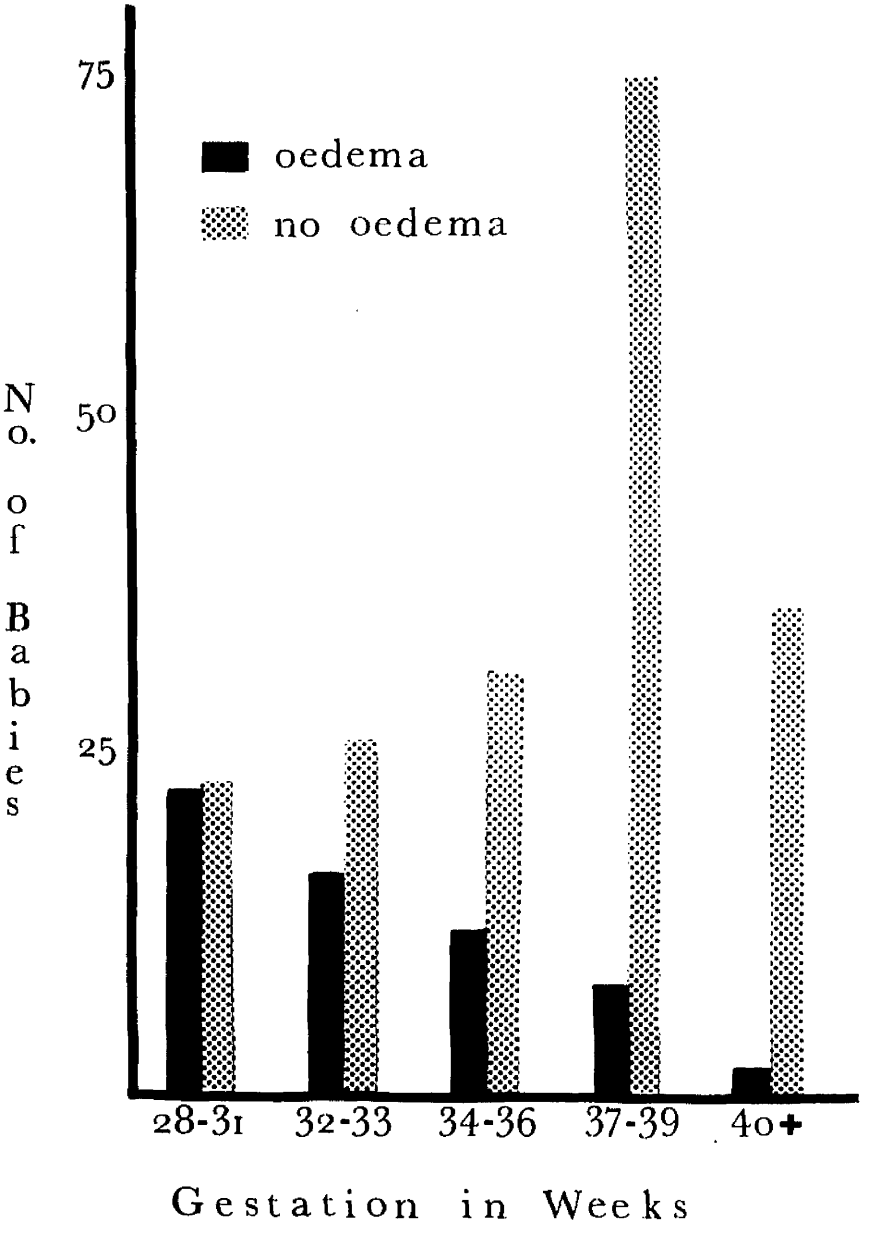

Figure 10b.

The duration of gestation in 60 low-weight babies with oedema and 191 without oedema.

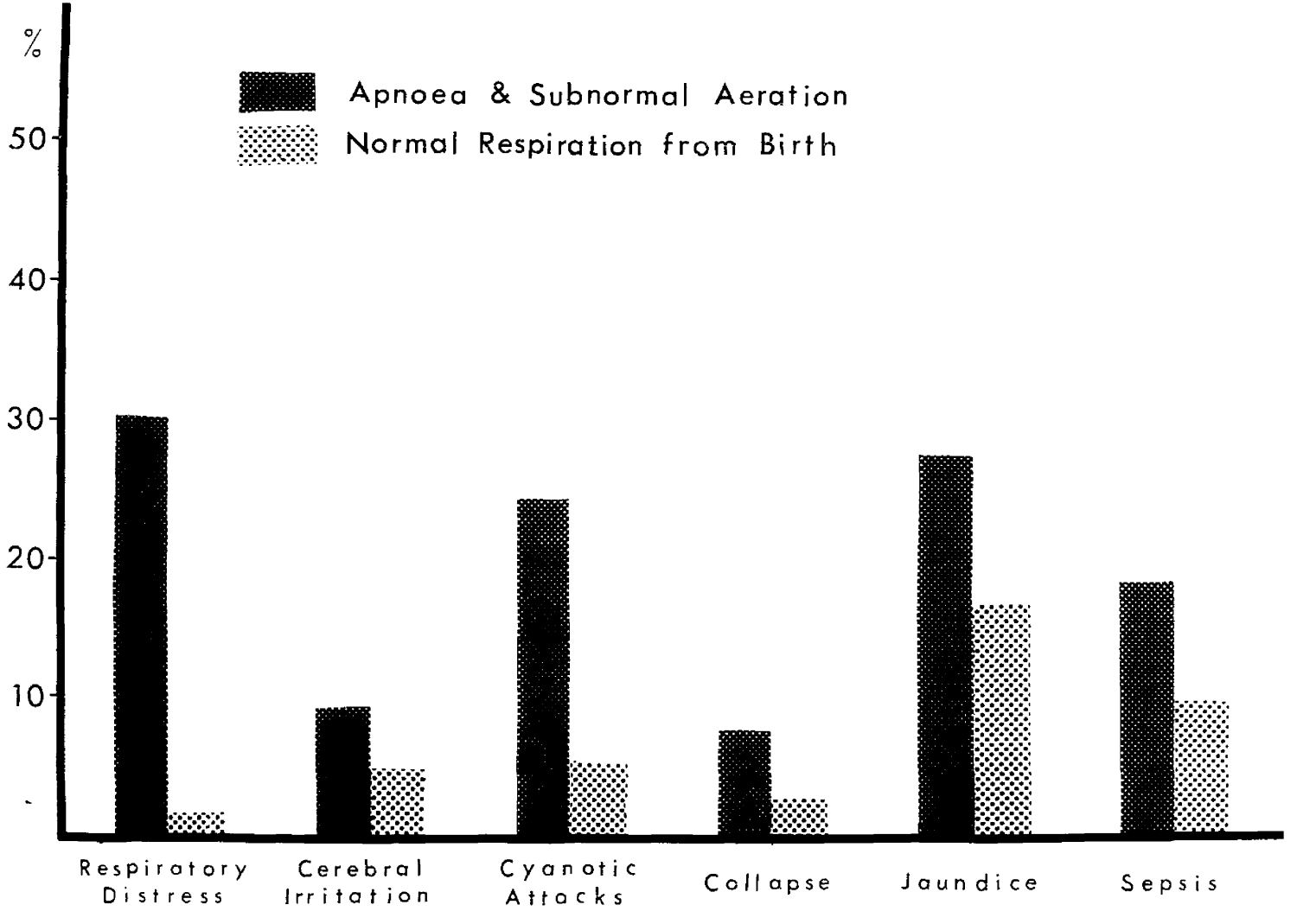

Figure 11.

The relation of respiratory abnormality at birth and under four hours to six abnormalities after four hours of age.

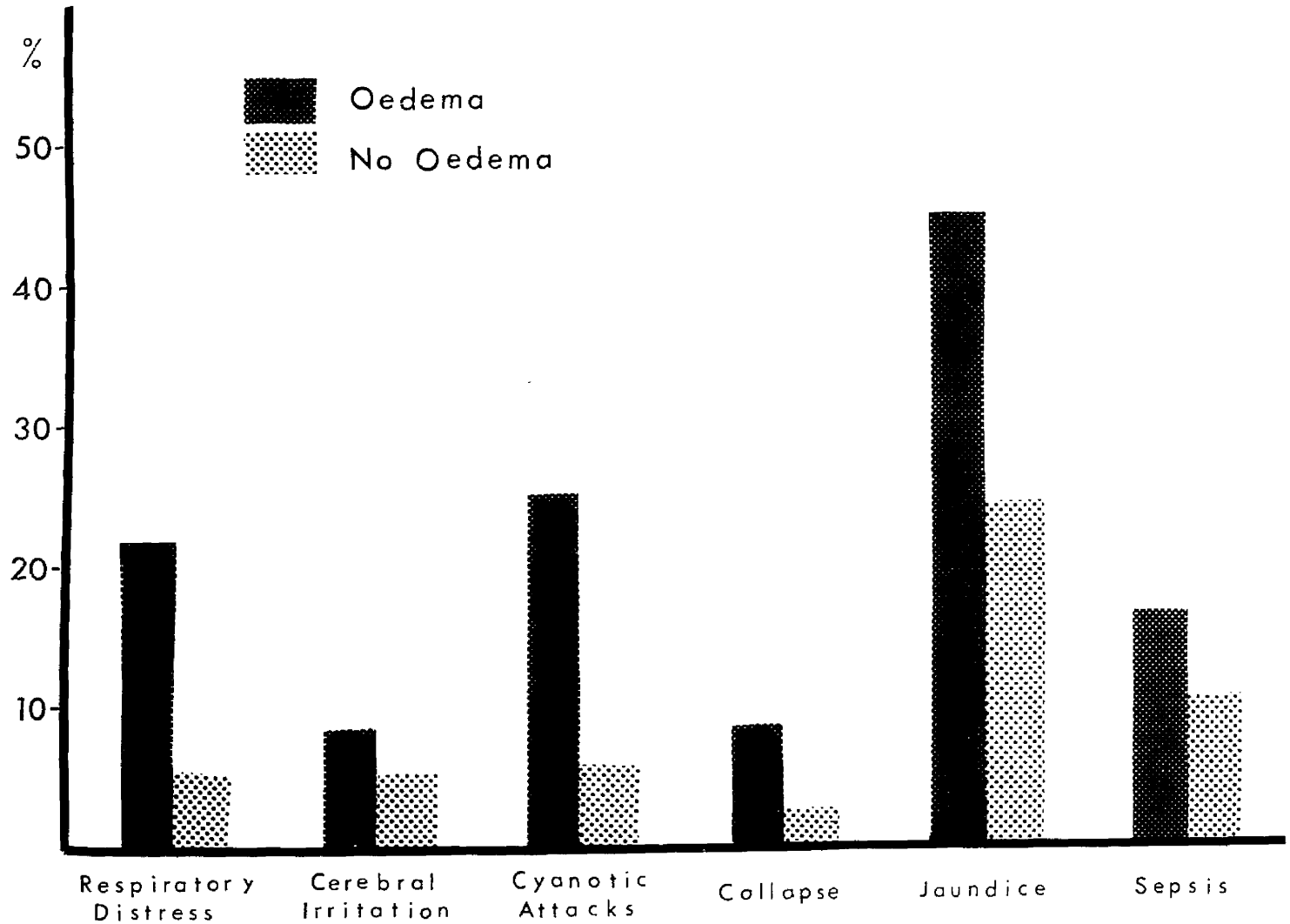

Figure 12.

The relation of oedema at birth and under four hours to six abnormalities after four hours of age.

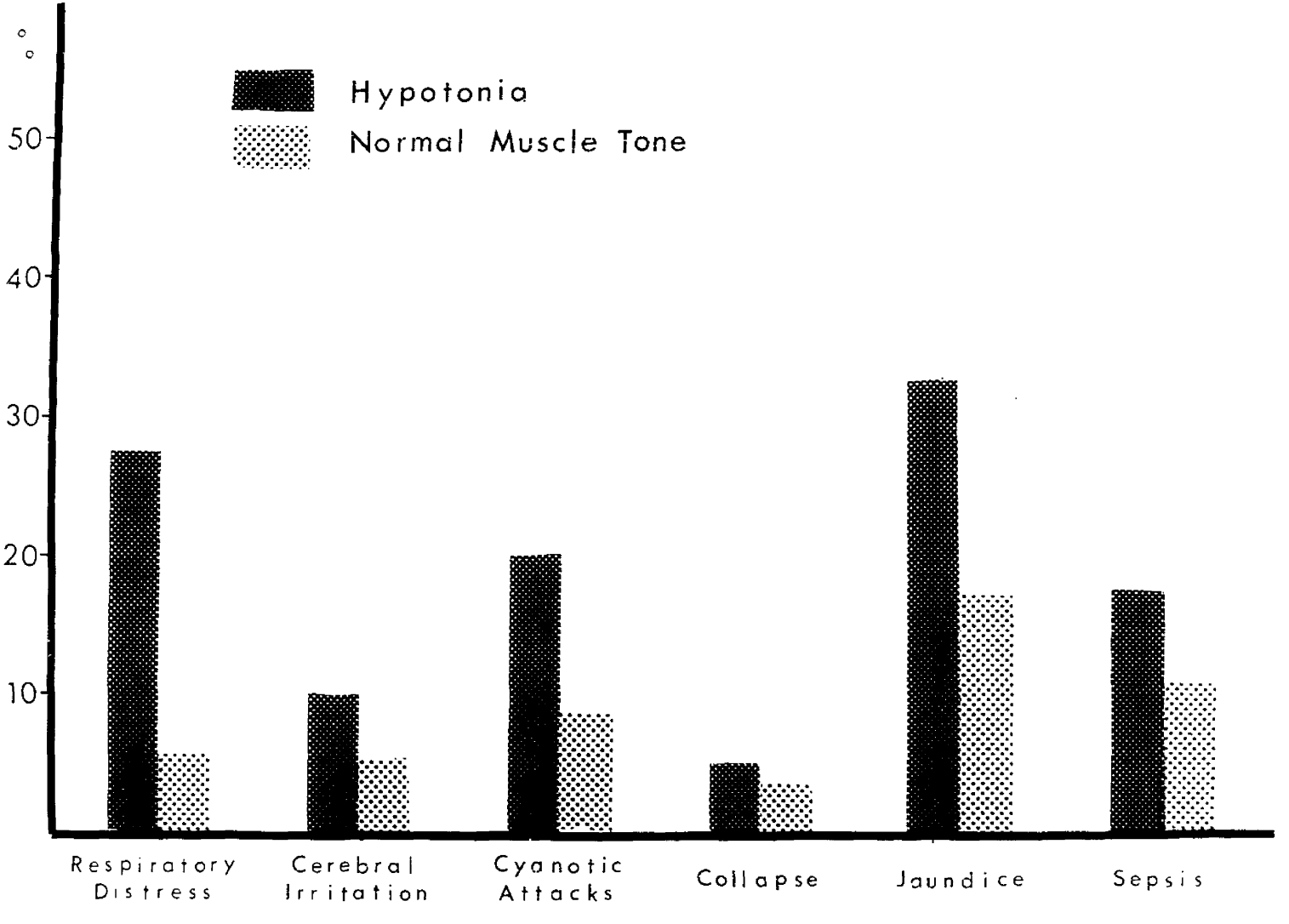

Figure 13.

The relation of hypotonia at birth and under four hours to six abnormalities after four hours of age.

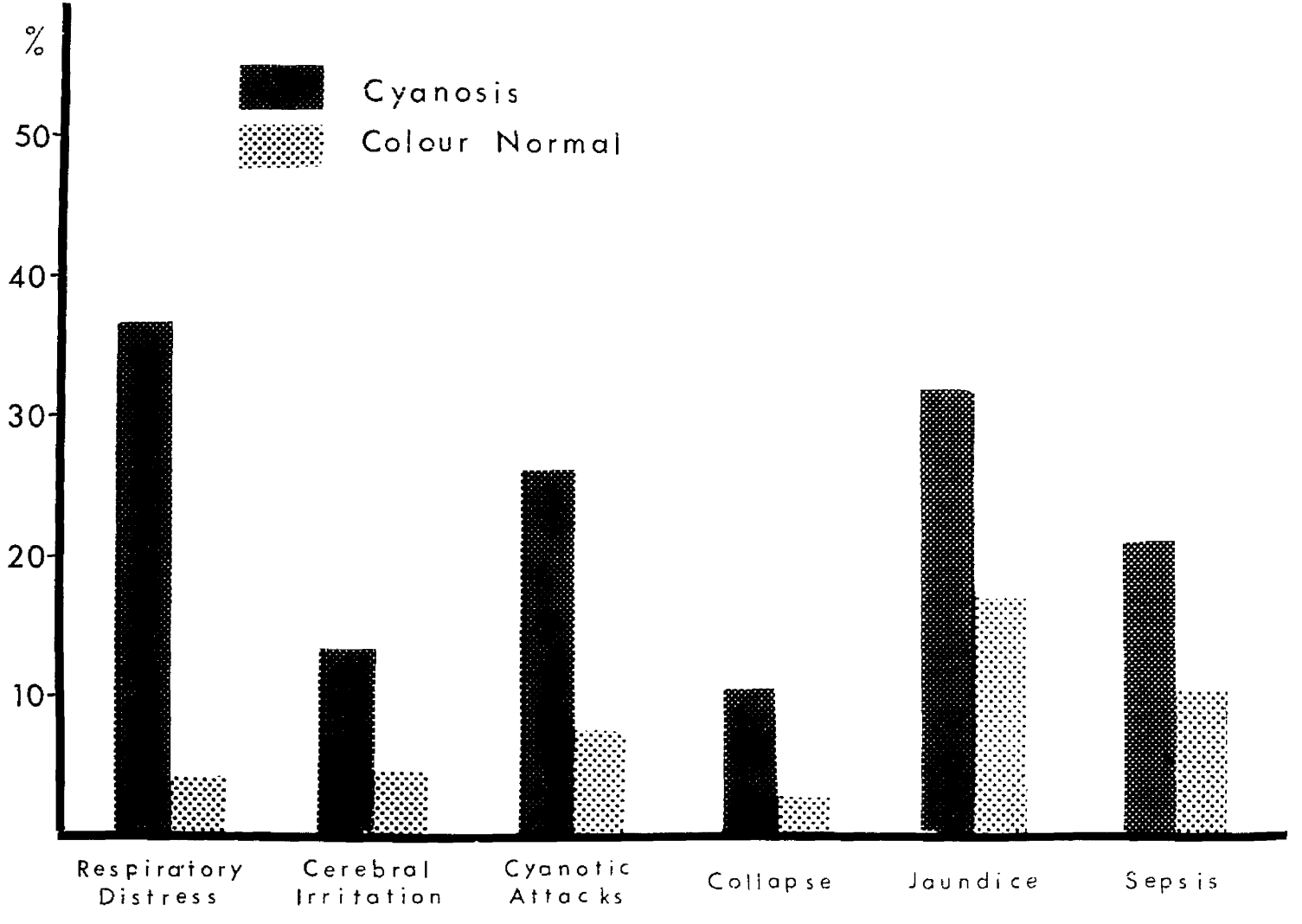

Figure 14.

The relation of cyanosis at birth and under four hours to six abnormalities after four hours of age.

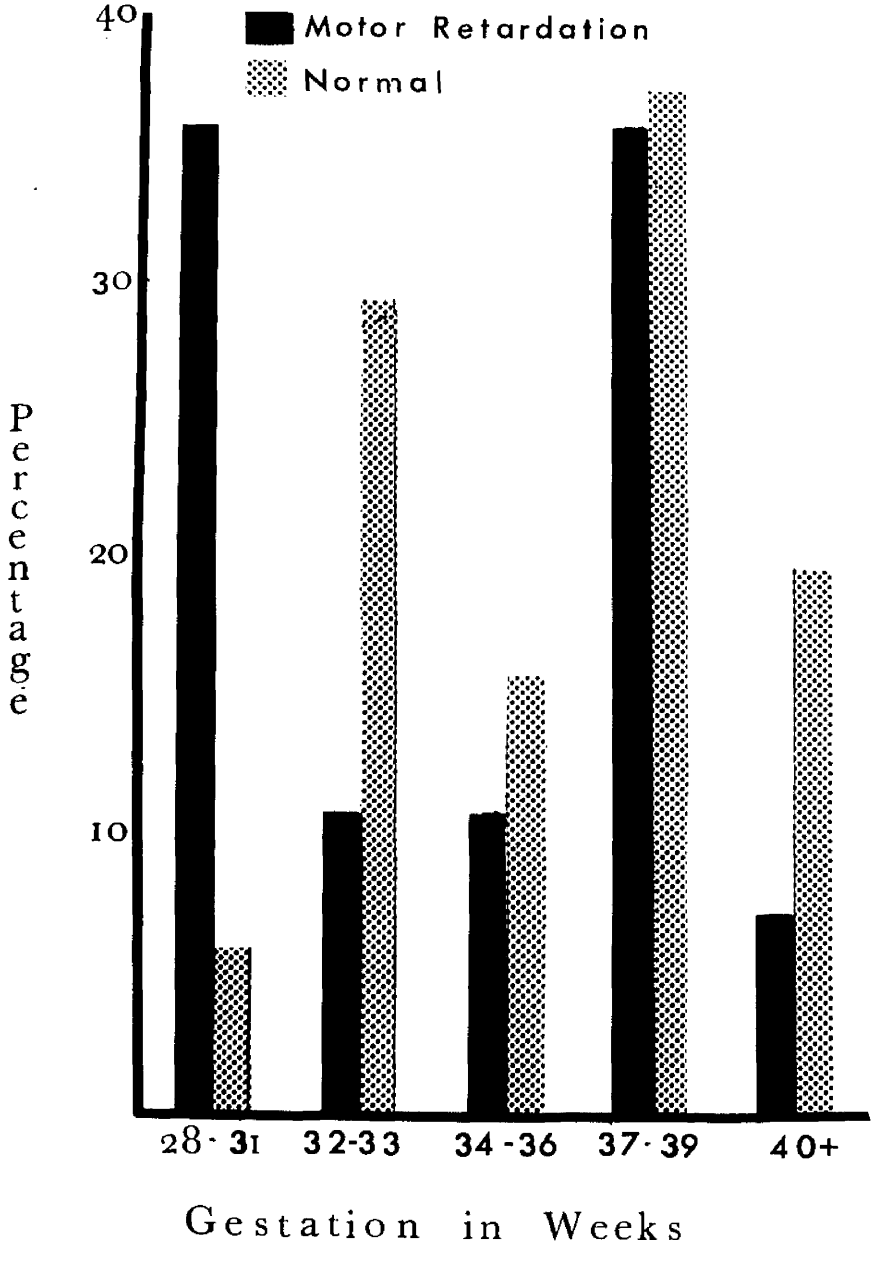

Figure 15a

The duration of gestation in 28 low-weight babies with motor retardation and 55 with normal motor development (as % in each group).

