"THE THEORETICAL AND PRACTICAL SIGNIFICANCE OF CERTAIN PLACENTAL ANOMALIES."

THESIS SUBMITTED FOR THE DEGREE

OF

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BY

JAMES STEEL SCOTT

ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

Preface

This thesis has been prepared while working in the Department of Obstetrics and Gynaecology, the University of Liverpool. It is based on an intensive study of all placentae delivered at Mill Road Maternity Hospital in 1956-1957 but material obtained from that hospital and Liverpool Maternity Hospital during 1954-1958 and the Birmingham Maternity Hospital 1952-1954, is also included in certain sections.

Section C of the thesis is an expanded version of the William Blair-Bell Memorial Lecture delivered to the Royal College of Obstetricians and Gynaecologists on 30th May, 1958. The substance of this lecture will in due course be published in the Journal of Obstetrics and Gynaecology of the British Empire. Part of the material in Section D has been presented in brief to the Royal Society of Medicine (Section of Obstetrics and Gynaecology) in conjunction with Dr. A.D. Bain. A reprint of this is enclosed together with another joint paper to which reference is made at several points in the text.

For the opportunity to do this work and for advice, encouragement and painstaking, constructive criticism at all stages I am indebted to Professor T.N.A. Jeffcoate. For making the routine placental study possible and for much help, I must thank the labour ward staff of Mill Road Maternity Hospital.

For advice on various aspects of the work in Section C I am grateful to Sir Arthur Gemmell, Professor J.B. Lynch and Dr. Olive Scott and for help with statistical aspects Mr. R.L. Plackett. The help from Dr. A.D. Bain in the form of material for Section D is acknowledged in full in the text.

Mr. J. Greenough and Miss Margaret Dargue were responsible for the photographs, Dr. A.S. Woodcock for the micro-photographs and Miss Ann Carter for the typing and I am indebted to them all.

Introduction and General Placental Survey

PLACENTA EXTRACHORIALIS

THE PLACENTA IN HYDROPS FOETALIS

AMNION NODOSUM

S E C T I O N A.

GENERAL PLACENTAL SURVEY

Following an introductory section a report is given of a personal detailed examination of the placentae from 3,161 consecutive deliveries. The incidence of various placental anomalies is recorded and their significance discussed. The three abnormalities which aroused particular interest and which have been studied in detail with their clinical associations, are dealt with in the subsequent sections.

Introduction and General Placental Survey

INTRODUCTION.

Once upon a time, three Eastern potentates from Serendip, as Ceylon was then known, went journeying through the Orient. In their travels they were continually making discoveries, by a combination of accident and sagacity, concerning matters other than those of which they were in deliberate quest. From the moral of this fairy-tale - "The Three Princes of Serendip" - Horace Walpole in 1754 coined the term "serendipity" to cover such chance addition to our knowledge and experience.

Sir J.Y. Simpson commenting on such occurrences in his own experience of medicine put it thus:- "But often when we enter on a subject of pathological study, we really know not to what ultimate results it may lead, and therefore never ought to condemn or eschew any pathological investigation because we do not immediately see any practical advantage to which it may tend."

The placenta is all things to all men at the intra-uterine stage of existence. Its functions known to date range from respiratory, nutritional, excretory, haemopoetic and metabolic to that of hormone production which in diversity compares well with the activity of the whole endocrine system in the adult. However, the details of placental function and structure in health and disease remain very much an enigma,

and the present picture appears so complicated as to deter most obstetricians from seriously attempting its elucidation. No matter how much interest may be taken in the mother and the baby, the placenta - the one tissue which is always available for detailed study - generally receives but a cursory glance before being discarded.

This study was commenced merely as a routine personal examination of the placentae from all the deliveries at one maternity hospital in the hope of acquiring a greater familiarity with various placental abnormalities and a better understanding of their significance.

In the course of this general placental survey, however, three abnormalities attracted particular interest. These have been studied in particular detail and the attempt to elucidate as far as possible the practical and theoretical significance of these anomalies has lead to the consideration of organs far removed from the placenta. In each case there has been an apparently logical connection and the extent and complexity of the functional inter-relation of various organs has been repeatedly evident. It has also been remarkable to discover how much it is possible to deduce with regard to the function of an organ from a detailed study of a particular pathological feature and its effects.

This method of approach to physiology is perhaps less favoured to-day than formerly. As Kremer said in his recent Oliver-Sharpey

Lecture to the Royal College of Physicians :-

> "There is now perhaps a tendency to swing away from the technique of meticulous clinical observation as a basis for the observation of function, whether in the nervous system or elsewhere. Instead there is often the substitution of the results of investigations carried out by technical experts who may see only a part of the patient - - - - - - there is still room for the elucidation of physiological mechanisms by the careful clinical study of disease processes aided, whenever necessary, by planned laboratory investigation."