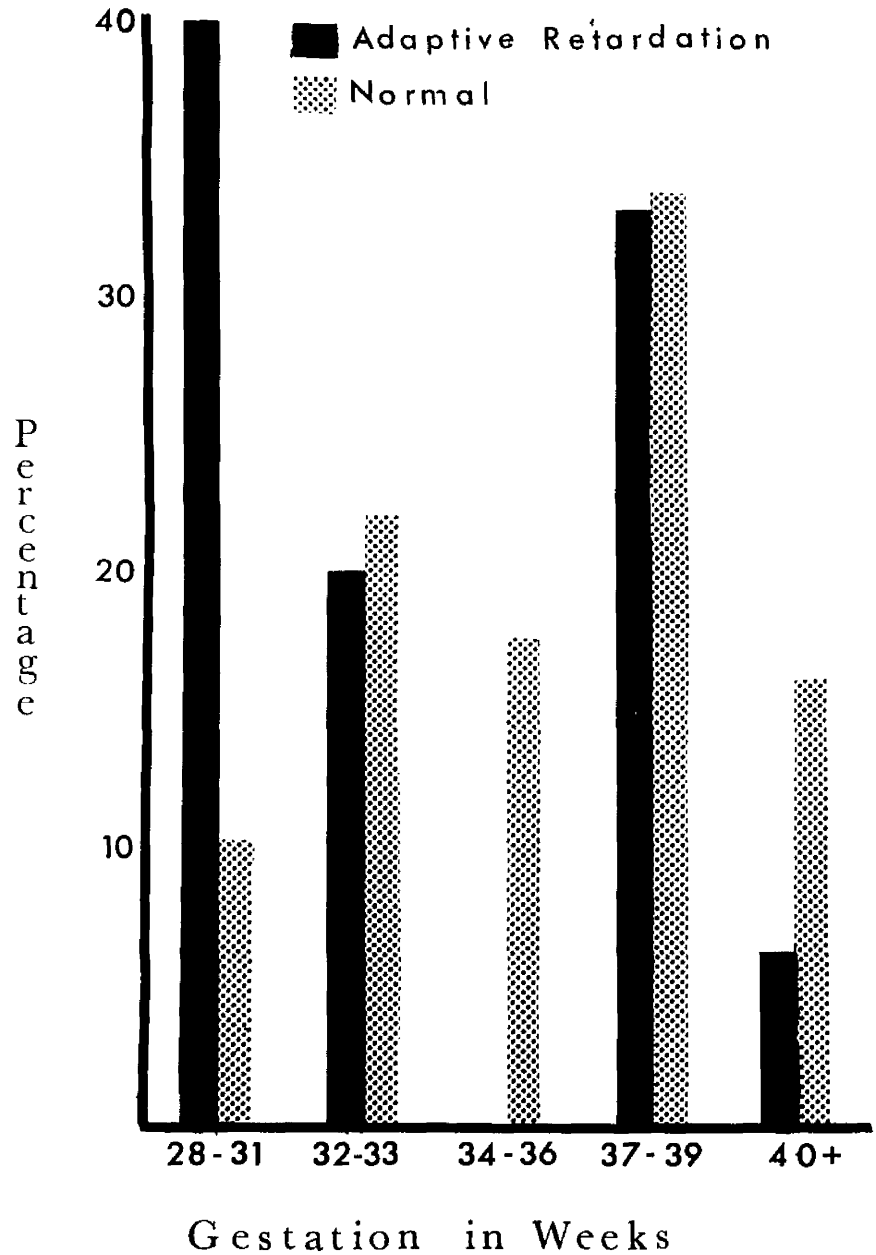

Figure 15b.

The duration of gestation in 15 low-weight babies with adaptive retardation and 68 with normal adaptive development (as % in each group).

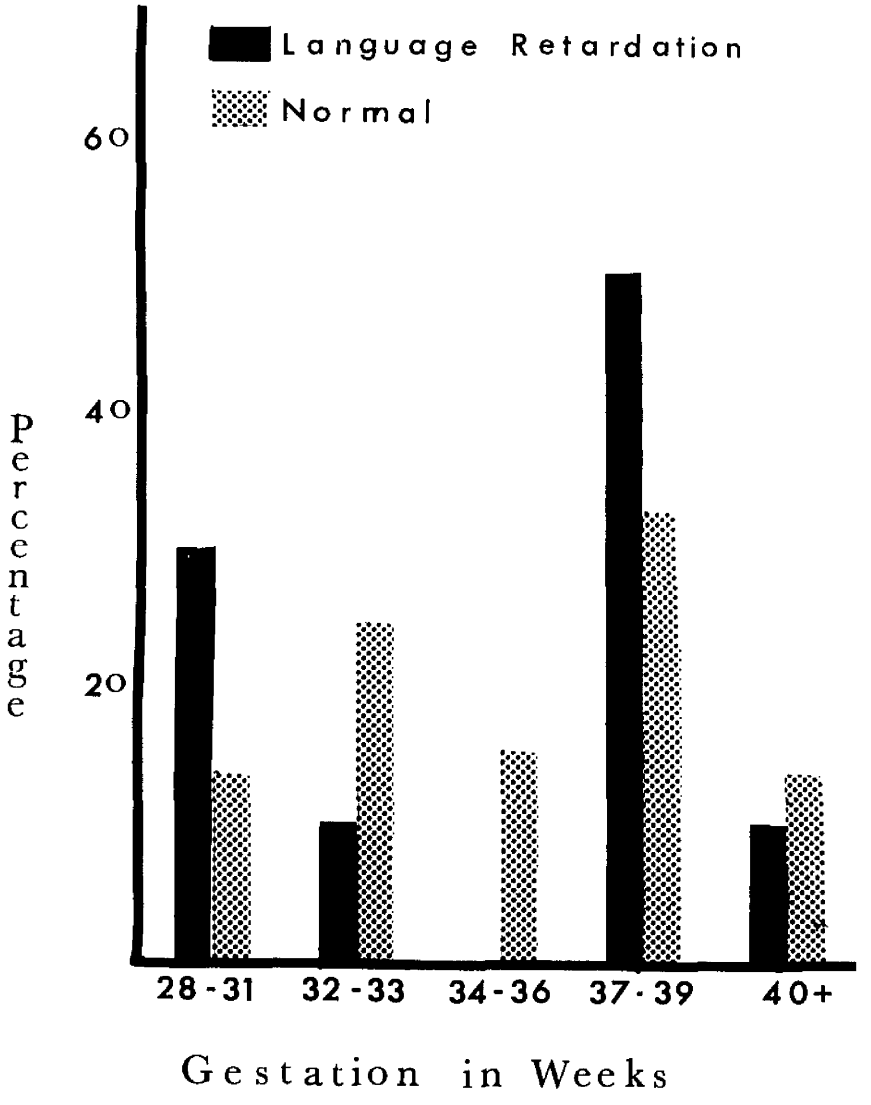

Figure 15c.

The duration of gestation in 10 low-weight babies with language retardation and 73 with normal language development (as % in each group).

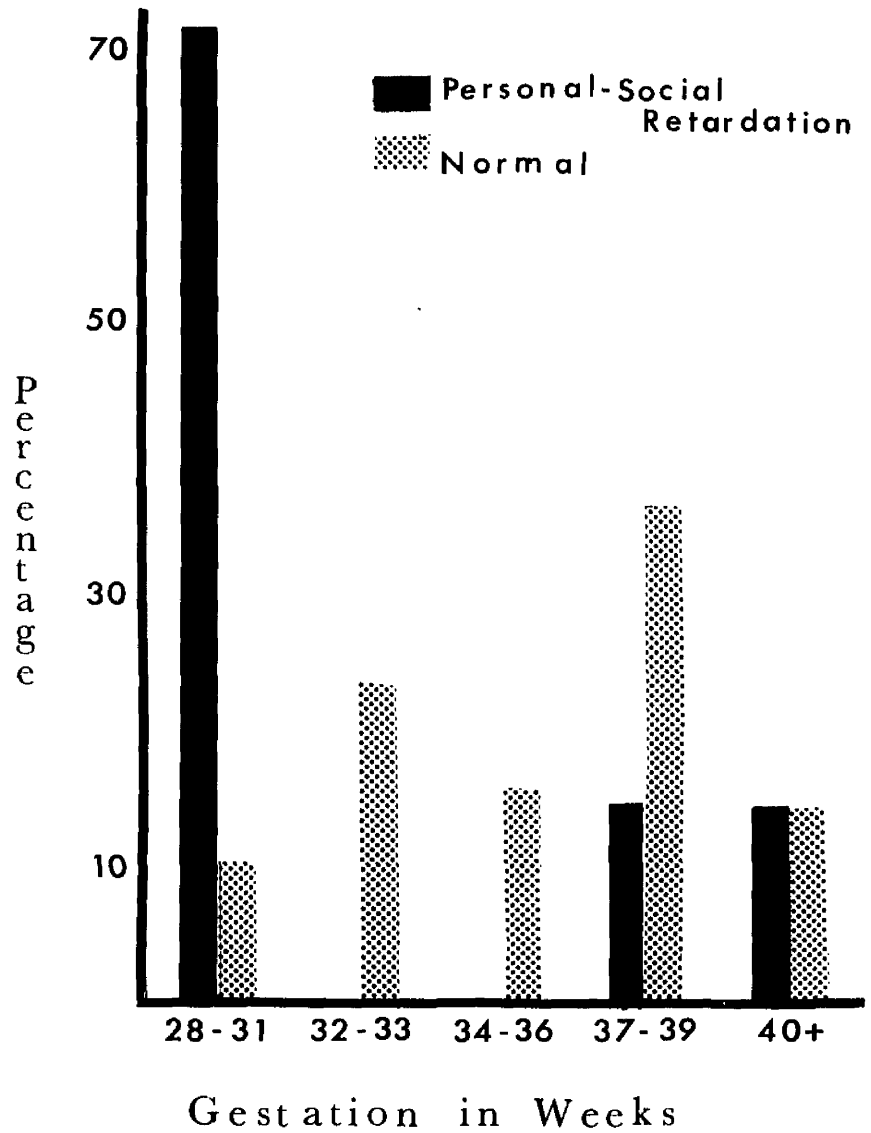

Figure 15d.

The duration of gestation in 7 low-weight babies with personal-social retardation and 77 with normal personal-social development (as % in each group).

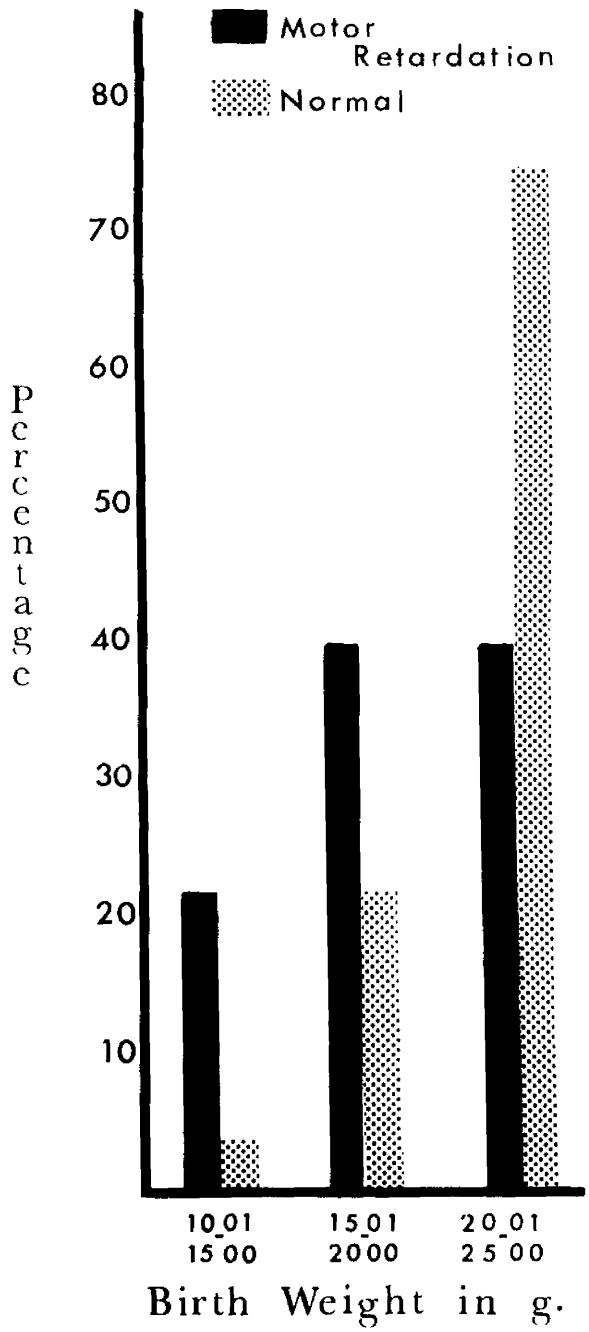

Figure 16a.

The birth-weight in 28 babies with motor retardation and 55 with normal motor development (as % in each group).

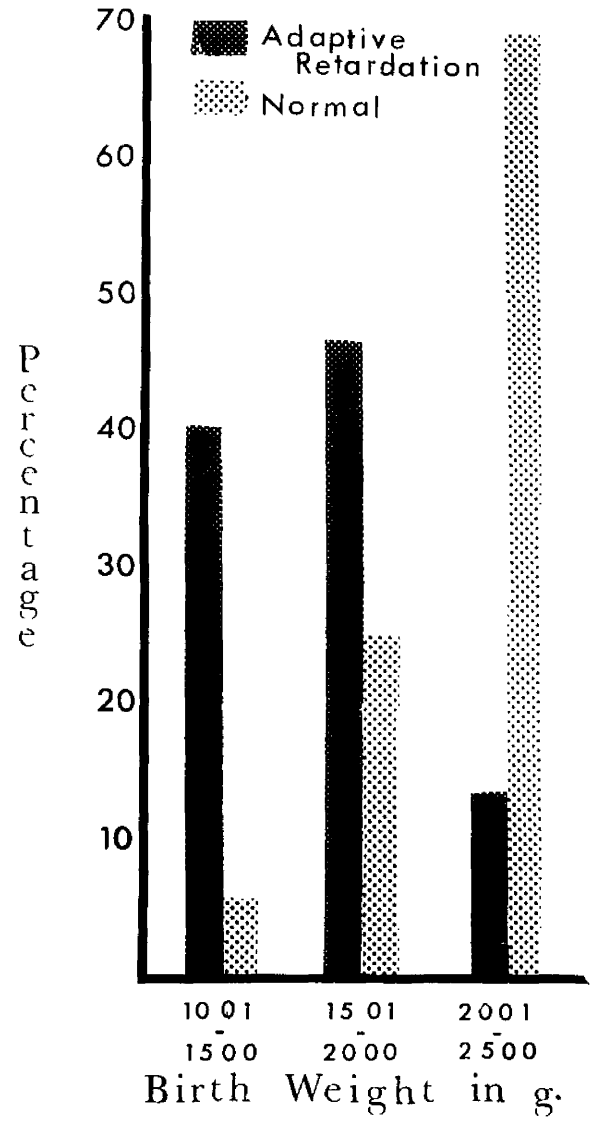

Figure 16b.

The birth weight in 15 babies with adaptive retardation and 68 with normal adaptive development (as % in each group).

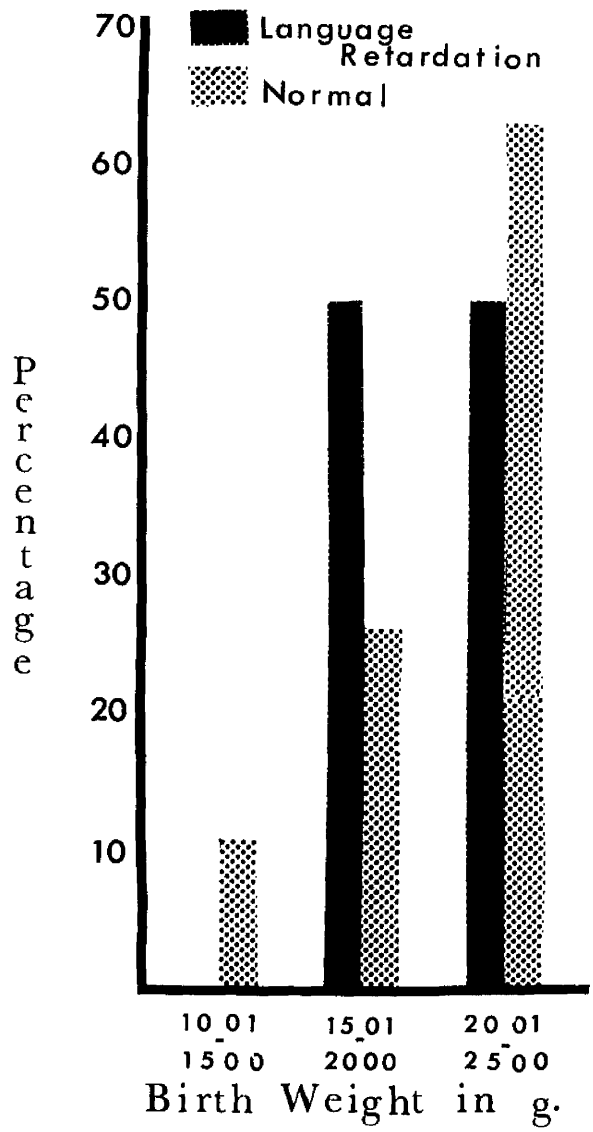

Figure 16c.

The birth weight in 10 babies with language retardation and 73 with normal language development (as % in each group).

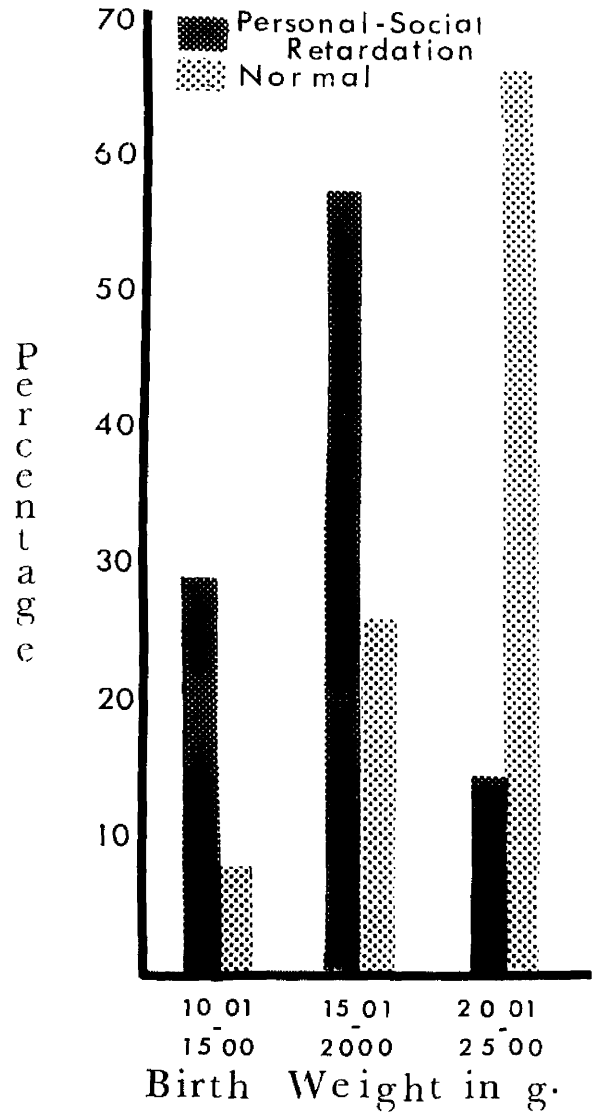

Figure 16d.

The birth weight in 7 babies with personal-social retardation and 77 with normal personal-social development (as % in each group).

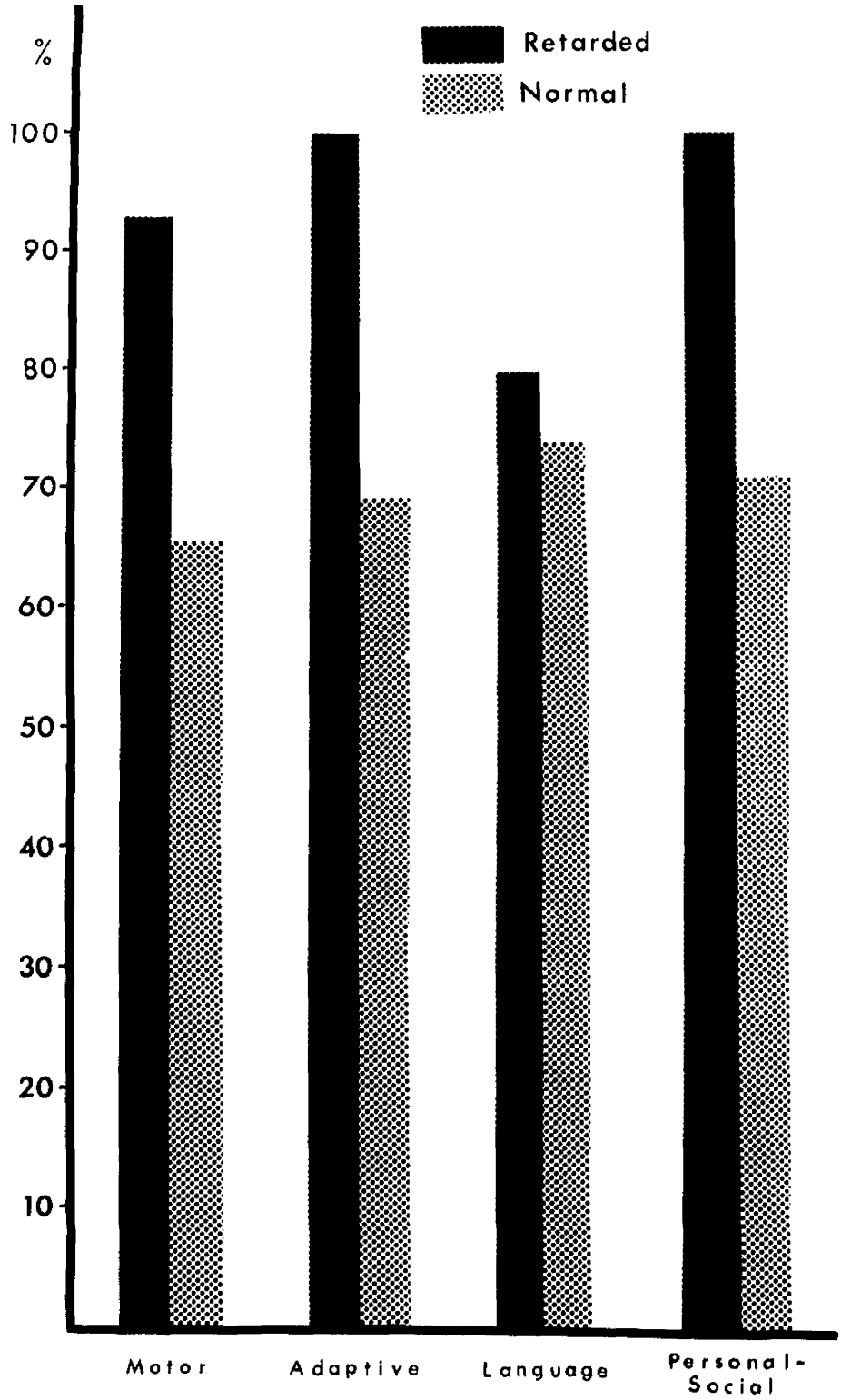

Figure 17.

The incidence of maternal illness (shown as a %) in low weight babies with and without retardation in the four fields of development.

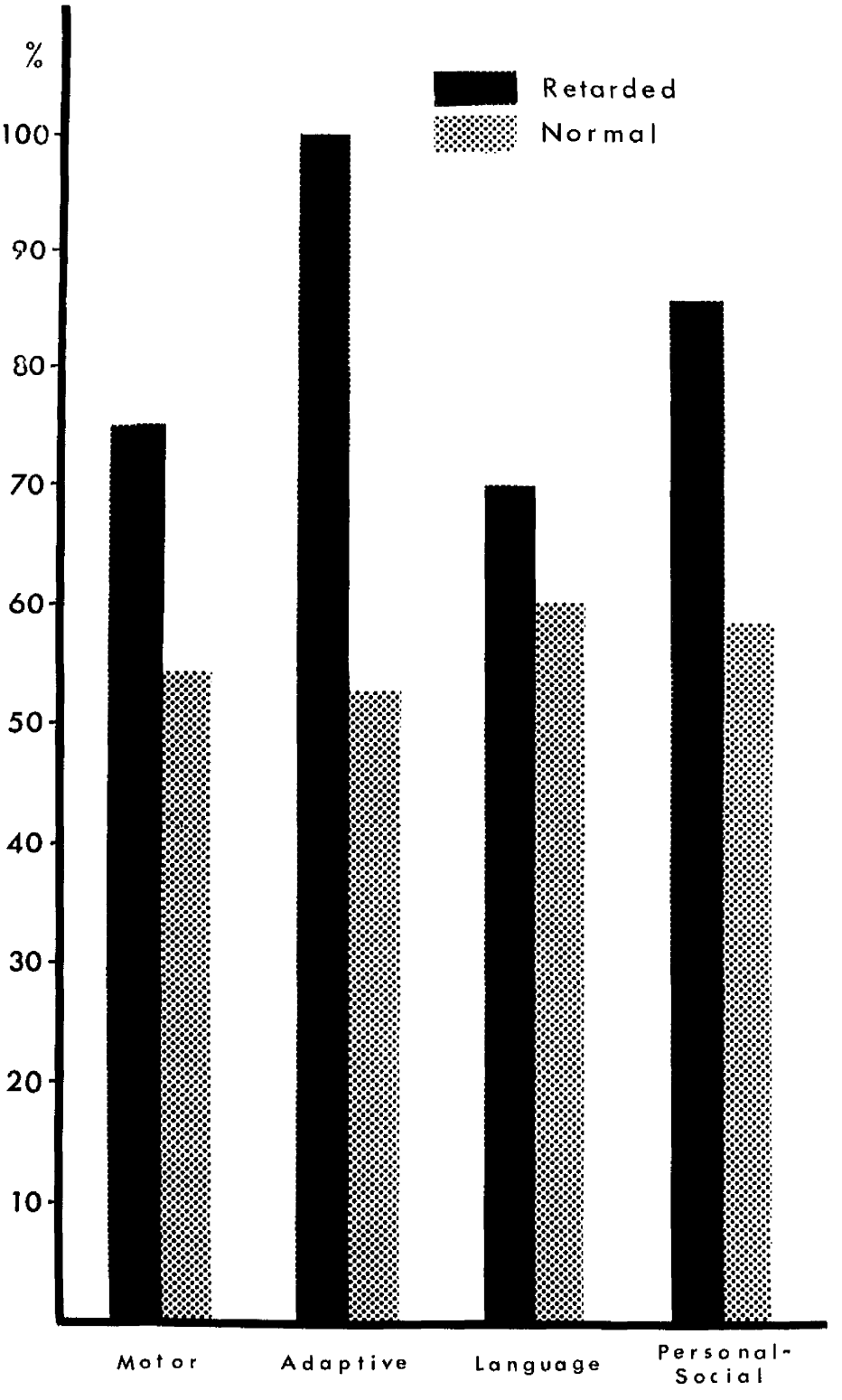

Figure 18.

The incidence of neonatal abnormality at birth and under four hours (shown as a %) in low-weight babies with and without retardation in the four fields of development.

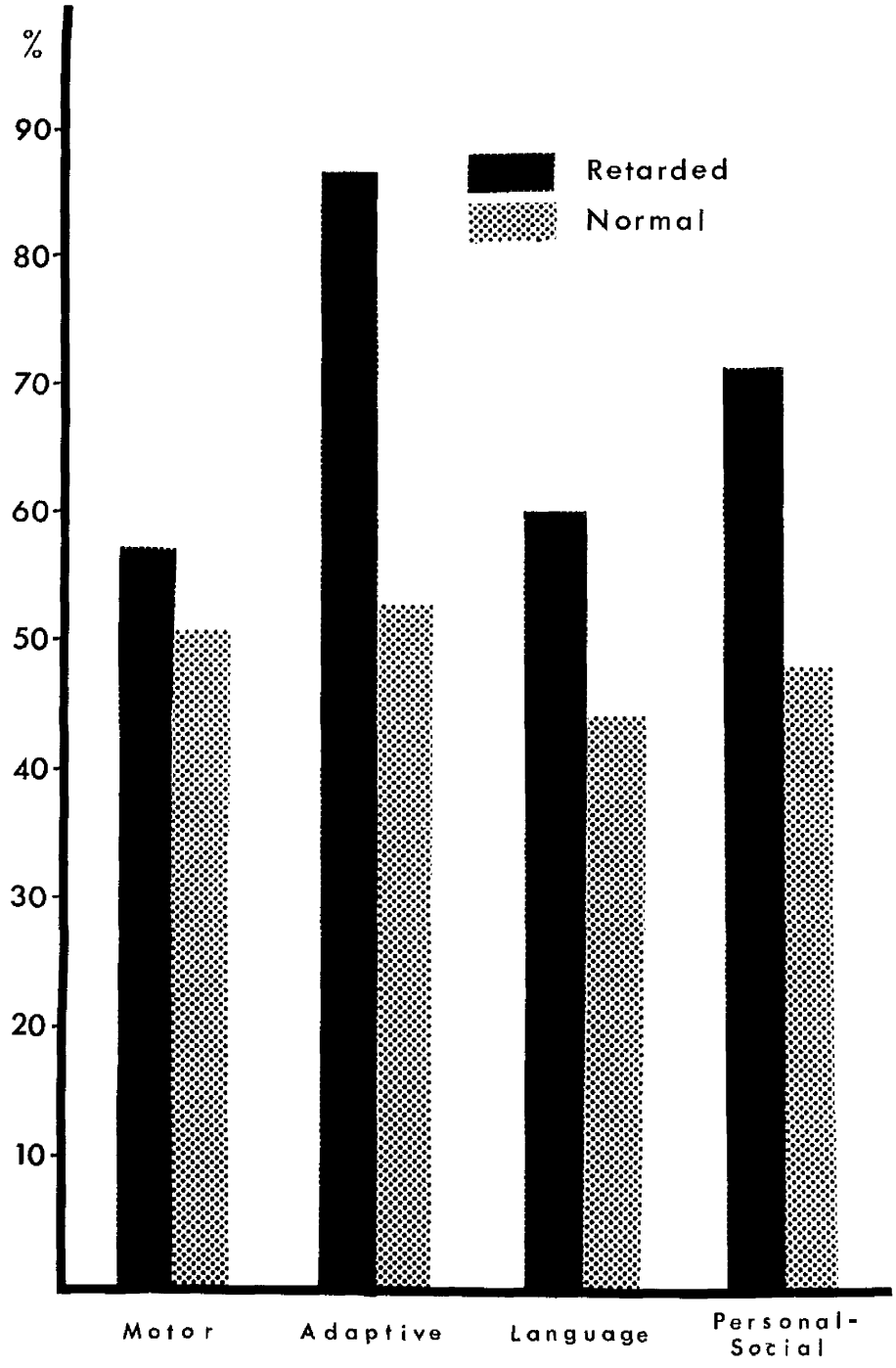

Figure 19.

The incidence of neonatal abnormality after four hours of age (shown as a %) in low-weight babies with and without retardation in the four fields of development.

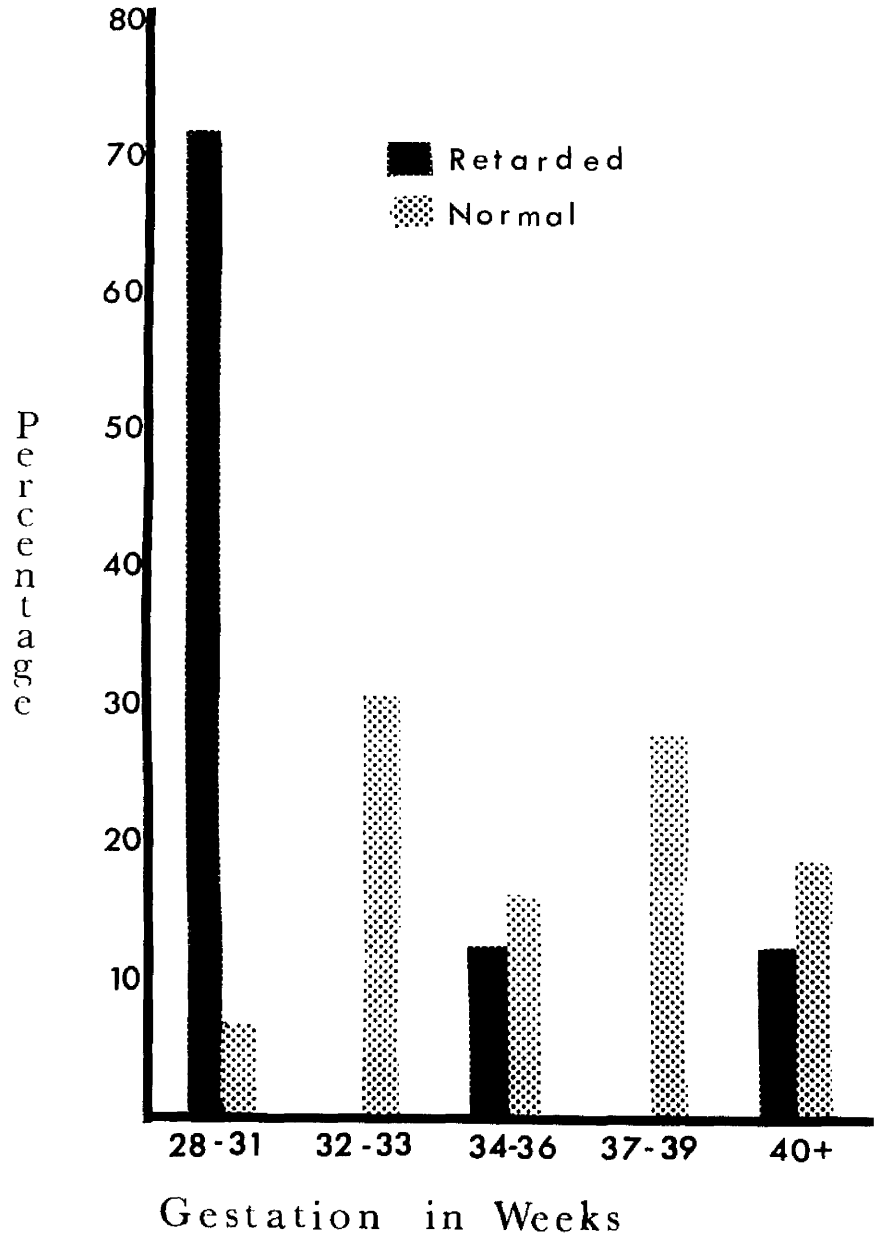

Figure 20.

The duration of gestation in 7 low-weight babies with retardation in more than two fields of development and 43 with no retardation (as % in each group).

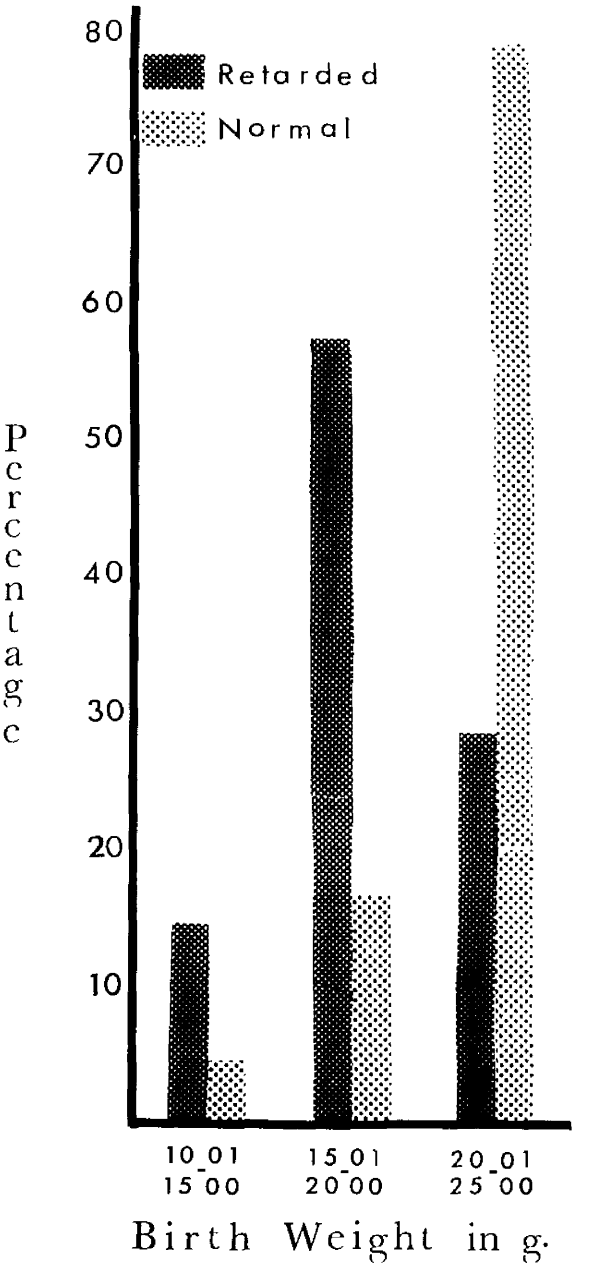

Figure 21.

The birth weight in 7 babies with retardation in more than two fields of development and 43 with no retardation (as % in each group).

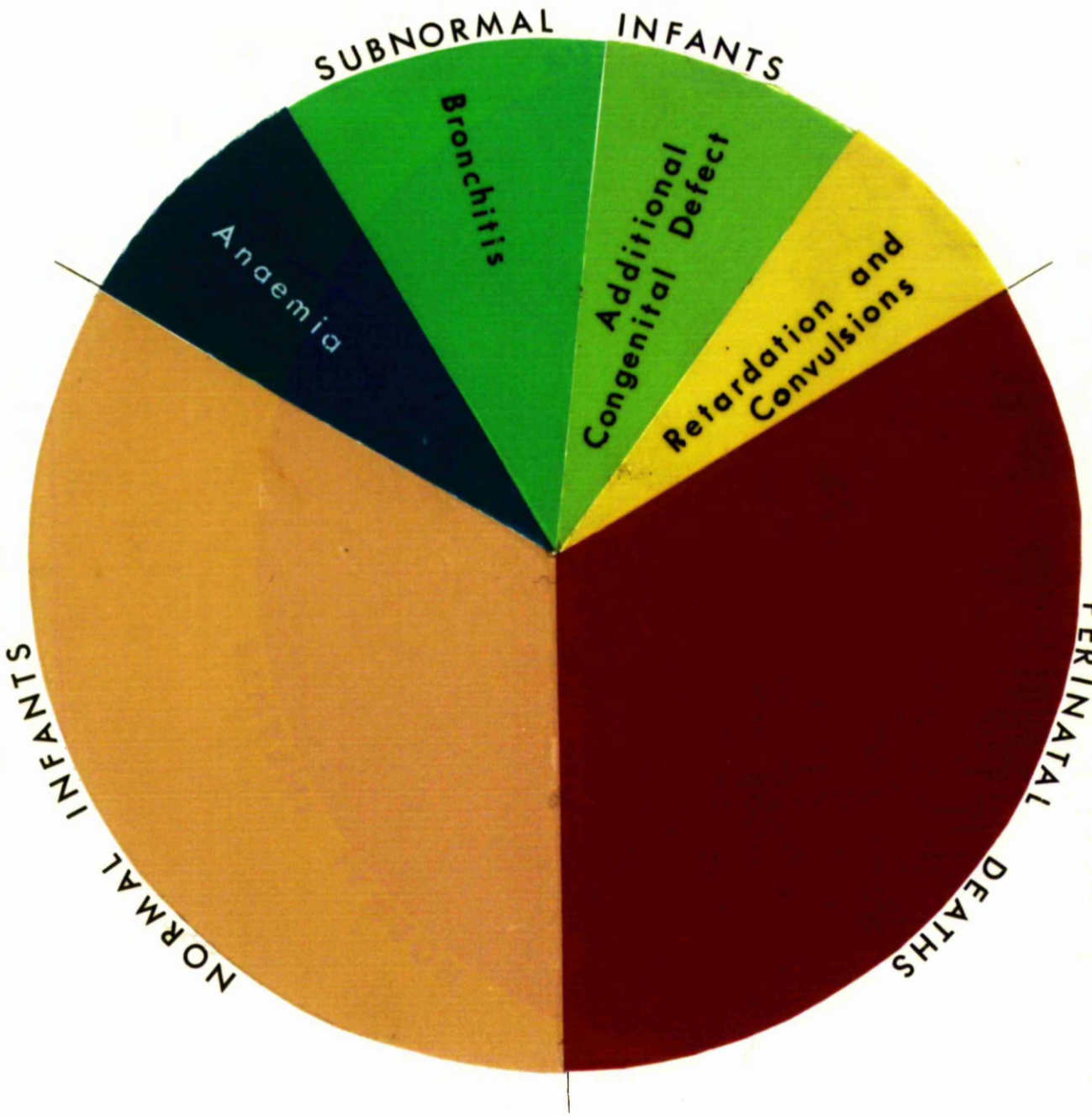

Figure 23.

Summary of perinatal mortality and infant morbidity in 302 low birth-weight babies.

PART III

THE SMALL, "TERM" BABY

TABLE LVIII

NUMBERS OF *MATURE AND IMMATURE LOW BIRTH-WEIGHT BABIES GROUPED ACCORDING TO THE DURATION OF GESTATION

Gestation Period (in Weeks)	Infant Group			
	Mature		Immature	
	No.	%	No.	%
28 and 29	0	0	13	8.0
30 and 31	0	0	44	27.0
32 and 33	0	0	31	19.0
34, 35 and 36	0	0	75	46.0
37 and over	139	100.0	0	0
Total Infants	139	100.0	163	100.0

* Of 37 weeks gestation and over.

TABLE LIX

NUMBERS OF MATURE AND IMMATURE LOW BIRTH-WEIGHT BABIES GROUPED ACCORDING TO BIRTH WEIGHT

Birth Weight (in Grams)	Infant Group			
	Mature		Immature	
	No.	%	No.	%
1000 and less	1	0.7	11	6.7
1001 to 1500	3	2.1	33	20.3
1501 to 2000	24	17.3	54	33.1
2001 to 2500	111	79.9	65	39.9
Total Infants	139	100.0	163	100.0

TABLE LX

NUMBERS OF MATURE AND IMMATURE LOW BIRTH-WEIGHT BABIES GROUPED ACCORDING TO MATERNAL AGE

Maternal Age (in years)	Infant Group			
	Mature		Immature	
	No.	%	No.	%
Under 20	6		11	
20 to 24	50	64.7	44	61.3
25 to 29	34		45	
30 to 34	21		35	
35 to 39	23	35.3	17	38.7
40 and over	5		11	
Total Mothers	139	100.0	163	100.0

TABLE LXI

NUMBERS OF MATURE AND IMMATURE LOW BIRTH-WEIGHT BABIES GROUPED ACCORDING TO THE PARITY OF THEIR MOTHERS

Parity	Infant Group			
	Mature		Immature	
	No.	%	No.	%
0	59	42.4	67	41.1
1 and 2	48	34.5	44	27.0
3 and more	32	23.1	52	31.9
Total Mothers	139	100.0	163	100.0

TABLE LXII

PREVIOUS OBSTETRICAL HISTORY OF 80 MOTHERS OF MATURE LOW BIRTH-WEIGHT BABIES AND 96 MOTHERS OF IMMATURE LOW BIRTH-WEIGHT BABIES

Abnormality	Infant Group				p value
	Mature		Immature		
	No.	%	No.	%	
Miscarriage	34	42.5	35	36.4	<0.50 >0.30
Stillbirth	12	15.0	11	11.4	<0.50 >0.30
Premature Live Birth	28	35.0	39	40.6	<0.30 >0.20
Illness	30	37.5	35	36.4	<0.95 >0.90

TABLE LXIII

NUMBERS OF MATURE AND IMMATURE LOW BIRTH-WEIGHT BABIES GROUPED ACCORDING TO THE NUMBER OF ILLNESSES IN INDIVIDUAL MOTHERS

No. of Illnesses	Infant Group			
	Mature		Immature	
	No.	%	No.	%
None	41	29.5	39	23.9
1	56	40.3	65	39.9
2	32	23.0	45	27.6
3	7	5.0	12	7.4
4	3	2.2	2	1.2
Total Illnesses	153		199	
Total Mothers	139		163	100.0

TABLE LXIV

INCIDENCE AND TYPE OF ILLNESS OCCURRING IN 139 MOTHERS WITH MATURE LOW BIRTH-WEIGHT BABIES AND 163 MOTHERS WITH IMMATURE LOW BIRTH-WEIGHT BABIES

Type of Illness	Infant Group				p value
	Mature		Immature		
	No.	%	No.	%	
*Antepartum Haemorrhage	22	15.8	53	32.5	<0.01
Pre-eclamptic Toxaemia	37	26.6	43	26.4	>0.95
Oedema	1	0.7	0	0	-
Hypertension	14	10.0	8	5.0	<0.50 >0.30
Albuminuria	0	0	0	0	-
Overt Urinary Infection	15	10.8	24	14.7	<0.50 >0.30
Iron Deficiency Anaemia (Haemoglobin < 10.5 g./100 ml.)	33	23.7	41	25.2	<0.90 >0.80
Megaloblastic Anaemia	2	1.4	1	0.6	-
Hydramnios	7	5.0	7	4.3	>0.95
Other	22	15.8	22	13.5	-
Total Illnesses	153		199		

* Excluding that due to placenta praevia and local cervical lesions.

TABLE LXV

NUMBERS OF MATURE AND IMMATURE LOW BIRTH-WEIGHT BABIES GROUPED ACCORDING TO THE DURATION OF MEMBRANE RUPTURE PRIOR TO DELIVERY

Time Interval	Infant Group			
	Mature		Immature	
	No.	%	No.	%
Under 12 hours	84	71.2	77	60.6
12 to 47	24	20.3	30	23.6
48 to 7 days	10	8.5	11	8.7
8 days and longer	0	0	9	7.1
Total Infants	118	100.0	127	100.0

TABLE LXVI

TYPE AND INCIDENCE OF ABNORMALITY AT BIRTH AND UNDER FOUR HOURS OF AGE IN 121 LIVE-BORN, MATURE LOW-WEIGHT BABIES AND 130 LIVE-BORN, IMMATURE LOW-WEIGHT BABIES

Abnormality	Infant Group				p value
	Mature		Immature		
	No.	%	No.	%	
* Respiratory	18	14.9	48	36.9	<0.01
Oedema	10	8.3	50	38.4	<0.01
Hypotonia	15	12.4	25	19.2	<0.20 >0.10
Cyanosis	13	10.7	25	19.2	<0.20 >0.10

* Respiratory abnormality includes apnoea at birth, and subnormal aeration.

TABLE LXVII

TYPE AND INCIDENCE OF ABNORMALITY AT OVER FOUR HOURS OF AGE IN 120 SURVIVING MATURE LOW-WEIGHT BABIES AND 125 SURVIVING IMMATURE LOW-WEIGHT BABIES

Abnormality	Infant Group				p value
	Mature		Immature		
	No.	%	No.	%	
Respiratory Distress	6	5.0	17	13.6	<0.05 >0.02
*Cerebral Irritation	7	5.8	8	6.4	>0.95
Cyanotic Attacks	4	3.3	22	17.5	<0.01
Collapse	3	2.5	7	5.6	<0.30 >0.20
Jaundice	14	11.7	35	28.0	<0.01
Sepsis	9	7.5	21	16.4	<0.10 >0.05

* Cerebral irritation includes twitching, tremor, irritability and abnormal cry.

TABLE LXVIII

NUMBERS OF MATURE AND IMMATURE LOW BIRTH-WEIGHT BABIES GROUPED ACCORDING TO THEIR AGE AT DISCHARGE FROM HOSPITAL

Age in Days	Infant Group			
	Mature		Immature	
	No.	%	No.	%
10 and less	63	57.3	13	14.1
11 to 20	25	22.7	26	28.3
21 to 35	13	11.8	23	25.0
36 to 49	6	5.5	15	16.3
50 and over	3	2.7	15	16.3
Total Infants	110	100.0	92	100.0

TABLE LXIX

NUMBERS OF MATURE AND IMMATURE LOW BIRTH-WEIGHT BABIES DYING PERINATALLY, GROUPED ACCORDING TO THE TIME OF DEATH

Time of Death	Infant Group			
	Mature		Immature	
	No.	%	No.	%
Before Delivery (Stillbirth)	18	62.1	33	46.5
Before 4 hours of age	1	3.4	5	7.0
After 4 hours of age	10	34.5	33	46.5
Total Infants	29	100.0	71	100.0

PART IV

PERINATAL CHARACTERISTICS OF TWIN PREGNANCY ASSOCIATED WITH LOW BIRTH WEIGHT

TABLE LXX

NUMBERS OF TWIN PREGNACIES, WHERE ONE OR BOTH BABIES WERE OF LOW BIRTH-WEIGHT, GROUPED ACCORDING TO THE DURATION OF GESTATION

Gestation Period (in weeks)	Pairs of Twins No.	%	
Under 28	2	3.9	
28 and 29	0	0	
30 and 31	5	9.8	64.6
32 and 33	9	17.6	
34, 35 and 36	17	33.3	
37, 38 and 39	11	21.7	35.4
40 and over	7	13.7	
Total Pairs	51	100.0	

TABLE LXXI

NUMBERS OF TWIN BABIES, WHERE ONE OR BOTH BABIES WERE OF LOW BIRTH-WEIGHT, GROUPED ACCORDING TO BIRTH WEIGHT

Birth Weight (in grams)	Twin Babies		
	No.	%	
1500 and less	12	11.8	
1501 to 2000	24	23.5	79.4
2001 to 2500	45	44.1	
2501 and over	21	20.6	
Total Babies	102	100.0	

TABLE LXXII

NUMBERS OF MOTHERS OF TWINS, WHERE ONE OR BOTH BABIES WERE OF LOW BIRTH-WEIGHT, AND OF SINGLE BABIES OF NORMAL BIRTH-WEIGHT CLASSIFIED ACCORDING TO AGE

Maternal Age (in years)	Group of Mothers					
	With Twins			With Single Normal-Weight Babies		
	No.	%		No.	%	
Under 20	2	3.9		8	8.0	
20 to 24	16	31.4	62.7	34	34.0	76.0
25 to 29	14	27.5		34	34.0	
30 to 34	14	27.5		10	10.0	
35 to 39	5	9.8	37.3	11	11.0	24.0
40 and over	0	0		3	3.0	
Total Mothers	51	100.0		100	100.0	

TABLE LXXIII

NUMBERS OF MOTHERS OF TWINS, WHERE ONE OR BOTH BABIES WERE OF LOW BIRTH-WEIGHT, AND OF MOTHERS OF SINGLE BABIES OF LOW BIRTH-WEIGHT CLASSIFIED ACCORDING TO AGE

Maternal Age (in years)	Group of Mothers					
	With Twins			With Single Low-Weight Babies		
	No.	%		No.	%	
Under 20	2	3.9		17	5.6	
20 to 24	16	31.4	62.7	94	31.1	62.9
25 to 29	14	27.5		79	26.2	
30 to 34	14	27.5		56	18.5	
35 to 39	5	9.8	37.3	40	13.3	37.1
40 and over	0	0		16	5.3	
Total Mothers	51	100.0		302	100.0	

TABLE LXXIV

NUMBERS OF MOTHERS OF TWINS, WHERE ONE OR BOTH BABIES WERE OF LOW BIRTH-WEIGHT, AND OF MOTHERS OF SINGLE BABIES OF NORMAL BIRTH WEIGHT CLASSIFIED ACCORDING TO PARITY

Parity	Group of Mothers			
	With Twins		With Single Normal-Weight Babies	
	No.	%	No.	%
0	18	35.3	44	44.0
1 and 2	23	45.1	42	42.0
3 and more	10	19.6	14	14.0
Total Mothers	51	100.0	100	100.0

TABLE LXXV

NUMBERS OF MOTHERS OF TWINS, WHERE ONE OR BOTH BABIES WERE OF LOW BIRTH-WEIGHT, AND OF MOTHERS OF SINGLE BABIES OF LOW BIRTH WEIGHT CLASSIFIED ACCORDING TO PARITY

Parity	Group of Mothers			
	With Twins		With Single Low-Weight Babies	
	No.	%	No.	%
0	18	35.3	126	41.7
1 and 2	23	45.1	92	30.5
3 and more	10	19.6	84	27.8
Total Mothers	51	100.0	302	100.0

TABLE LXXVI

TYPE AND INCIDENCE OF ILLNESS IN 51 MOTHERS WITH TWIN PREGNANCY WHERE ONE OR BOTH BABIES WERE OF LOW BIRTH WEIGHT AND 100 MOTHERS OF NORMAL-WEIGHT SINGLETON INFANTS

Type of Illness	Group of Mothers				p value
	With Twins		With Singletons		
	No.	%	No.	%	
*Antepartum Haemorrhage	9	17.6	13	13.0	<0.50 >0.30
Pre-eclamptic Toxaemia	19	37.3	14	14.0	<0.01
Hypertension	2	3.9	8	8.0	<0.50 >0.30
Oedema	2	3.9	0	0	-
Overt Renal-Tract Infection	7	13.7	9	9.0	<0.50 >0.30
Iron-deficiency Anaemia (Hb. < 10.5 g./100 ml.)	ǂ22	51.1	°35	35.3	<0.10 >0.05
Megaloblastic Anaemia	2	3.9	0	0	-
Hydramnios	3	5.9	1	1.0	<0.10 >0.05
Miscellaneous	6	-	7	7.0	-

* Excluding that due to placenta praevia and local cervical lesions.

ǂ 43 cases only. ° 99 cases only.

TABLE LXXVII

TYPE AND INCIDENCE OF ILLNESS IN 51 MOTHERS WITH TWIN PREGNANCY WHERE ONE OR BOTH BABIES WERE OF LOW BIRTH WEIGHT AND 302 MOTHERS OF LOW-WEIGHT SINGLETON INFANTS

Type of Illness	Group of Mothers				p value
	With Twins		With Low-weight Singletons		
	No.	%	No.	%	
*Antepartum Haemorrhage	9	17.6	75	24.8	÷
Pre-eclamptic Toxaemia	19	37.3	80	26.5	<0.30 >0.20
Hypertension only	2	3.9	22	7.3	÷
Oedema only	2	3.9	1	0.33	÷
Overt Renal-Tract Infection	7	13.7	39	12.9	÷
Iron-deficiency Anaemia	†22	51.1	°74	24.5	<0.01
Megaloblastic Anaemia	2	3.9	3	0.9	÷
Hydramnios	3	3.9	14	4.0	÷
Miscellaneous	6	-	44	-	-

* Excluding that due to placenta praevia and local cervical lesions.
÷ Not Statistically significant. † 43 cases only. ° 263 cases only.

TABLE LXXVIII

INCIDENCE OF CERTAIN ABNORMALITIES OCCURRING AT UNDER FOUR HOURS OF AGE IN TWIN BABIES, WHERE ONE OR BOTH BABIES WERE OF LOW BIRTH WEIGHT, GROUPED ACCORDING TO BIRTH SIZE AND ORDER

Abnormality	Infant Group							
	Big 1st		Big 2nd		Small 1st		Small 2nd	
	No.	% of whole group (25)	No.	% of whole group (22)	No.	% of whole group (22)	No.	% of whole group (26)
*Respiratory	1	4.0	7	31.8	6	27.3	5	21.7
Oedema	3	12.0	9	40.9	7	31.8	5	21.7
Hypotonia	3	12.0	3	13.6	0	0	5	21.7
Cyanosis	1	4.0	6	27.3	2	9.1	3	13.0

* Respiratory abnormality comprises apnoea and subnormal aeration.

TABLE LXXIX

INCIDENCE OF CERTAIN ABNORMALITIES OCCURRING AT OVER FOUR HOURS OF AGE IN TWIN BABIES, WHERE ONE OR BOTH BABIES WERE OF LOW BIRTH WEIGHT, GROUPED ACCORDING TO BIRTH SIZE AND ORDER

Abnormality	Infant Group							
	Big 1st		Big 2nd		Small 1st		Small 2nd	
	No.	% of whole group (24)	No.	% of whole group (22)	No.	% of whole group (21)	No.	% of whole group (23)
Respiratory Distress	0	0	3	13.6	1	4.5	1	4.3
*Cerebral Irritation	3	12.5	1	4.5	0	0	4	17.4
Cyanotic Attacks	0	0	2	9.1	1	4.5	0	0
Collapse	0	0	2	9.1	0	0	0	0
Jaundice	4	16.6	6	27.3	5	22.7	3	13.0
Sepsis	4	16.6	3	13.6	3	13.6	4	17.4

* Cerebral irritation comprises irritability, tremor, twitching and abnormal cry.

TABLE LXXX

NUMBER OF TWIN BABIES, WHERE ONE OR BOTH BABIES WERE OF LOW BIRTH-WEIGHT, CLASSIFIED ACCORDING TO THEIR AGE AT DISCHARGE AND SHOWING RELATIVE BIRTH SIZE AND ORDER

Age in Days	Group of Babies							
	Big 1st		Big 2nd		Small 1st		Small 2nd	
	No.	%	No.	%	No.	%	No.	%
10 and less	11	47.8	7	30.5	4	19.0	3	16.7
Over 10	12	52.2	13	69.5	17	81.0	15	83.3
Total Babies	23	100.0	20	100.0	21	100.0	18	100.0

TABLE LXXXI

NUMBERS OF TWIN BABIES STILLBORN OR DYING BEFORE DISCHARGE FROM HOSPITAL GROUPED ACCORDING TO THE DURATION OF GESTATION

Gestation Period (in weeks)	All Stillbirths and Deaths No.	%	Stillbirths No.	Deaths No.
Under 32	8	80.0	4	4
32 and 33	3		0	3
34, 35 and 36	5		3	2
37, 38 and 39	2	20.0	1	1
40 and over	2		2	0
Total Infants	20	100.0	10	10

TABLE LXXXII

NUMBERS OF TWIN BABIES STILLBORN OR DYING BEFORE DISCHARGE FROM HOSPITAL GROUPED ACCORDING TO BIRTH WEIGHT

Birth Weight (in grams)	All Stillbirths and Deaths No.	%	Stillbirths No.	Deaths No.
1500 and less	12	60.0	7	5
1501 to 2000	6	30.0	1	5
2001 to 2500	2	10.0	2	0
Total Babies	20	100.0	10	10

TABLE LXXXIII

NUMBERS OF TWIN BABIES STILLBORN OR DYING BEFORE DISCHARGE FROM HOSPITAL GROUPED ACCORDING TO THE SUM OF THE BIRTH WEIGHTS OF EACH PAIR

Sum of Birth Weights (in grams)	Total No. of Pairs	All Stillbirths and Deaths	Pairs Lost	Single Infants Lost
3000 and less	5	10	5	0
3001 to 4000	12	7	2	3
4001 and over	34	3	0	3
Total Pairs and Single Infants Lost	51	20	7	6

TABLE LXXXIV

NUMBERS OF TWIN PAIRS IN WHICH ONE OR BOTH INFANTS WERE STILLBORN OR DIED GROUPED ACCORDING TO THE PERCENTAGE DIFFERENCE IN THE BIRTH WEIGHTS OF EACH PAIR

Difference In Birth Weights (%)	Twin Pairs No.	All Stillbirths and Deaths No.	All Stillbirths and Deaths %
Under 10	26	7	13.5
10 to 19	18	3	8.3
20 to 49	5	6	60.0
50 and over	1	2	100.0
Total	*50	*18	-

* One pair of conjoined twins has been excluded.

TABLE LXXXV

NUMBERS OF TWIN BABIES STILLBORN AND DYING BEFORE DISCHARGE FROM HOSPITAL, GROUPED ACCORDING TO BIRTH SIZE AND ORDER, AND CORRECTED FOR INTRAUTERINE DEATH

Mode of Loss	Group of Infants			
	Big 1st	Big 2nd	Small 1st	Small 2nd
Stillbirth				
Macerated	0	2	1	3
Fresh	1	0	1	0
Neonatal Death	2	2	1	5
Total Loss (Uncorrected)	3 (11.6%)	4 (15.4%)	3 (12.5%)	8 (30.8%)
Net Loss (Corrected for Macerated Stillbirths)	3 (11.6%)	2 (7.7%)	2 (8.3%)	5 (19.2%)

TABLE LXXXVI

NUMBERS OF TWIN PAIRS GROUPED ACCORDING TO SEX AND SHOWING STILLBIRTHS AND DEATHS

Sex of Pairs	All Twin Pairs No.	%	Stillbirths and Deaths: Total Infants	Twin Pair	Single Infant
Male	17	33.3	7	3	1
Female	16	31.4	7	2	3
Mixed	18	35.3	6	2	2
Total Pairs and Single Babies	51	100.0	20	7	6

TABLE LXXXVII

INCIDENCE OF TWIN PREGNANCY IN THIS AND OTHER SERIES

Series	Date	Place	Incidence
The Present Study	1959 to 1960	Glasgow, Scotland	1 in 44
Dunn	1965	Birmingham, England	1 in 26
Waddell and Hunter	1960	Rochester, U.S.A.	1 in 73
Benirscke	1961	Boston, U.S.A.	1 in 83
Danielson	1960	Stockholm, Sweden	1 in 85
Potter	1963	Chigago, U.S.A.	1 in 90
Seski and Miller	1963	Detroit, U.S.A.	1 in 99
Aborted Twin Pregnancy			
Potter	1963	Chigao, U.S.A.	1 in 110
Benirscke	1961	Boston, U.S.A.	1 in 223

TABLE LXXXVIII

PERINATAL MORTALITY RATES IN TWIN PREGNANCIES IN THIS AND OTHER SERIES EXPRESSED AS A PERCENTAGE OF THE TOTAL NUMBER OF TWIN BABIES DELIVERED

Series	Date	Place	Rate (%)
The Present Study	1959 to 1960	Glasgow, Scotland	10.3
Ferguson	1964	Alberta, Canada	9.2
Seski and Miller	1963	Detroit, U.S.A.	9.7
Waddell and Hunter	1960	Rochester, U.S.A.	10.0
Potter	1963	Chigago, U.S.A.	10.5
Danielson	1960	Stockholm, Sweden	12.0
Spurway	1962	Guilford, England	12.2
Dunn	1965	Birmingham, England	12.3
Gittelsohn and Milham	1965	New York, U.S.A.	12.8
Robertson	1964	Edinburgh, Scotland	14.0
Graves, Adams and Schreier	1962	Memphis, U.S.A.	14.4

PART V

RENAL-TRACT INFECTION IN PREGNANCY

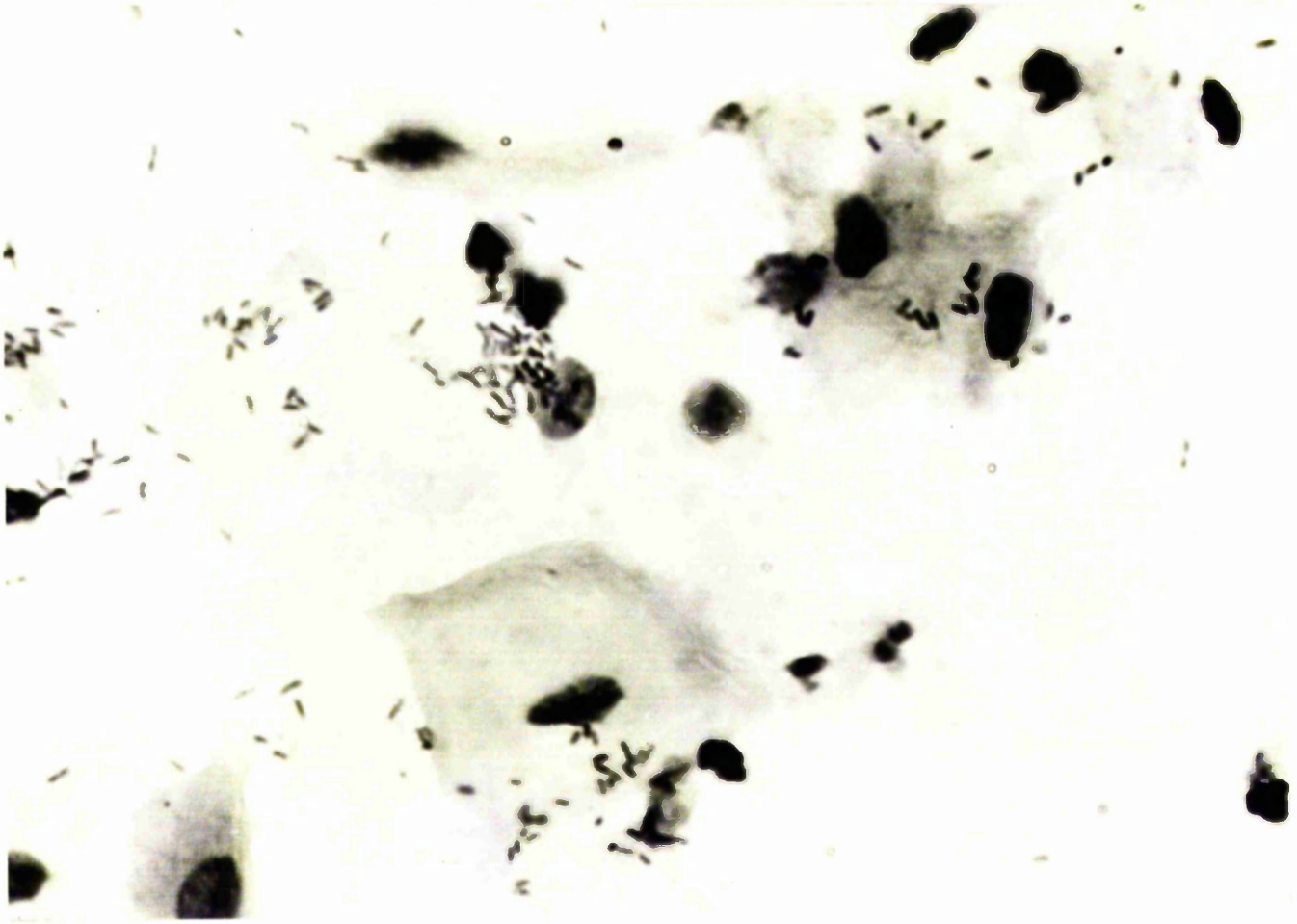

Figure 24.

Drop-preparation of urine showing numerous coliform organisms, pus cells and desquamated, epithelial cells (Gram x 1130).

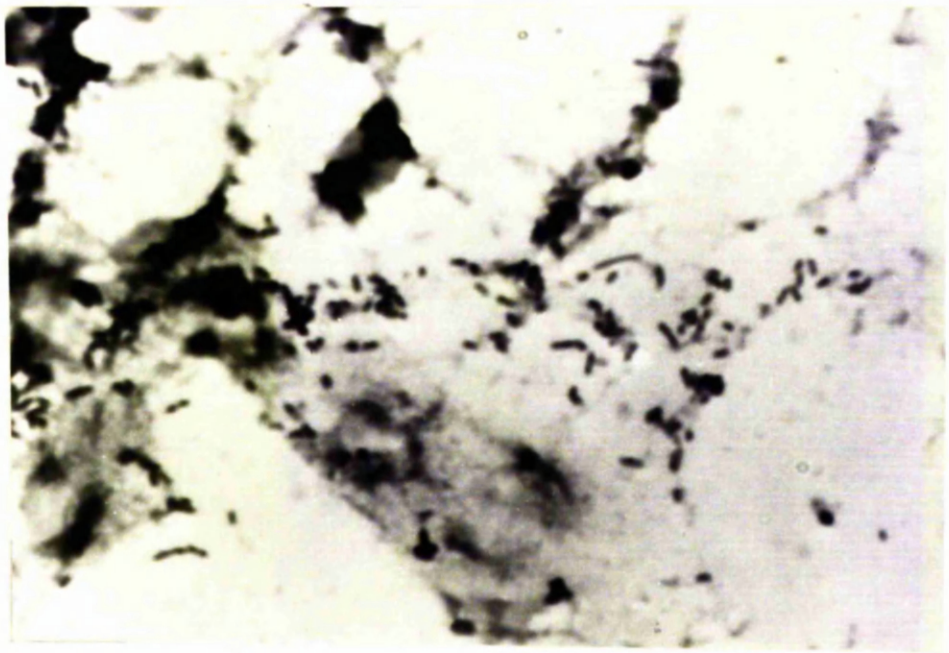

Figure 25.

Drop-preparation of urine showing numerous coliform organisms and pus cells (Gram x 1130).

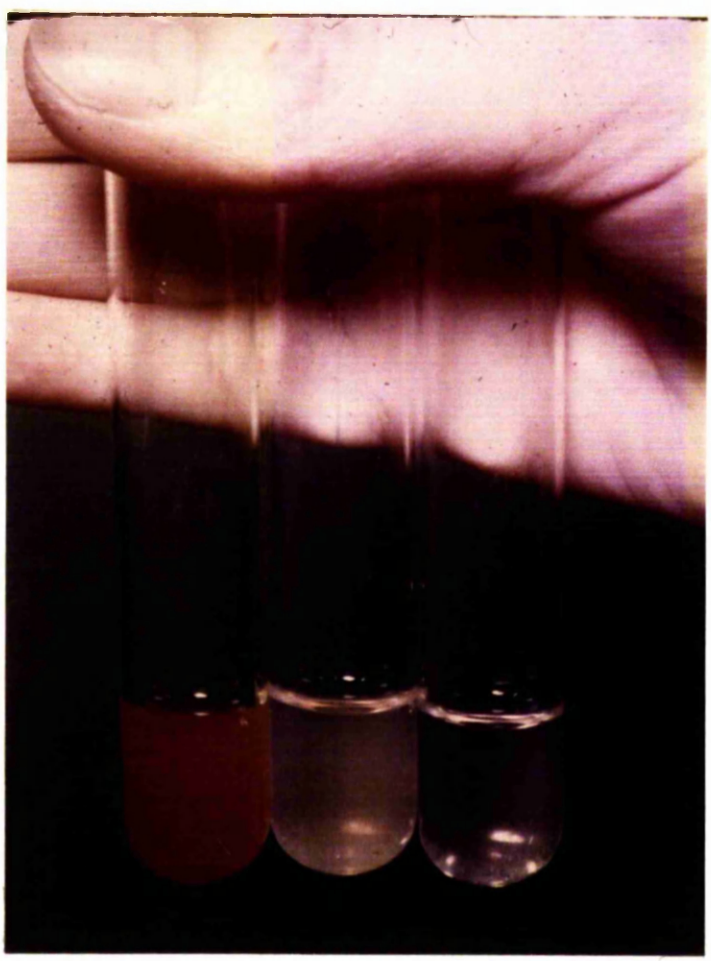

Figure 26.

T.T.C. test on the same specimen of urine. The diffuse red colouration of a strongly positive result is seen in the tube on the left. The other two tubes show negative results. The bacterial count was 20×10^6 per ml.

Figure 27.

Agar plate culture of urine which contained 40 x 10^6 organisms per ml.

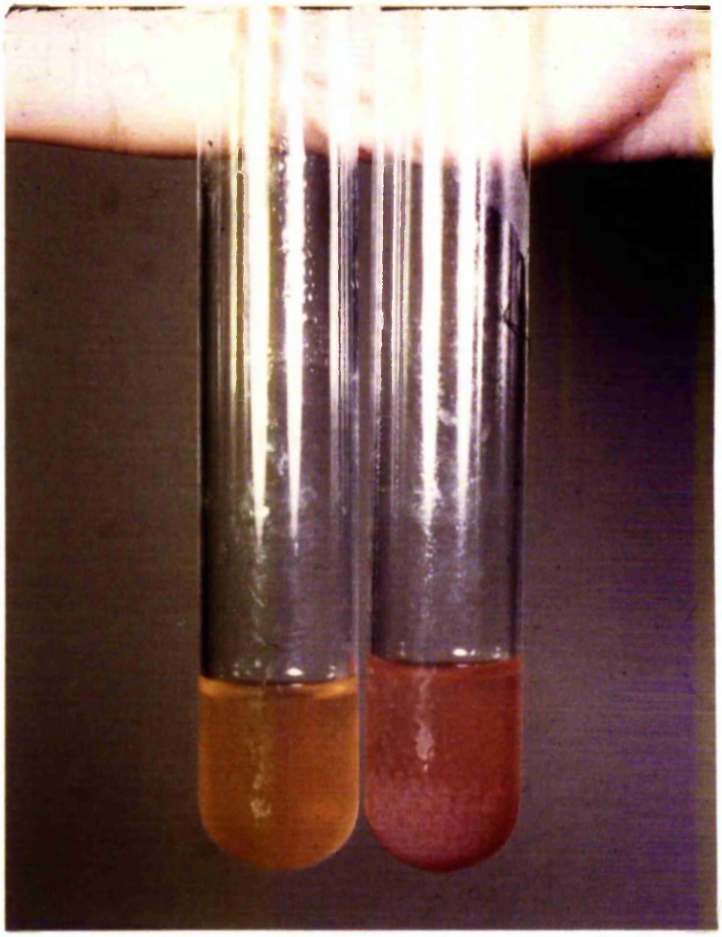

Figure 28.

The T.T.C. test on the same specimen. The positive reaction, a diffuse red colouration and deposit, is shown on the right.

Figure 29.

Bacterial count plate of 0.48×10^6 organisms per ml. of urine

Figure 30.

The T.T.C. test on the same specimen. A faint positive result is seen on the left.

TABLE LXXXIX

NUMBERS OF SPECIMENS OF URINE TESTED, GROUPED ACCORDING TO THE TEST USED AND SHOWING THE INCIDENCE OF INFECTION

Test Used	No. of Specimens	Positive Specimens	
		No.	%
Gram's Stain only	234	15	6.4
*T.T.C.	402	18	4.5
Bacterial Count only	1885	°78	4.0

* Includes 197 specimens tested by Gram's stain and 49 specimens tested by bacterial count.

° Includes levels of organisms over 10^5 per ml.

TABLE XC RESULTS OF BACTERIAL COUNTS

	No. of Specimens	% of Total
Group I Coliform Organisms only		
Over 100,000 per ml.	75	4.0
10,000 to 100,000 per ml.	51	2.6
Under 10,000 per ml.	78	4.0
Total	204	10.6
Group II Coliform Organisms with Other Organisms		
Over 100,000 per ml.	1	0.0
10,000 to 100,000 per ml.	0	0.0
Under 10,000 per ml.	21	1.0
Total	22	1.0
Group III Non-Coliform Organisms		
Over 100,000 per ml.	20	1.0
10,000 to 100,000 per ml.	15	0.7
Under 10,000 per ml.	345	17.7
Total	380	19.4
Group IV		
Sterile	1328	69.0
Total Bacterial Counts	1934	100.0

TABLE XCI CONSTITUTION OF TOTAL RENAL INFECTION IN PREGNANCY (SYMPTOMATIC AND ASYMPTOMATIC)

	Number	
Positive gram stains	15	
Significant* bacterial count, 1st visit	78+	
Significant* bacterial count, subsequent visit	42	
Significant* bacterial count, early puerperium (known to originate ante partum)	4	
Clinical pyelonephritis, with bacteriuria decreasing on treatment	5	
Total cases of renal infection	144 = 5.7%	6.9%
Clinical pyelonephritis arising in control group	1.2%	
"Cystitis", "pyelitis", prior to 1st visit	1.8%	
Gross percentage of renal infection	8.7%	

* $>10^5$ organisms per ml.

\+ Includes two patients with significant non-coliform bacteriuria.

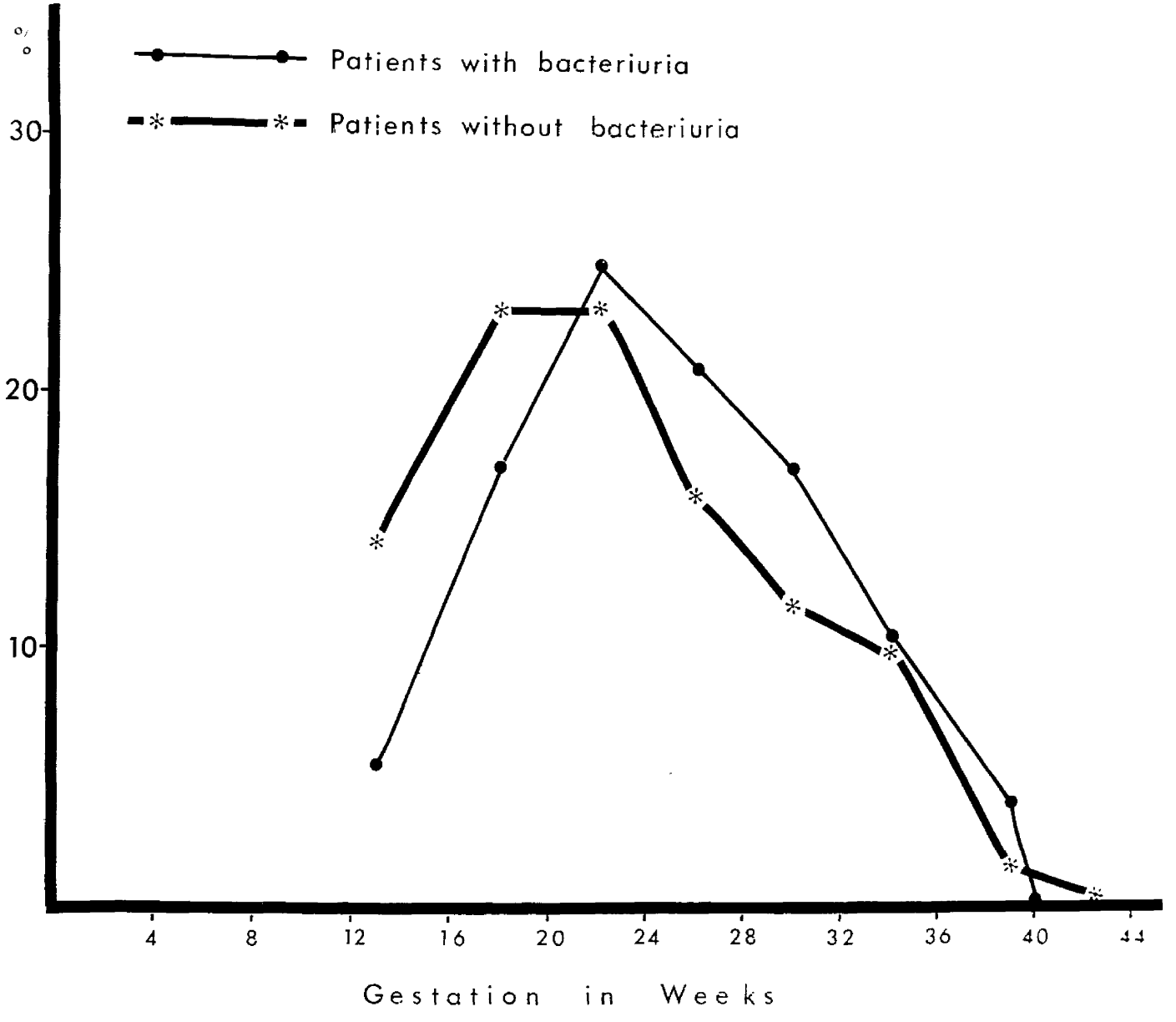

Figure 31.

The duration of gestation in 76 patients with bacteriuria and 500 without bacteriuria at their first visit to the Ante-natal Clinic, shown as a percentage of each group.

TABLE XCII

NUMBERS OF ANTENATAL PATIENTS WITH MINIMAL AND SUSPICIOUS BACTERIURIA GROUPED ACCORDING TO THE TIME TAKEN FOR THE DEVELOPMENT OF SIGNIFICANT BACTERIURIA

Time Interval (in weeks)	No. of Patients	%
Under 2	2	5.4
2 to 4	14	
4 to 6	7	
6 to 8	2	
8 to 10	2	94.6
10 to 12	2	
12 to 14	2	
14 to 16	4	
16 to 18	*1	
18 to 20	0	
Over 20	1	
Total Patients	37	

* No interim specimen.

TABLE XCIII TIME TAKEN FOR DIFFERENT LEVELS OF BACTERIURIA TO REACH 100,000 ORGANISMS PER ML. OR MORE IN *36 PREGNANT WOMEN

Initial Level of Bacteriuria (per ml.)	Number of Patients	Interval of Time Taken to Reach 100,000 Organisms per ml. (in weeks)							
		Under 4		4 to 8		8 to 12		over 12	
		No.	%	No.	%	No.	%	No.	%
Under 25,000	17	4	23.5	2	35.3	4	58.8	7	100.0
25,000 to 50,000	8	3	37.5	5	100.0	0	100.0	0	100.0
50,000 to 75,000	8	6	75.0	2	100.0	0	100.0	0	100.0
75,000 to 100,000	3	3	100.0	0	100.0	0	100.0	0*	100.0
Total Patients	36	16		9		4		7	

* 1 patient deleted because there was no interim specimen.

TABLE XCIV

NUMBERS OF BACTERIURIC ANTE-NATAL PATIENTS GROUPED ACCORDING TO THE PRESENCE OR ABSENCE OF CLINICAL RENAL TRACT INFECTION

Clinical Renal-Tract Infection		Ante-natal Patients No.	%	
Present	Before 1st visit	11	17.0	49.3
	After 1st visit	21	32.3	
Absent		33	50.7	
Total Patients		65	100.0	

TABLE XCV

NUMBERS OF ANTE-NATAL PATIENTS GROUPED ACCORDING TO THE TIME INTERVAL FROM THE DETECTION OF SIGNIFICANT BACTERIURIA TO THE DEVELOPMENT OF CLINICAL PYELONEPHRITIS

Interval (in weeks)	Ante-natal Patients No.	%
Under 2	5	18.5
2 to 4	6	
4 to 6	3	
6 to 8	1	
8 to 10	4	
10 to 12	1	81.5
12 to 14	2	
14 to 16	2	
16 to 18	1	
18 to 20	0	
Over 20	2	
Total Patients	27	

TABLE XCVI INCIDENCE RATE OF BACTERIURIA IN PREGNANCY REPORTED BY OTHER WORKERS

Author	Area	Year	No. of Patients	% Positive
Kass	Boston, Mass.	1960	4000	6 - 7
Kaitz & Hodder	Boston, Mass	1961	616	4.4
Turner	Aberdeen, Scotland	1961	1500	7.0
Chard & Cole	London, England	1963	100	7.0
Goss et al.	Houston, Texas	1963	1093	4.7
Monzon et al.	Los Angeles, California	1963	1400	7.0
Schamadan	Columbus, Ohio	1964	901	7.0
Low et al.	Toronto, Canada	1964	774	10.3
Carleton et al.	Los Angeles, California	1965	481	4.5
Kincaid-Smith & Bullen	Melbourne, Australia	1965	4000	6.0
Whalley et al.	Dallas, Texas	1965	4357	6.9
Hipple & Schulman	Palo Alto, California	1965	1635	6.6
Little	London, England	1966	5000	5.3
Cavanagh & Sandberg	Miami, U.S.A.	1966	270	11.0
Dixon & Brant	London, England	1967	1309	5.4

TABLE XCVII

NUMBERS OF BACTERIURIC AND NON-BACTERIURIC ANTE-NATAL PATIENTS GROUPED ACCORDING TO AGE

Age (in years)	Group of Ante-natal Patients			
	Bacteriuric		Non-Bacteriuric	
	No.	%	No.	%
Under 20	18	13.5	39	7.8
20 to 24	42	31.8	170	34.0
25 to 29	32	24.0	146	29.2
30 to 34	24	18.0	92	18.4
35 to 39	10	7.5	37	7.4
40 and over	7	5.2	16	3.2
Total Patients	133	100.0	500	100.0

TABLE XCVIII

NUMBERS OF BACTERIURIC AND NON-BACTERIURIC ANTE-NATAL PATIENTS GROUPED ACCORDING TO PARITY

Parity	Group of Ante-natal Patients			
	Bacteriuric		Non-Bacteriuric	
	No.	%	No.	%
0	44	33.0	180	36.0
1 and 2	44	33.0	213	42.6
3 and over	45	34.0	107	21.4
Total Patients	133	100.0	500	100.0

TABLE XCIX NUMBERS OF MOTHERS WITH FOETAL LOSS IN PREVIOUS PREGNANCIES IN 89 PRESENTLY BACTERIURIC AND 320 NON-BACTERIURIC ANTENATAL PATIENTS

Outcome of Pregnancy	Bacteriuric Patients		Non-Bacteriuric Patients	
	No.	%	No.	%
Loss	40	45.0	96	30.0
Live infant	49	55.0	224	70.0
Total mothers	89	100.0	320	100.0

TABLE C NUMBER OF SURVIVING LOW-BIRTHWEIGHT INFANTS IN PREVIOUS PREGNANCIES IN 89 CURRENTLY BACTERIURIC AND 320 NON-BACTERIURIC ANTENATAL PATIENTS

Birth Group	Bacteriuric Mothers		Non-Bacteriuric Mothers	
	No.	%	No.	%
Low birth weight surviving	13	14.6	19	5.9
All others	76	85.4	301	94.1
Total infants	89	100.0	320	100.0

TABLE CI

TYPE AND INCIDENCE OF COMMON COMPLICATIONS OF PREGNANCY IN 75 BACTERIURIC AND 500 NON-BACTERIURIC ANTE-NATAL PATIENTS

Complication	Group of Ante-natal Patients				p value
	Bacteriuric		Non-Bacteriuric		
	No.	%	No.	%	
Pre-eclamptic Toxaemia	1	1.3	61	12.2	<0.01
Hypertension	2	2.6	40	8.0	<0.10 >0.05
Anaemia (Haemoglobin < 10 g./100 ml.)	8	10.7	26	5.2	<0.10 >0.05
*Uterine Bleeding					
Before 16 weeks	4	5.3	28	5.6	<0.80 >0.70
16 to 28	3	4.0	11	2.2	<0.50 >0.30
After 28	4	5.3	11	2.2	<0.10 >0.05

* Excluding that due to placenta praevia or local cervical lesions.

TABLE CII

NUMBERS OF MOTHERS WHO WERE BACTERIURIC AFTER THE 37th WEEK, CLEAR BY THE 37th WEEK, OR NON-BACTERIURIC CONTROLS, GROUPED ACCORDING TO THE PRESENCE OR ABSENCE OF CLINICAL PYELONEPHRITIS WITHIN SEVEN DAYS OF DELIVERY

Clinical Pyelonephritis	Group of Mothers					
	Bacteriuric After 37 Weeks		Clear At 37 Weeks		Non-Bacteriuric Controls	
	No.	%	No.	%	No.	%
Present	16	21.3	5	8.6	13	2.6
Absent	*59	78.7	53	91.4	487	97.4
Total Mothers	75	100.0	58	100.0	500	100.0

* Includes 14 patients starting chemotherapy after the 37th week.

TABLE CIII

NUMBERS OF MOTHERS WHO WERE BACTERIURIC AFTER THE 37th WEEK, CLEAR BY THE 37th WEEK, OR NON-BACTERIURIC CONTROLS, GROUPED ACCORDING TO THE PRESENCE OR ABSENCE OF ASYMPTOMATIC BACTERIURIA ON THE THIRD POST-PARTUM DAY

Asymptomatic Bacteriuria (organisms/ml.)	Group of Mothers: Bacteriuric After 37 Weeks No.	%	Clear At 37 Weeks No.	%	Non-Bacteriuric Controls No.	%
Present						
Over 100,000	25	62.5	5	11.9	12	3.6
10,000 to 100,000	3	7.5	2	4.8	6	1.8
Under 10,000	2	5.0	0	0	0	0
Absent	‡10	25.0	35	83.3	318	94.6
Total Mothers	40	100.0	42	100.0	336	100.0

N.B. Cases of clinical pyelonephritis are not included.

‡ All starting chemotherapy after the 37th week.

TABLE CIV

NUMBERS OF MOTHERS WHO WERE BACTERIURIC AFTER THE 37th WEEK, AND CLEAR BY THE 37th WEEK, GROUPED ACCORDING TO THE PRESENCE OR ABSENCE OF BACTERIURIA BETWEEN 2 AND 6 WEEKS AFTER DELIVERY

Bacteriuria (organisms/ml.)	Group of Mothers					
	Bacteriuric After 37 weeks			Clear At 37 weeks		
	No.	%		No.	%	
Present						
Over 100,000	10	28.6		6	17.1	
10,000 to 100,000	4	11.4	40.0	0	0	17.1
Under 10,000	2	5.7		0	0	
Absent	19	54.3		29	82.9	
Total Mothers	35	100.0		35	100.0	

TABLE CV

NUMBERS OF MOTHERS WHO WERE BACTERIURIC AFTER THE 37th WEEK, AND CLEAR BY THE 37th WEEK, GROUPED ACCORDING TO THE PRESENCE OR ABSENCE OF BACTERIURIA AT OR AFTER THE 6th POST-PARTUM WEEK

Bacteriuria	Group of Mothers			
	Bacteriuric After 37 Weeks		Clear At 37 Weeks	
	No.	%	No.	%
Present	13	65.0	7	31.8
Absent	7	35.0	15	68.2
Total Mothers	20	100.0	22	100.0

TABLE CVI

PERSISTENCE OF RENAL TRACT INFECTION POST PARTUM

SUMMARY OF THE FINDINGS OF OTHER WORKERS

Author	Percentage With Persistent Infection	Time After Delivery
Kass (1960)	75	3 months
	25	3 to 12 months
Kincaid-Smith and Bullen (1965)	65	6 weeks to 9 months
Whalley et al. (1965)	81	8 to 12 months (no treatment)
Pinkerton et al. (1961)	78	Up to 5 years

FIGURE 32.

Ultimate Course of 127 Ante-Natal Patients with Significant Bacteriuria

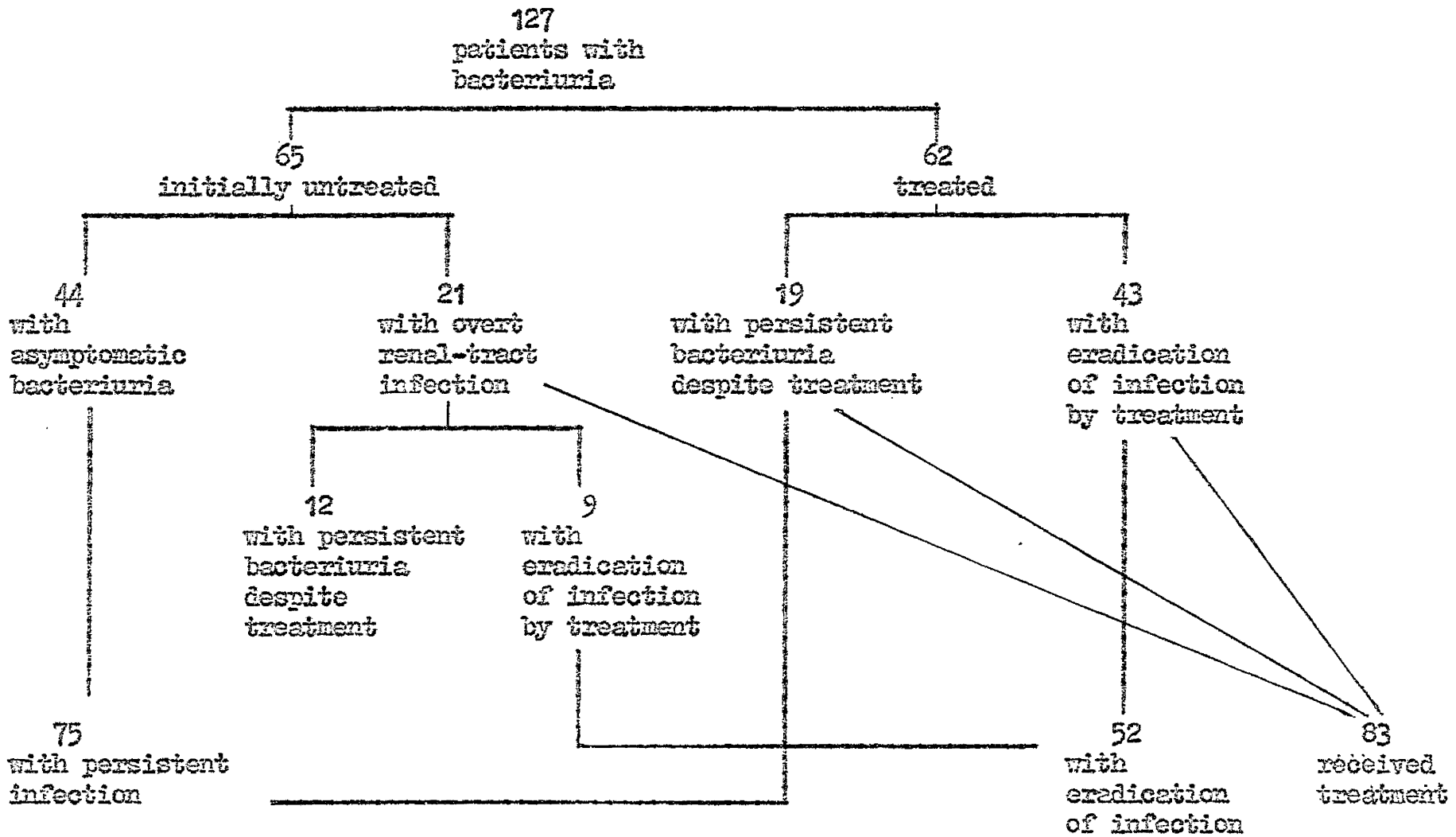

TABLE CVII FOUR DRUGS COMPARED FOR SUCCESS IN ERADICATION OF BACTERIURIA

Drug	Total No. of Courses	Successful Eradication of Bacteriuria	
		No.	%
*Sulphonamide	35	26	74.2
Ampicillin	36	24	66.7
Nitrofurantoin	25	17	68.0
Nalidixic Acid	11	8	72.7
No. of Courses	107	75	70.2

* Sulphadiazine or sulphadimidine

TABLE CVIII

NUMBERS OF PATIENTS TREATED AND THE DURATION OF TREATMENT WITH EACH OF FOUR DRUGS

Drug	No. of Patients	Duration of Treatment (in weeks)			Total No. of Weeks	Average No. of Weeks	Longest Use in One Patient (in weeks)
		2 and less	Over 2 Under 5	Over 5 Under 10	10 and Over		
Sulphonamide*	33	11	4	4	14	283	8.6	19
Ampicillin	26	13	4	3	6	155	6.0	18
Nitrofurantoin	17	4	4	3	6	160	9.4	23
Nalidixic Acid	7	7	0	0	0	7	1.0	1

* Sulphadiazine or sulphadimidine.

TABLE CIX APPARENT REASONS FOR FAILURE OF ERADICATION OF BACTERIURIA ACCORDING TO THE DRUG USED

Drug	No. of Courses	Organism Becoming Resistant	Inadequate Dosage or Duration of Therapy	"Difficult" Lesion
*Sulphonamide	9	4	5	0
Ampicillin	12	1	8	3†
Nitrofurantoin	8	0	6	2+
Nalidixic Acid	3	0	2°	1
Total Courses	32	5	21	6

* Sulphadiazine or sulphadimidine.
° One patient receiving two courses.
† Two patients receiving three courses.
+ One patient receiving two courses.

TABLE CX

NUMBERS OF ABORTIONS, STILLBIRTHS AND NEONATAL DEATHS IN 75 BACTERIURIC MOTHERS, 58 SUCCESSFULLY-TREATED MOTHERS AND 500 NON-BACTERIURIC MOTHERS

Type of Loss	Group of Mothers					
	Bacteriuric		Successfully-Treated		Non-bacteriuric	
	No.	%	No.	%	No.	%
Abortion	1	1.3	0	0	4	0.8
Stillbirth	1	1.3	1	1.7	*8	1.6
Neonatal Death	3	4.0	2	3.5	ǂ2	0.4
Total foetal and infant loss	5	6.6	3	5.2	14	2.8

* Three stillbirths excluded (1 hydrops foetalis; 2 postmature)

ǂ Two neonatal deaths excluded (both due to Rhesus haemolytic disease)

TABLE CXI

NUMBERS OF LOW BIRTH-WEIGHT AND SHORT-GESTATION BABIES IN 75 BACTERIURIC MOTHERS, 58 SUCCESSFULLY-TREATED MOTHERS AND 500 NON-BACTERIURIC MOTHERS

Birth Group	Group of Infants					
	With Bacteriuric Mothers		With Successfully-Treated Mothers		With Non-Bacteriuric Mothers	
	No.	%	No.	%	No.	%
2500 g. and less, and under 37 weeks	2	2.7	1	1.7	13	2.6
2500 g. and less, and over 37 weeks	5	6.7	3	5.2	24	4.8
Over 2500 g. and under 37 weeks	2	2.7	3	5.2	8	1.6
Total Infants at Disadvantage	9	12.1	7	12.1	45	9.0

TABLE CXII

TYPE AND INCIDENCE OF CONGENITAL DEFECT IN INFANTS OF 133 MOTHERS WITH BACTERIURIA AND 500 MOTHERS WITH NO BACTERIURIA DURING PREGNANCY

Type of Defect	Group of Infants			
	With Bacteriuric Mothers		With Non-Bacteriuric Mothers	
	No.	%	No.	%
Dorsal Mid-line Fusion				
Meningocoele	2		0	
Meningocoele with Talipes Equino Varus	1		0	
		5 3.8		
Anencephaly	1		0	
Hydrocephaly	1		1	0.2
Talipes Equino Varus	1	0.8	0	0
Congenital Heart Disease	1	0.8	0	0
Hypospadias	0	0	2	0.4
Cleft Palate	0	0	1	0.2
Renal Agenesis and Endocardial Fibroelastosis	0	0	1	0.2
Oesophageal Atresia with Limb Deformities	0	0	1	0.2
Total Infants	7	5.4	6	1.2

TABLE CXIII

NUMBERS OF INFANTS WITH SIGNIFICANT COLIFORM BACTERIURIA BORN OF BACTERIURIC MOTHERS, SUCCESSFULLY-TREATED MOTHERS AND NON-BACTERIURIC MOTHERS

Bacterial State of Infant's Urine	Group of Infants					
	With Bacteriuric Mothers		With Successfully-Treated Mothers		With Non-Bacteriuric Mothers	
	No.	%	No.	%	No.	%
Significant Coliform Bacteriuria	10	24.4	5	17.9	0	0
All others	31	75.6	23	82.1	29	100.0
Total Infants	41	100.0	28	100.0	29	100.0

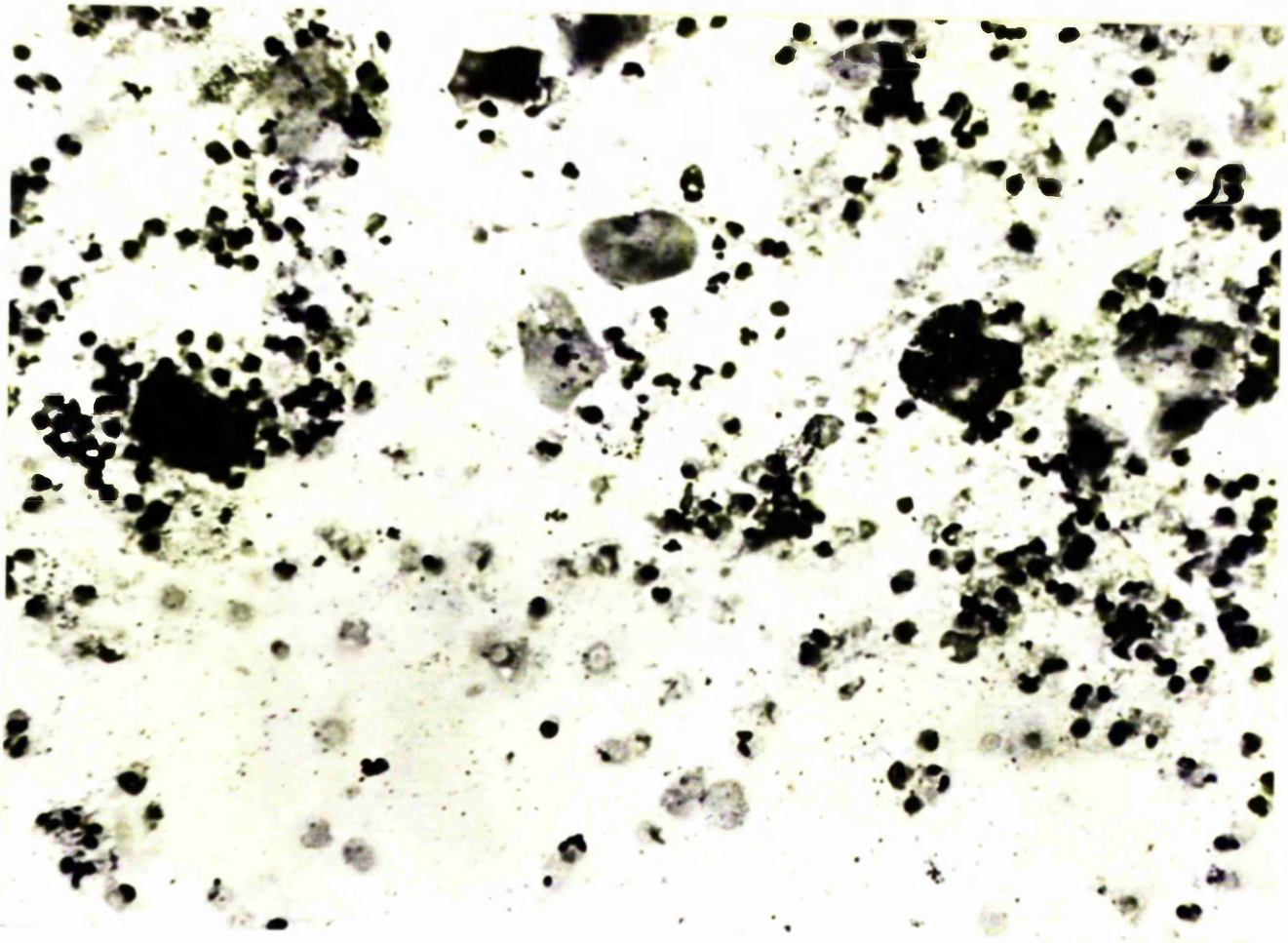

Figure 33.

Smear-preparation of amniotic fluid showing numerous pus cells. (Gram x 280)

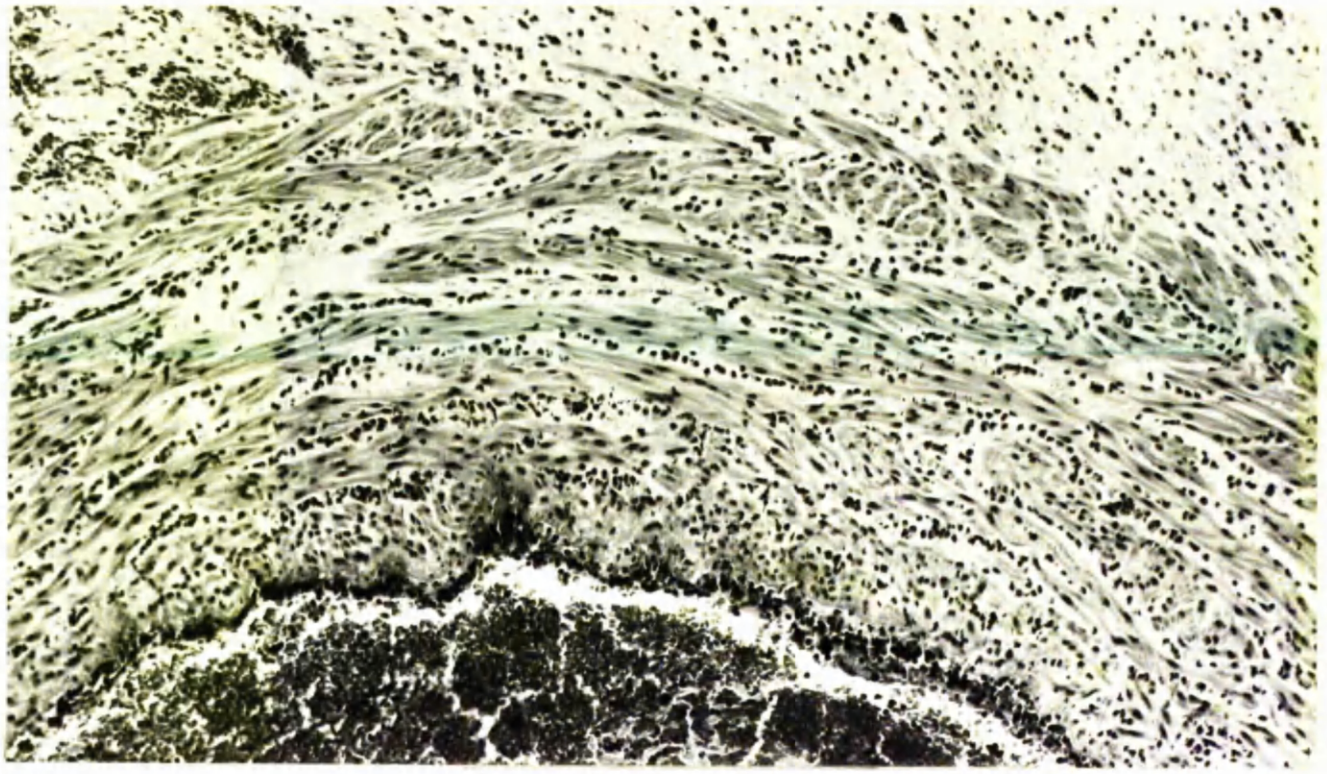

Figure 34.

Wall of umbilical vessel showing acute inflammatory cells.

(H. and E. x 140)

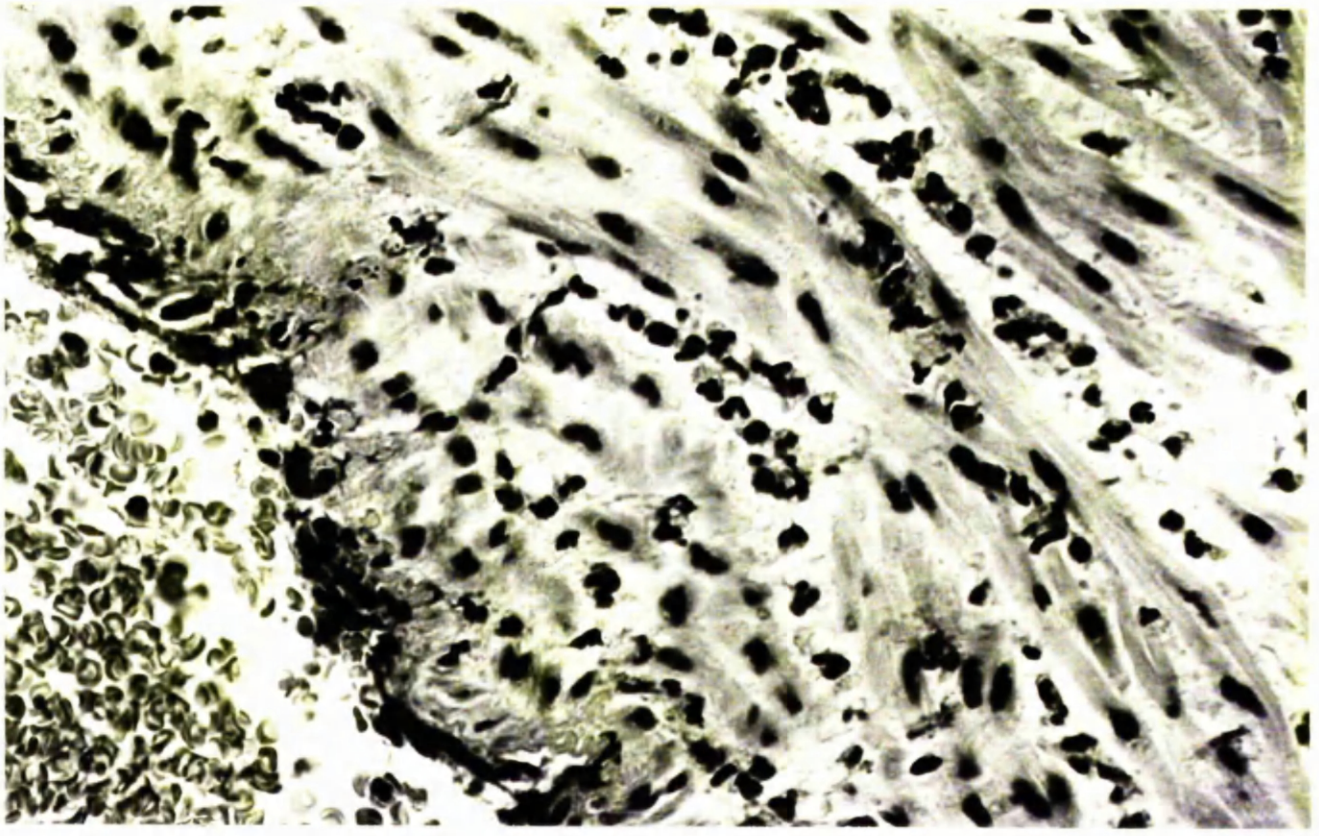

Figure 35.

Neutrophil polymorphs infiltrating wall of umbilical vessel.

(H. and E. x 550)

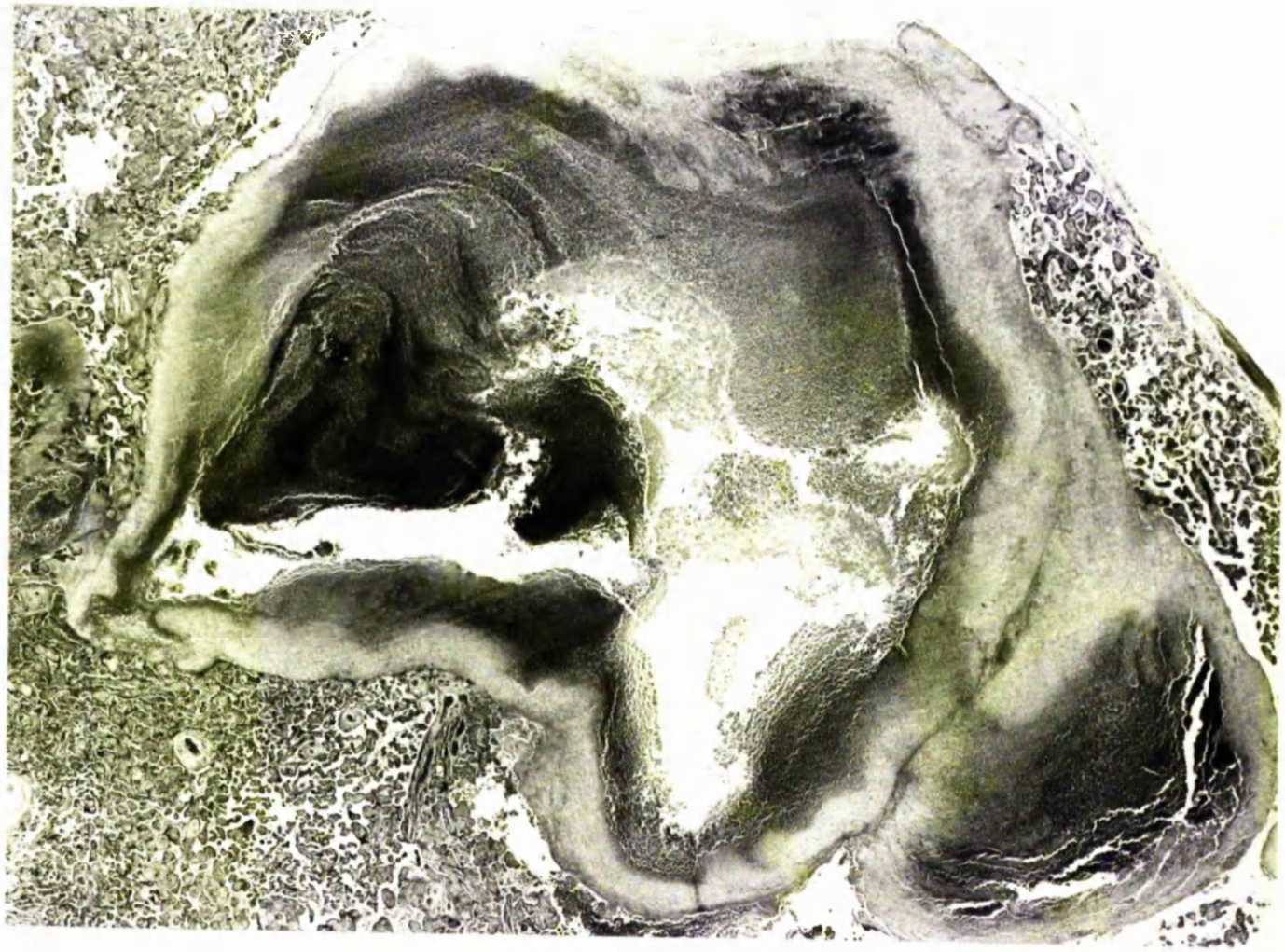

Figure 36.

Abscess in placenta. (H. and E. x 10.5)

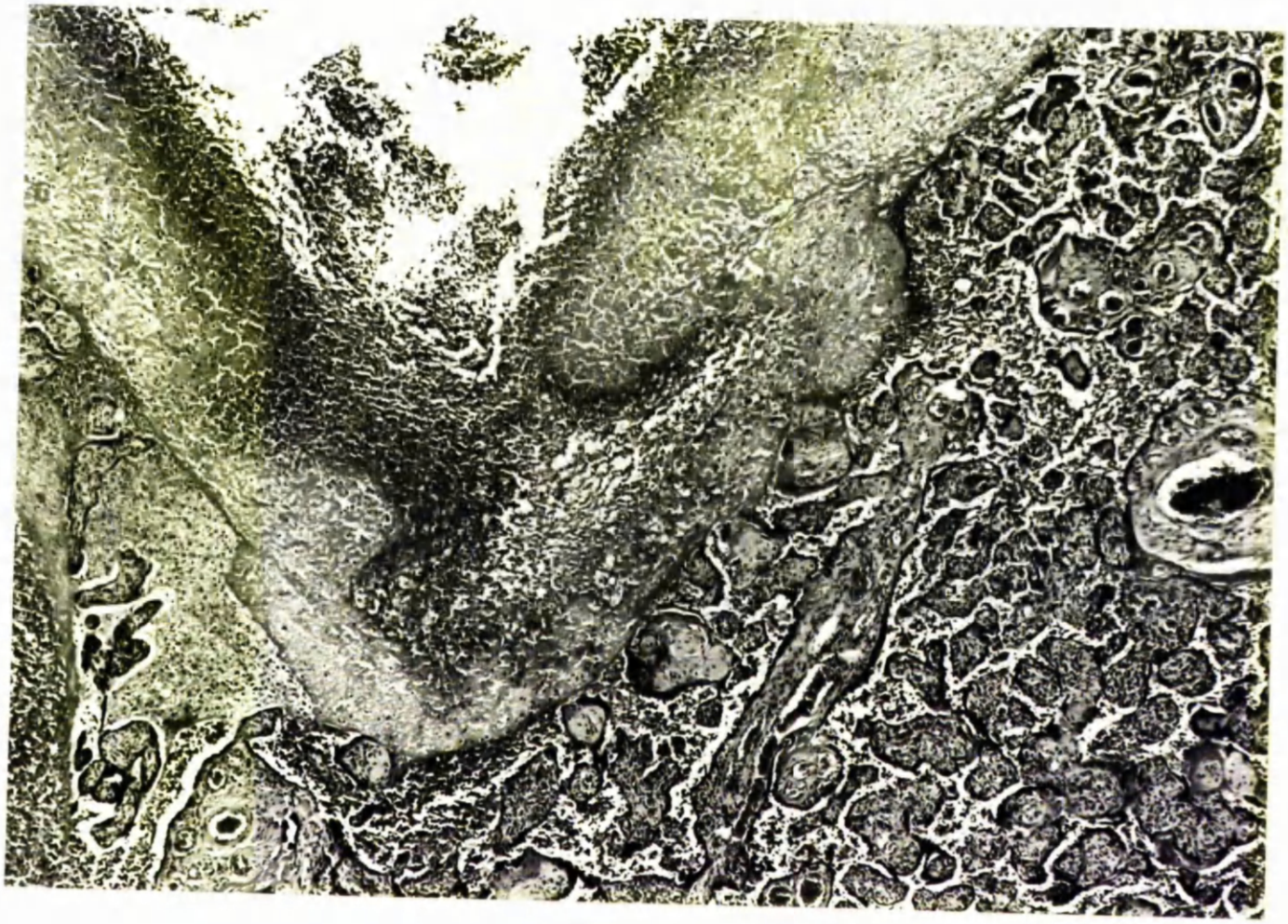

Figure 37.

Same as Figure 36. (H. and E. x 55)

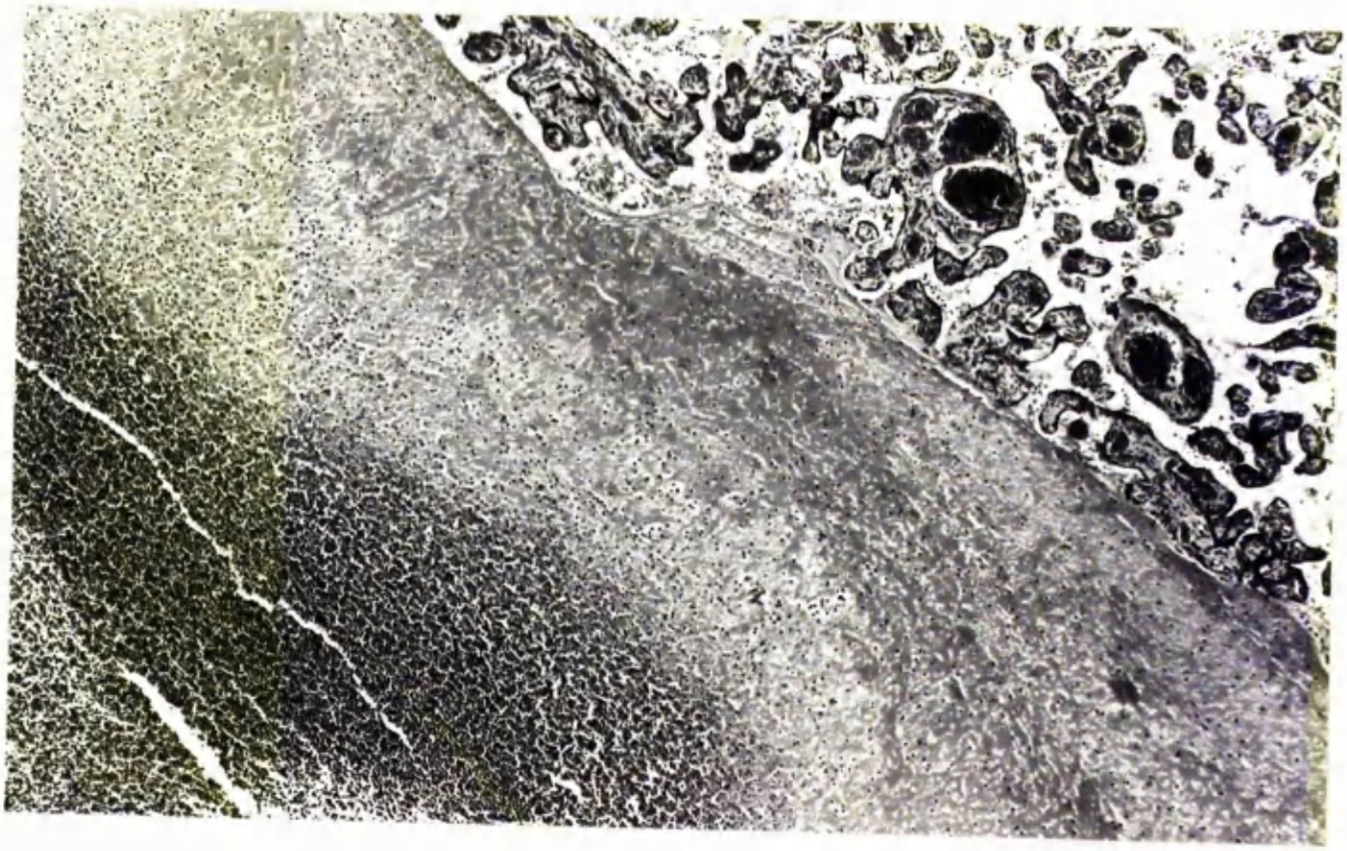

Figure 38.

Same as Figure 36. (H. and E. x 55)

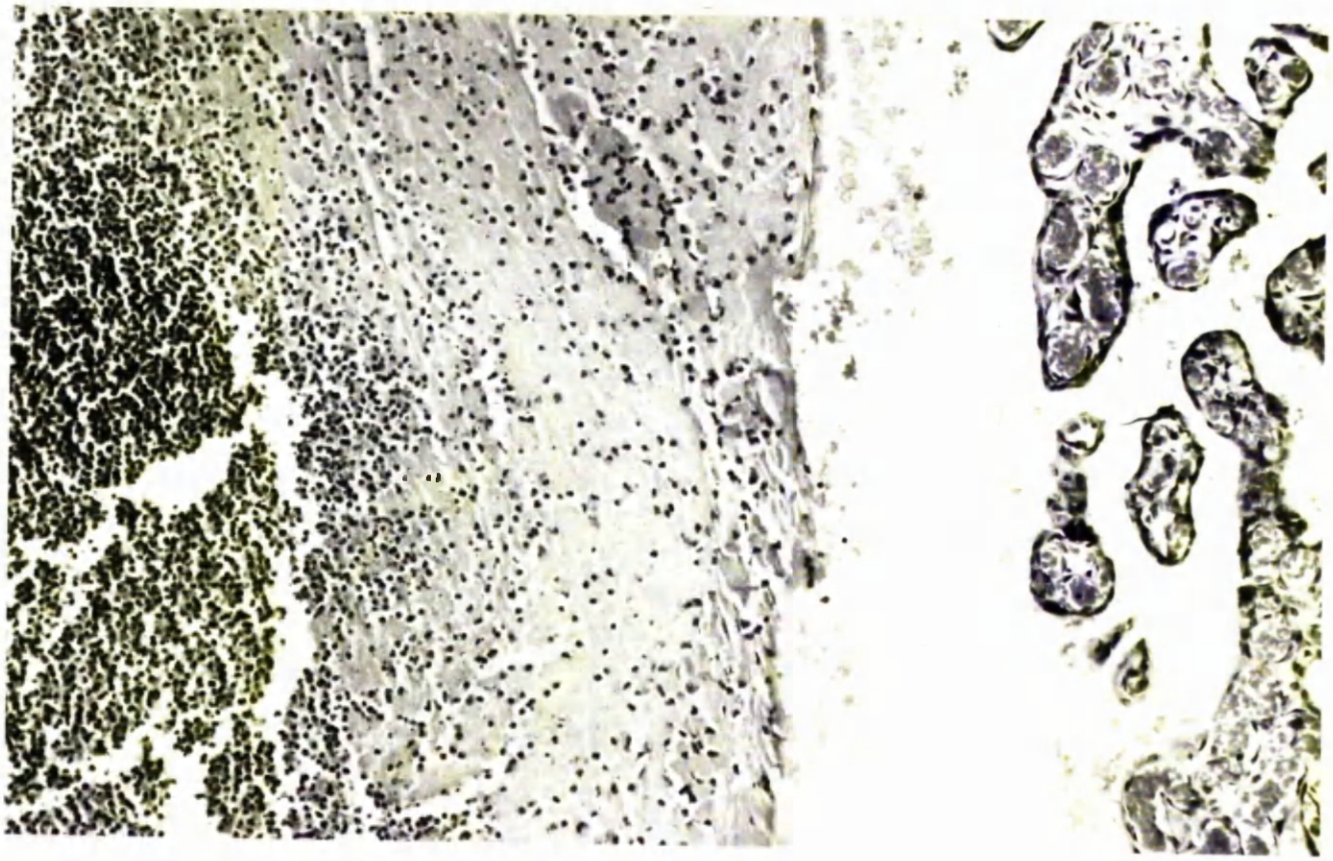

Figure 39.

Same as Figure 36. (H. and E. x 140)

TABLE CXIV

NUMBERS OF SPECIMENS OF AMNIOTIC FLUID, UMBILICAL CORD BLOOD, PLACENTAE AND CORDS FROM BACTERIURIC, SUCCESSFULLY-TREATED AND NON-BACTERIURIC MOTHERS CLASSIFIED ACCORDING TO THE PRESENCE OR ABSENCE OF EVIDENCE OF INFECTION

Material Examined	Group of Mothers					
	Bacteriuric		Successfully-Treated		Non-Bacteriuric	
	+ve	-ve	+ve	-ve	+ve	-ve
Amniotic Fluid	4	4	0	3	0	8
Umbilical Cord Blood	6	13	2	10	0	20
Placentae and Cords	1	4	3	9	1	11

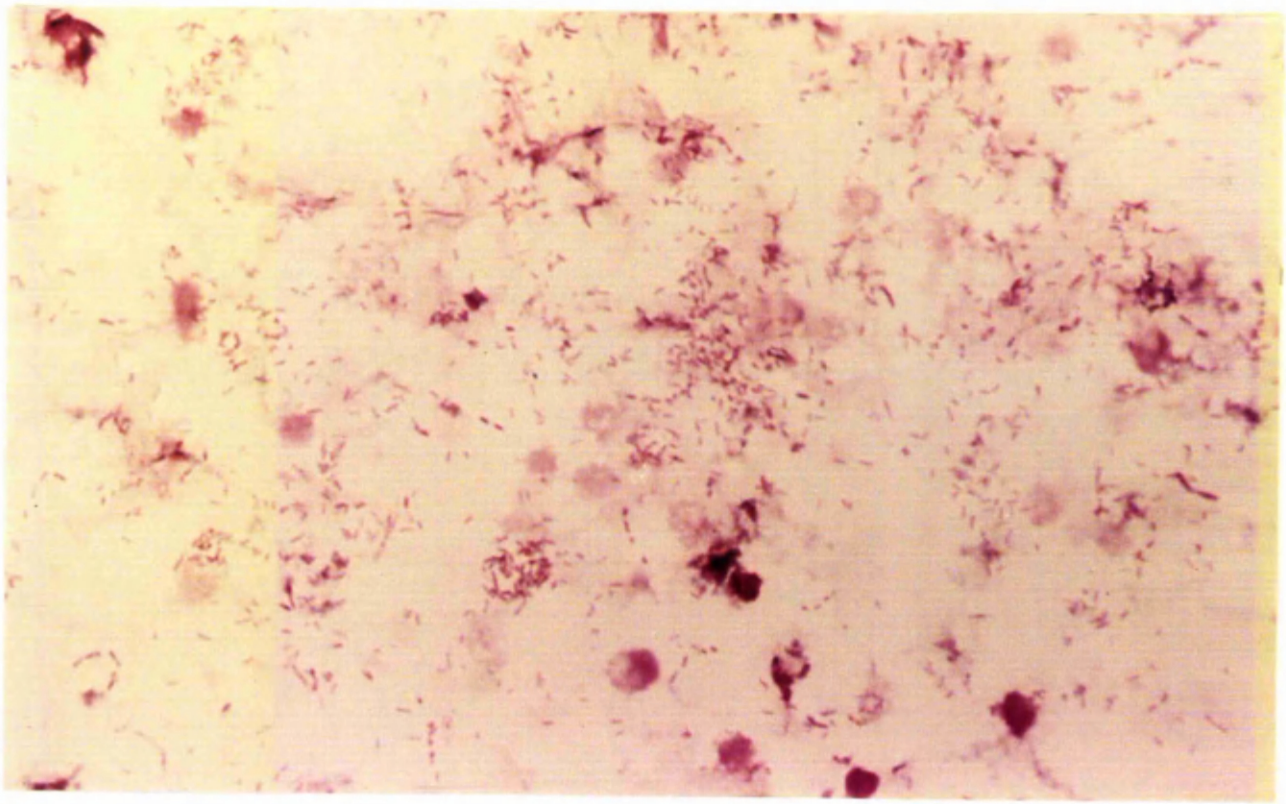

Figure 40.

Drop-preparation of urine showing numerous coliform organisms, before treatment. (Gram x 60)

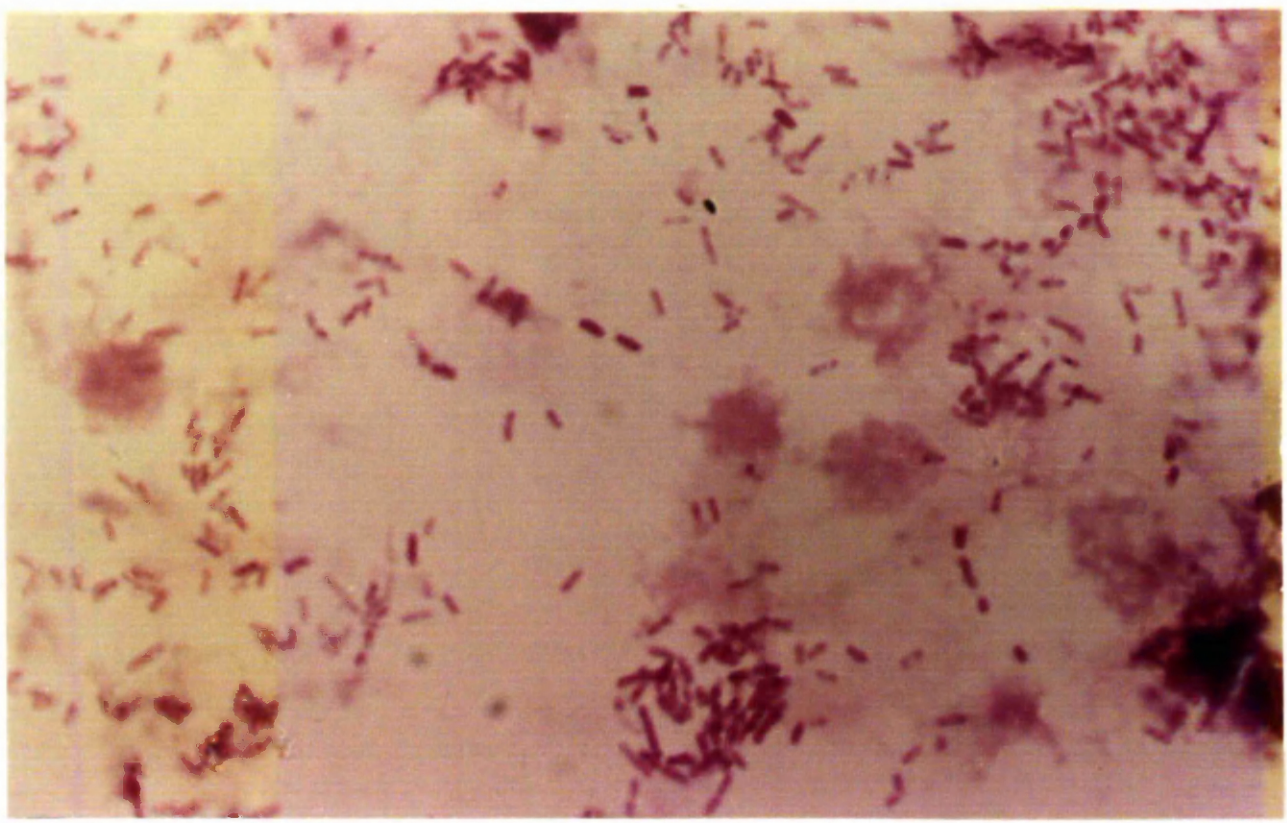

Figure 41.

The same as Figure 40. (Gram x 1500)

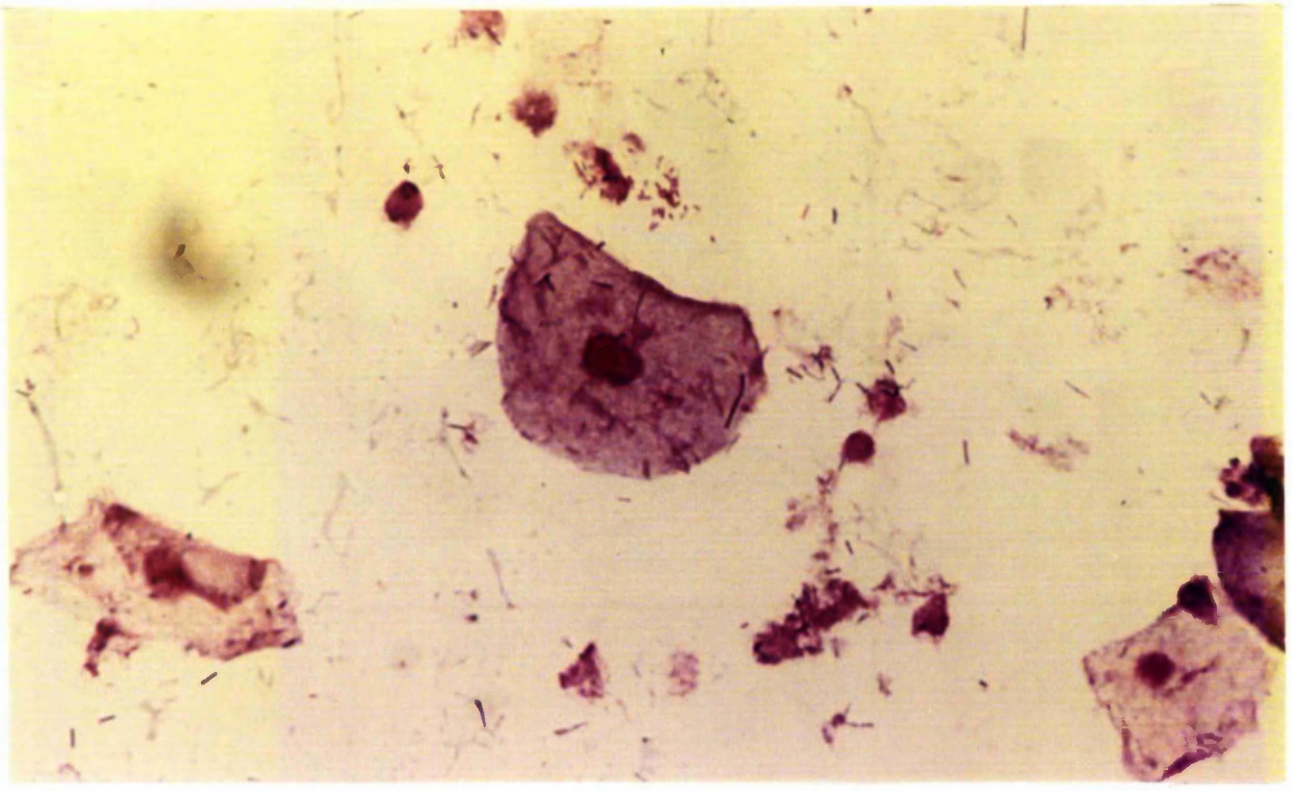

Figure 42.

Drop-preparation of urine from the same patient as Figures 40 and 41, after a one-week course of sulphadimidine with alkali. The specimens show great reduction in the numbers of coliform organisms, and the presence now of Gram-positive rods. One clump of Gram-negative bacilli are seen in this field. (Gram x 600)

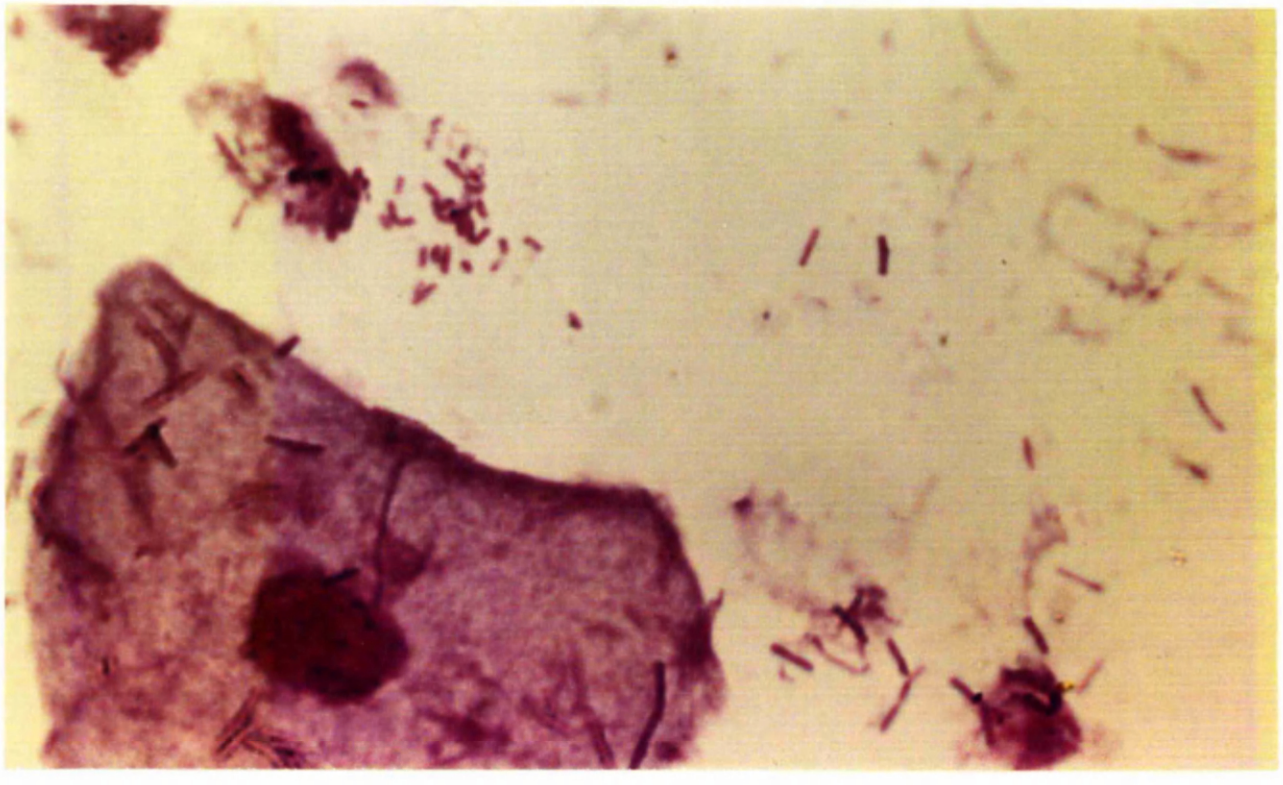

Figure 43.

The same as Figure 42 (Gram x 1500)

APPENDIX A

Details of Group I Infants with Lethal Congenital Defects

Since congenital defect accounted for 26.1 per cent of the total perinatal mortality in the Unit, it was thought worthwhile to consider these pregnancies further.

Defects of Dorsal Mid-line Fusion.

Twenty babies suffered from defects of dorsal mid-line fusion, five male (all stillbirths), and 15 female (ten stillbirths and 5 neonatal deaths).

Duration of Gestation. Anencephalic babies tend to be of short gestation, while the babies with hydrocephalus or meningocoele approximate more closely to full term. Fourteen of twenty infants (70 per cent) were of over 37 weeks gestation.

Range of Birth Weights. The anencephalic infants tended to be of low birth-weight and the hydrocephalic babies and those with meningocoeles to be nearer to normal birth weight.

Maternal Factors in Defects of Dorsal Mid-Line.

Age. When compared with the ages of the mothers of 100 healthy babies, it is seen that significantly more mothers bearing such defective infants are over 30 years of age than mothers bearing healthy infants ($P < 0.01$).

Parity. There were significantly more mothers who were pregnant for the fourth time or more in the group with defective babies than in the group having healthy babies ($P < 0.01$).

Previous Obstetrical History. Miscarriages, stillbirths, previous surviving low birth-weight babies, and illness in a previous pregnancy were not related significantly to the subsequent birth of a baby with a dorsal mid-line fusion defect.

Maternal Illness in the Current Pregnancy. There was no significant difference in the numbers of mothers with and without illness during their pregnancy in the defective and in the healthy group ($P < 0.20 > 0.10$). Hydramnios was the only condition significantly associated with the birth of infants with defects of mid-line fusion.

Contributory Cause of Death. In one baby, with an encephalocoele, suprarenal hypoplasia was present.

Comment

Increasing maternal age and parity, and the presence of hydramnios are the relevant features of dorsal mid-line defects amongst the factors considered in this study.

Genetic Defects.

Eight infants died in the perinatal period as a result of genetic or chromosomal defects. The types of defects present were Down's syndrome (four), achondroplasia (two), fibrocystic disease of the pancreas (one), and hypophosphotasia (one). There was one stillbirth due to achondroplasia, and seven neonatal deaths.

Duration of Gestation. Only two infants were of under 37 weeks' gestation, one with achondroplasia and one with hypophosphatasia.

Range of Birth Weights. Three were low birth-weight babies, but no pattern is seen according to the lesion present.

Maternal Factors in Lethal Genetic Defects. The age of the mothers of these eight infants was compared with the age of 100 mothers of healthy infants. The numbers are small but still show the weighting in the older mothers produced by the Mongol babies. The difference in incidence in mothers of under 30 years and over 30 years is statistically significant at P value < 0.01. The parity of these mothers was of no significance.

It is doubtful if any further analysis of this group of infants is of any value.

Contributory Cause of Death. Contributory factors to a fatal outcome were seen in four infants with genetic defects. These were duodenal atresia (one), atelectasis (one), gangrene of the legs thought to be due to aortic embolism from congenital heart lesion (one), all complicating Down's syndrome, and fourthly ileostomy and aspiration pneumonia complicating fibrocystic disease of the pancreas.

Comment

Mongols of older mothers, with accompanying lethal lesions made the biggest contribution of genetic defects to perinatal mortality.

Miscellaneous Defects.

There were twelve perinatal deaths due to miscellaneous congenital defects. The defects included congenital heart disease (four), oesophageal atresia (three), multiple deformity (four), and renal

agenesis (one).

Duration of Gestation. Eight of the twelve infants were of 37 weeks gestation or over.

Range of Birth Weights. No lesion was characterized by either low or high birth-weight in this small series.

Contributory Causes of Death. In this group of twelve infants with miscellaneous congenital defects contributory causes of loss were considered to be present in eight. These were -

Meningitis and suprarenal haemorrhage with multiple defects.

Tentorial tears and subarachnoid haemorrhage with congenital heart disease.

Aspiration pneumonia with congenital heart disease.

Rhesus haemolytic disease with congenital heart disease.

Operative difficulties in oesophageal atresia.

Anterior thoracic spina bifida and patent foramen ovale with oesophageal atresia.

Operative difficulty and duodenal atresia with oesophageal atresia.

Tentorial tear and bilateral subdural haematomata with renal agenesis.

Comment

The range of abnormalities here is wide and contributory causes frequent.

APPENDIX B

Details of Accidents of Labour Causing Perinatal Loss

Abnormal Presentations

Case No.	Sex	Duration of Gestation (in weeks)	Birth Weight (in gms)	Maternal Age	Parity	Intra-uterine Death Fresh Still-Birth or Neonatal Death	Comment
1	Male	32½	1698	31	0	Fresh Stillbirth	Cordiform uterus. Premature labour. Presentation both feet. Prolapsed cord. Foetus 101% of expected weight for gestation.
2	Male	35	1956	25	2	Fresh Stillbirth	Premature labour. Breech presentation. Ruptured liver.
3	Male	37	3227	39	7	Fresh Stillbirth	Shoulder and hand presentation, internal version, assisted breech delivery.
4	Male	41½	4708	27	1	Fresh Stillbirth	Shoulder presentation, internal version, without difficulty, Breech delivery.
5	Female	41½	2326	25	4	Fresh Stillbirth	Transverse lie, Shoulder presentation, Prolapsed arm and cord, External version, Assisted breech delivery.

APPENDIX B

Prolapsed Cord

Case No.	Sex	Duration of Gestation (in weeks)	Birth Weight (in gms)	Maternal Age	Parity	Intra-uterine Death Fresh Still-Birth or Neonatal Death	Comment
6	Male	40	3700	39	4	Fresh Stillbirth	Long-ruptured membranes (56 hrs.). Short labour.
7	Male	41	3800	44	7	Neonatal Death	Prolapsed cord, Failed manual rotation to breech, Forceps with "fair traction". Tentorial tears and cerebral haemorrhage.
8	Female	41½	3700	34	5	Neonatal Death	Prolapsed cord. Forceps delivery.

APPENDIX B

Prolonged Labour

Case No.	Sex	Duration of Gestation (in weeks)	Birth Weight (in gms)	Maternal Age	Parity	Intra-uterine Death Fresh Still-Birth or Neonatal Death	Comment
9	Male	40+	4170	36	3	Fresh Stillbirth	Big baby. 1st stage of labour 51 hours 40 minutes, 2nd stage 20 minutes, Spontaneous vertex delivery.
10	Female	41	3514	26	0	Intra- uterine Death 14 hours before delivery	Primigravida. 1st stage 68 hours, 30 minutes. "Inertia" - intended for caesarian section at 55 hours but foetal heart ceased. Persistent occipito - posterior.
11	Female	43	2800	26	0	Intra-uterine Death	Primigravida, at 43 weeks gestation delay in 2nd stage - (1 hour, 5 mins.) Oblique occiput anterior converted to direct occiput anterior, and delivered with forceps. Foetus described as "slightly macerated". Cord obstructed - round neck tightly.

APPENDIX B

Rupture of Uterus

Case No.	Sex	Duration of Gestation (in weeks)	Birth Weight (in gms)	Maternal Age	Parity	Intra-uterine Death Fresh Still-Birth or Neonatal Death	Comment
12	Male	37½	3178	44	7+	Intra-abdominal Death	Grand multipara. Previous caesarian section. Not in labour. Amniotic sac intact in abdomen. Hysterectomy.
13	Male	41	3178	25	1	Intra-uterine Death	Delayed 2nd stage - rupture of uterus, intra-uterine death. Craniotomy, forceps delivery, Hysterectomy.

APPENDIX C

Perinatal Deaths Due to Rhesus Haemolytic Disease of the Newborn

Case No.	Sex	Duration of Gestation (in weeks)	Birth Weight in Gms	Parity	Previous loss due to Haemolytic Disease of the Newborn	Previous Exchange Transfusion	Intrauterine of Neonatal Death: Time	Antibody Titre Week	Antibody Titre Level
14	F	34½ (Spontaneous Premature Labour)	2236	1	0	0	Neonatal Death, at 3 days	Not Done	
								Other Comment: Died during 2nd exchange transfusion. Autopsy: Prematurity, Haemolytic disease of the Newborn, Kernicterus, small subarachnoid Haemorrhage.	
15	F	35 (Caesarian Section for bad Obstetrical History)	2608	4	0	0	Neonatal Death at 3 hours	27 - 28	1/512 Albumin Anti-D
								30 - 31	1/512 Albumin Anti-D
								33 - 34	1/2048 Albumin Anti-D
								Other Comment: Died after withdrawal of 1st 10ml. at beginning of exchange transfusion. Autopsy: Complete Atelectasis.	

APPENDIX C (Continued)

Case No.	Sex	Duration of Gestation (in weeks)	Birth Weight in Gms	Parity	Previous loss due to Haemolytic Disease of the Newborn	Previous Exchange Transfusion	Intra-uterine or Neonatal Death: Time	Antibody Titre	
								Week	Level
16	F	37	2836	2	0	1	Intra-Uterine Death	25 - 26	1/2 Saline Anti-C and -D
									1/64 Albumin Anti-D
									1/16 Albumin Anti-C
								33 - 34	1/64 Saline Anti-D
									1/16 Saline Anti-C
									1/512 Albumin Anti-D
									1/64 Albumin Anti-C
17	F	37½	2040	3	2 Still-births	0	Intra-uterine Death	22 - 23	1/128 Albumin Anti-D
								33 - 34	1/256 Albumin Anti-D

APPENDIX C (Continued)

Case No.	Sex	Duration of Gestation (in weeks)	Birth Weight in Gms	Parity	Previous loss due to Haemolytic Disease of the Newborn	Previous Exchange Transfusion	Intra-uterine or Neonatal Death: Time	Antibody Titre		
								Week		Level
18	M	39	1991	1	0	0	Intra-Uterine Death	33 - 34	1/64	Saline Anti-D
									1/2	Saline Anti-C
									1/256	Albumin Anti-D
									1/4	Albumin Anti-C
								35 - 36	1/128	Saline Anti-D
									1/8	Saline Anti-C
									1/256	Albumin Anti-D
									1/8	Albumin Anti-C
19	F	39	3290	2	0	0	Intra-Uterine Death	38	1/256	Saline Anti-D and-E
									1/4	Saline Anti-C
									1/512	Albumin Anti-D and-E
									1/32	Albumin Anti-C

APPENDIX C (Continued

Case No.	Sex	Duration of Gestation (in weeks)	Birth Weight in Gms	Parity	Previous loss due to Haemolytic Disease of the Newborn	Previous Exchange Transfusion	Intra-uterine or Neonatal Death: Time	Antibody Titre	
								Week	Level
20	F	39½	2948	1	0	0	Intra-uterine Death	35 - 36	1/16 Saline Anti-D 1/64 Albumin Anti-D
								38 - 39	1/64 Saline Anti-D 1/256 Albumin Anti-D Weak saline and albumin Anti-C
21	F	40	3290	1	0	0	Intra-uterine Death	39	1/128 Albumin Anti-D

APPENDIX D

Perinatal Deaths Due to Placenta Praevia

Case No.	Stillbirth or Death	Duration of Gestation (in weeks)	Birth Weight (in gms)	% Expected Weight	Maternal Age	Parity	Mode of Delivery	Grade of Placental Abnormality	Comment
22	Neonatal Death	31	2354	160	31	4	Caesarian Section	I	Maternal Diabet Large Foetus
23	Neonatal Death	31½	1928	123	30	5	Caesarian Section	II	
24	Neonatal Death	31½	1202	77	35	8	Breech	III	
25	Neonatal Death	33	1858	105	31	2	Caesarian Section	I	
26	Stillbirth	33½	1754	94	25	2	Breech	III	
27	Stillbirth	41	3060	96	31	3	Craniotomy, Forceps	I	Occipito-posteric presentation, converted to mento-posterior. Foetal heart stopped. Craniotomy, Forceps.

APPENDIX E

Perinatal Deaths Due to Intra-partum Sepsis

Case No.	Still-birth or Death	Duration of Gestation (in weeks)	Birth Weight (in gms)	% of Expected Weight	Maternal Age	Parity	Surgical Rupture of Membranes-Interval Before Delivery	Organism	Comment
28	Neo-natal Death	31½	1530	97	28	3	- 21 Hours	Staphylococcus Aureus	This patient had a poor obstetrical history of two stillbirths at 6 months, and a neonatal death following caesarian section for pre-eclamptic toxaemia, birth weight 1600 gms. Bleeding at time of each period in this pregnancy. Autopsy: Prematurity Partial atelectasis Staphylococcal Septicaemia
29	Still-birth	39½	3144	100	28	2	+ 57 Hours	Not stated	Indication for surgical induction was foetal distress and forceps delivery in a previous pregnancy. Labour started 46 hours after membrane rupture, by which time there was meconium staining of liquor. Labour lasted 11 hours. Autopsy: Broncho Pneumonia of intra-uterine origin.

APPENDIX E (Continued)

Case No.	Still-birth or Death	Duration of Gestation (in weeks)	Birth Weight (in gms)	% of Expected Weight	Maternal Age	Parity	Surgical Rupture of Membranes-Interval Before Delivery	Organism	Comment
30	Neo-natal Death	40½	2424	75	32	0	+ 34 Hours	Staphylococcus Aureus	Caesarian section carried out ultimately. Autopsy: Bronchopneumonia, Empyema, Pericarditis.

APPENDIX F

Miscellaneous Illnesses in 10 Mothers of Infants Dying Perinatally and 7 Mothers of Healthy Infants.

Type of Illness	Group of Mothers			
	With Perinatal Loss		With Healthy Infants	
Acute	Congestive Cardiac Failure due to:-	2	Intestinal Obstruction (laparotomy)	1
	a) megaloblastic anaemia		Traumatic Thrombophlebitis	1
	b) hypertension of pre-eclamptic toxaemia		Respiratory Tract Infection	2
	Herpes Zoster	1	a) Bronchitis	
	Intestinal Obstruction (laparotomy)	1	b) Otitis media	
	Hyperemesis	2		
Chronic	Rheumatic Heart Disease	1	Rheumatic Heart Disease	2
	Diabetes Mellitus	1	Idiopathis Epilepsy	1
	Carcinoma of Breast	1		
	Pyelonephritis	1		
	Obesity	1		
	10 mothers with illnesses	11	7 mothers with illnesses	7

APPENDIX G

Criteria Used in the Classification Of the Severity of Maternal Illness

Antepartum Haemorrhage

a) Severe. With retroplacental clot of 600 ml. or more or where the patient with revealed haemorrhage required intravenous administration of more than 1200 ml. of blood and/or plasma.

b) Moderate. With retroplacental clot of 300 to 600 ml., or with revealed haemorrhage for which the patient was transfused with a maximum of 1200 ml. of blood.

c) Mild. With retroplacental clot under 300 ml., or revealed haemorrhage without the need for transfusion.

Pre-eclamptic Toxaemia and Hypertension. This was considered:-

a) Severe. With blood pressure of 150/100 mm.Hg. and over, albuminuria recorded as "++" to severe, and oedema "++" to severe. Patients with oliguria, anuria and eclamptic fits were all included in the severely ill group.

b) Moderate. With any two or all three of the following:- blood pressure 150/100 mm.Hg. or more, albuminuria recorded as "+" to "++", and oedema as "+".

c) Mild. With any two or all three of the following:- blood pressure 140/90 mm.Hg. or more, on at least two occasions, but under 150/100 mm.Hg., albuminuria recorded as "a trace" to "+", and oedema as "a trace" to "+".

Anaemia. This was classified as follows:-

a) Severe - less than 8 g. per 100 ml.

b) Moderate - 8 g. per 100 ml. to 9.9 g. per 100 ml.

c) Mild - 10 g. per 100 ml. to 10.9 g. per 100 ml.

Urinary Tract Infection. This was classified as follows:-

a) Moderate if symptoms were generalized rather than confined to the urinary tract. Vomiting, rigors, and proteinuria in a non-toxaemic patient were regarded as constituting moderately severe illness. The need for admission to hospital was taken to indicate moderately severe illness.

b) Mild if symptoms were mild, localized to the urinary tract, and if there was no albuminuria.

"Miscellaneous" illnesses considered to render the patient severly ill were diabetes mellitus, herpes zoster, carcinoma of the breast, congestive cardiac failure, chronic pyelonephritis and laparotomy for intestinal obstruction.

APPENDIX H

Details of 42 Perinatal Death Where Adequate Cause was not Apparent

Case No.	Sex	Duration of Gestation in weeks	Birth Weight in Gms	% of Expected Weight	Maternal Age	Parity	Previous Obstetrical History	Intrauterine Death, Stillbirth or Neonatal Death	Maternal Illness				Other Comment
									Uterine Haemorrhage	Pre-Eclampsia	Anaemia	Urinary Tract Infection	
31	Female	29	748	64	27	4	1 Miscarriage 2 7-8, alive 3 8-0, alive 4 5-0, alive	Intrauterine death	+ Persistent	-	-	-	-
32	Female	29½	230	19	22	0	-	Intrauterine death	-	-	-	-	Missed abortion
33	Female	29½	1104	89	22	1	1 5-4, alive	Neonatal Death	+ Persistent	-	+	-	-
34	Male	29½	1230	100	21	0	-	Neonatal Death	-	-	-	-	-
35	Female	29½	1470	119	31	3	1 2-6, died 2 Miscarriage 3 Miscarriage	Neonatal Death	-	-	-	-	Absence of left ovary and fallopian tube (mother)
36	Male	30½	468	33	34	8	1 7-14 alive 2) 3) Still- 4) births 5) at 6) 7 months 7) 8 4-7, alive	Intrauterine death	-	-	-	-	-
37	Female	30½	936	68	25	3	1 6-0, alive 2 Not known, alive 3 Miscarriage	Intrauterine death	-	-	-	-	Clinical pyelonephritis within 24 hours of delivery

APPENDIX H (Continued)

Case No.	Sex	Duration of Gestation in weeks	Birth Weight in Gms	% of Expected Weight	Maternal Age	Parity	Previous Obstetrical History	Intra-uterine Death, Stillbirth or Neonatal Death	Maternal Illness				Other Comment
									Uterine Haemorrhage	Pre-Eclampsia	Anaemia	Urinary Tracts Infection	
38	Male	30½	964	69	29	4	1 2-2, blind and spastic following ante-partum haemorrhage 2 Miscarriage 3 Miscarriage 4 6-6, alive	Intra-uterine death	+	-	-	+	-
39	Female	30½	1328	96	29	2	1 6-0, alive 2 Miscarriage	Neonatal death	+	-	-	-	-
40	Male	30½	1480	107	20	0	-	Neonatal death	-	-	-	-	-
41	Male	30½	1614	117	30	0	-	Neonatal death	+	-	-	-	-
42	Male	30½	1840	133	25	1	1 6-5, alive	Neonatal death	-	-	-	-	-
43	Male	31½	1020	66	29	6	1 7-8, alive 2 9-12, alive 3 Miscarriage 4 Miscarriage 5 Miscarriage 6 Miscarriage	Neonatal death	-	-	-	+	-
44	Male	31½	1180	73	25	1	1 5-15, alive	Intra-uterine death	+	+	-	-	-
45	Female	31½	1440	94	20	0	-	Neonatal death	-	-	-	-	-

APPENDIX H (Continued)

Case No.	Sex	Duration of Gestation in weeks	Birth Weight in Gms	% of Expected Weight	Maternal Age	Parity	Previous Obstetrical History	Intra-uterine Death, Stillbirth or Neonatal Death	Maternal Illness				Other Comment
									Uterine Haemorrhage	Pre-Eclampsia	Anaemia	Urinary Tract Infection	
46	Male	31½	1460	95	19	1	1 6-10, alive	Neonatal Death	+	-	+	-	-
47	Female	31½	2130	139	27	0	-	Neonatal Death	-	-	-	-	-
48	Female	31½	2180	142	20	0	-	Neonatal Death	+	-	-	-	-
49	Female	32	960	56	20	1	1 6-1, alive	Neonatal Death	-	-	-	-	-
50	Male	32½	1670	99	31	1	1 7-0, alive	Neonatal Death	-	-	-	-	-
51	Male	33½	1816	97	23	4	1 Stillbirth at 8 months 2 7-12, alive 3 Miscarriage 4 6-10, alive	Intra-uterine death	+	-	-	-	-
52	Female	35½	2096	95	26	1	1 7-1, alive	Neonatal Death	+	-	-	-	"Very Oedematous Baby" No autopsy
53	Male	36	2490	108	29	2	1 7-7, alive 2 6-12, alive	Intra-uterine death	-	-	-	-	Hypertension, probably subsiding
54	Female	36½	3280	136	30	0	-	Neonatal Death	-	+	-	-	Caesarian section Atelectasis

APPENDIX H (Continued)

Case No.	Sex	Duration of Gestation in weeks	Birth Weight in Gms	% of Expected Weight	Maternal Age	Parity	Previous Obstetrical History	Intra-uterine Death, Stillborn or Neonatal Death	Maternal Illness				Other Comment
									Uterine Haemorrhage	Pre-Eclampsia	Anaemia	Urinary Tract Infection	
55	Male	37	2900	115	25	0	-	Intra-uterine death	+	+	+	-	Clinical findings probably subsiding
56	Female	37	1621	64	21	2	1 3-7, alive 2 8-9, alive	Intra-uterine death	-	+	-	-	Clinical findings probably subsiding
57	Male	37½	734	28	38	2	1 6-3, alive 2 6-5, alive	Intra-uterine death	-	-	-	-	Intra-uterine death at about 32 weeks
58	Female	37½	1244	47	24	3	1 7-2, alive 2 7-10, alive 3 Stillbirth at 6 months Folic acid deficiency	Fresh Stillbirth	+	-	+	-	1st Stage of labour 34 hours
59	Male	38½	3400	118	32	1	1 3-10, alive	Neonatal death	+	-	-	-	Caesarian section Atelectasis
60	Male	40	2354	73	38	1	1 7-0, alive (aged 18 years)	Intra-uterine death	-	-	-	-	Hypertension, obesity. Clinical findings subsiding.
61	Female	40	2800	87	23	0	-	Fresh Stillbirth	+	-	-	-	-

APPENDIX H (Continued)

Case No.	Sex	Duration of Gestation in weeks	Birth Weight in Gms	% of Expected Weight	Maternal Age	Parity	Previous Obstetrical History	Intra-uterine Death, Stillbirth or Neonatal Death	Maternal Illness				Other Comment
									Uterine Haemorrhage	Pre-Eclampsia	Anaemia	Urinary Tract Infection	
69	Male	42½	3700	116	30	4	1 Died at 6 weeeks of pneumonia 2 9-0, alive 3 7-5, alive 4 Not known, alive	Intra-uterine Death	-	-	-	-	Post mature Prolonged foetal distress prior to admission
70	Female	43	1614	50	22	1	1 7-15, alive	Intra-uterine death	+	-	+	-	Post mature
71	Male	46	3598	116	30	5	1) Not known, alive. 2) 3) 4 8-12, Neonatal death. 5 Stillbirth at term following ante-partum haemorrhage		-	-	+	-	Post mature
72	Male	47	3060	95	39	7	All well	Fresh Stillbirth	-	-	-	-	Post mature. Liquor golden. First stage 27 hours.

APPENDIX J

MISCELLANEOUS ABNORMALITIES PRESENT DURING PREGNANCY IN 44 MOTHERS OF LOW BIRTH-WEIGHT BABIES

	Type of Abnormality	No. of Mothers
Acute	Respiratory Infection	9
	Hyperemesis	8
	Surgical Procedures	5
	Virus Infections	3
	*Cardiac Failure	2
Chronic	Rheumatic Heart Disease	11
	Diabetes Mellitus	1
	Thyrotoxicosis	1
	Carcinoma of Breast	1
	+Pulmonary Tuberculosis	1
	Hysteria	1
	(Prednisolone administration)	1
	Total Abnormalities	44

* Due to (a) megaloblastic anaemia and (b) hypertension.

\+ Quiescent. Patient receiving PAS and INA.

APPENDIX K

Weight Progress in the First Year of Life of Twelve Infants Showing Severe Degrees of Intra-uterine Growth Retardation

Case No.	Birth Weight in Gms	Duration of Gestation (in weeks)	% of Expected Weight at Birth	Details of Weight Progress % of Expected Weight According to Age (in weeks)			Maternal Details			
				16 to 27	28 to 39	40 to 51	Height in cms	Age in Years	Parity	Other
73	1300	39	42	97	-	-	159.5	34	4	On prednisolone throughout
74	1858	40	58	-	85	79	159.5	27	0	Rubella at 16 weeks
75	1928	40	60	103	-	-	150.0	27	2	Hyperemesis. Mild pre-eclamptic toxaemia
76	1670	38	61	100	-	-	150.0	28	1	Recovered tuberculous meningitis. Deaf-mute.
77	1272	34½	63	72	-	73	147	20	1	Prolonged urinary-tract infection
78	1642	37½	63	99	-	-	-	21	1	Severe hypertension, trace of oedema.
79	1879	39	63	-	94	-	162.4	23	0	Acute bronchitis
80	1984	39	66	112	-	-	154.7	42	1	Anaemia and acute bronchitis
81	2138	40	67	114	-	-	149	22	0	-
82	2138	41	67	-	76	70	145.7	25	0	Hyperemesis. Bleeding before 16 weeks
83	1614	36½	68	-	112	-	165	28	1	Antepartum haemorrhage at 30 weeks
84	2180	42	68	113	-	-	159.5	25	2	-

APPENDIX L

Details of* 14 Low Birth-Weight Babies with Haemoglobin Values of Less than 80 per cent. (Sahli) in the First Year of Life

Case No.	Birth Weight in Gms	Duration of Gestation (in weeks)	Age at Hb Estim-ation (in weeks)	Hb level	% of Expected Weight at Birth and Follow-up Examination (in weeks)					Other Details	
					At Birth	Under 16	16 to 27	28 to 39	40 to 51	Maternal	Infant
85	1858	40	Under 16	55	58	68	-	84	79	Maternal Rubella at 16 weeks	
86	1300	39	16 to 27	50	42	68	97	-	96	On predni-solone throughout	Gastro-enteritis at 21 weeks
87	1188	28½	16 to 27	50	110	-	83	70	-	-	Bronchitis
88	1544	31½	16 to 27	60	99	-	94	-	91	-	Gastro-enteritis at 21 weeks
89	1900	35½	16 to 27	60	86	-	118	-	-	-	-
90	1642	37½	16 to 27	70	63	-	99	98	-	-	Eye infection

*The table includes details of four infants who were anaemic at more than one examination.

APPENDIX I (Continued)

Case No.	Birth Weight in Gms	Duration of Gestation (in weeks)	Age at Hb Estimation (in weeks)	Hb Level	% of Expected Weight at Birth and Follow-up Examination (in weeks)					Other Details	
					At birth	Under 16	16 to 27	28 to 39	40 to 51	Maternal	Infant
91	1698	31	16 to 27	70	114	-	79	-	-	-	Bronchitis
87	1188	28½	28 to 39	50	110	83	70	-	-	-	Diarrhoea
90	1642	37½	28 to 39	55	63	-	99	98	-	-	Bronchitis
92	2236	36½	28 to 39	55	94	-	-	86	85	-	Gastro-enteritis Otitis media
93	1450	30½	28 to 39	65	107	-	-	93	101	-	-
88	1544	31½	28 to 39	70	99	-	94	-	91	-	Diarrhoea
94	1300	31	28 to 39	75	97	-	89	100	100	-	-

APPENDIX I (Continued)

Case No.	Birth Weight in Gms	Duration of Gestation (in weeks)	Age at Hb Estimation (in weeks)	Hb Level	% of Expected Weight at Birth and Follow-up Examination (in weeks)					Other Details	
					At Birth	Under 16	16 to 27	28 to 39	40 to 51	Maternal	Infant
95	1928	40	28 to 39	80	60	72	103	82	108	-	Pyloric stenosis
96	1362	29½	40 to 51	60	111	-	-	87	79	Thyro-toxicosis	Bronchitis
97	1844	31½	40 to 51	70	118	-	-	111	111	-	Bronchitis
88	1544	31½	40 to 51	75	99	-	94	-	91	-	Colds
94	1300	31	40 to 51	75	87	-	80	100	100	-	-
98	1362	31½	40 to 51	80	87	74	75	-	83	-	Dysentery. Whooping cough. Diarrhoea. Upper respiratory tract infection

PART I

PERINATAL INFLUENCES RESULTING IN THE DEATH OF THE SINGLETON FOETUS OR INFANT

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PART II

PERINATAL INFLUENCES RELATING TO LOW BIRTH-WEIGHT BABIES AND TO THEIR DEVELOPMENT IN THE FIRST YEAR OF LIFE

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