As a result of the diversions from the general placental survey to study in detail the three anomalies which attracted particular interest, information has been acquired which would seem to have a bearing on three important practical problems of obstetrics - ante-partum haemorrhage, toxaemia of pregnancy and the factors influencing foetal growth in-utero.

One other diversion from the study has been the introduction to the writings of the early masters of obstetrics - and for that alone it has been worthwhile. William Hunter's famous atlas and his less well known description of the human gravid uterus and its contents, stand as

models of clarity in perception and lucidity of exposition. It has been a humiliating experience to compare the present efforts at describing simple anatomical features and expressing simple ideas, with the writings of Hunter.

In the course of the study it has become evident the extent to which thinking is influenced and inquisitiveness blunted by the uncritical acceptance of "facts" - which frequently turn out to be mere half-truths or dubious theories in disguise. It has been realised with regret that the effects of such uncritical acceptance are not to be eradicated overnight. As the apostle Paul expressed it to the Corinthians :- "When I was a child - - - I understood as a child, I thought as a child - - - For now we see through a glass darkly; but then face to face; now I know in part - - - - "

Material and Method :-

This study was carried out on the placentae of women delivered at Mill Road Maternity Hospital, Liverpool from September 1st, 1956 to September 30th, 1957. The placentae were for all practical purposes consecutive - the only interruptions being due to a period of 2 weeks leave and to the supply of 24 placentae at intervals to the Department of Bacteriology, Liverpool University. The amnion from these placentae was used for tissue culture purposes and it was necessary to deliver them directly into sterile containers without handling so they were not inspected. They were completely unselected, however, and their ommission should not affect this study.

At delivery each placenta and its membranes was collected in a kidney dish and the usual examination for completeness carried out by the attendant at the delivery. The placenta was then weighed. The weight and that of any accompanying blood clot was recorded separately, together with a note as to whether the clot appear old or fresh. The dishes were then covered, labelled and stored for the purposes of this study. The detailed examination of the stored specimens was carried out daily or, in Summer weather, twice daily.

Each placenta and its membranes were examined personally and dictated notes were recorded by an assistant. The initial examination took the form of a detailed macroscopic examination. The membranes

were first inspected - particular attention being paid to the maternal surface of the chorion and the foetal surface of the amnion. Where possible, and known to be relevant, the site of rupture of the membranes in relation to the placenta was noted. The umbilical cord was then noted - and in particular its manner of attachment to the placenta and the distribution of its vessels on the placenta.

The placental substance was then examined, firstly by inspection of the foetal and maternal surfaces. Particular attention was paid to any abnormality of the chorionic plate and especially whether it extended to the periphery of the placenta. This was followed by multiple vertical sectioning at approximately half-inch intervals using a bread-board and knife. This was not done, however, if the placenta was required for photography or if histological examination was desired. In these circumstances the placenta was either deep-frozen (if for photography) or fixed in 10 per cent formal-saline (if for histology). These placentae were stored in this for at least 4 weeks to allow adequate fixing of the central tissues and multiple slicing was then carried out at the time blocks were being taken for histology. When it was realised that the histology of a particular placenta was likely to be of interest (e.g. in severe pre-eclampsia, diabetes mellitus, rhesus sensitisation etc.) a note was made in the case record during the ante-natal period requesting that the placenta be placed in 10 per cent formal-saline

immediately on delivery. In this way it was possible to obtain sections without autolytic change.

The mothers whose placentae had shown particular anomalies were questioned personally as to their health during the pregnancy with particular regard to early pregnancy illnesses, possible factors which might have lead to anoxia and the occurrence of vaginal haemorrhage at any time during the pregnancy. Their previous menstrual history was also obtained. This questioning was carried out between the second and ninth day of the puerperium. To serve as controls, 200 women whose placentae were entirely normal were personally questioned in an exactly similar manner. Any other information was obtained from the entries in the medical records during the ante-natal period and at the confinement.

In the findings which follow it will be noted that the incidence of various placental anomalies is probably higher than is the "impression" of most obstetricians. They are certainly higher than was expected when this study was begun. The reason for this is almost certainly that in the normal course of events the obstetrician tends to see only the placentae of the relatively small number of cases which he personally delivers.

The total number of placentae examined in this consecutive series was 3,161 and of these 1,353 were from primiparae and 1,808 from multiparae. Placentae collected at other times are referred to in the text

where they serve to amplify some particular aspect of the study but the calculation of incidence of the various anomalies is strictly confined to the consecutive series.

In addition 4 placentae were obtained from cases of maternal death in late pregnancy (3 from other hospitals). In each the uterus was obtained intact and with the placenta still attached. Three of these were used for injection studies and as the findings bear on the problem of the marginal sinus which is discussed in Section B., they are described there.

Histological sections were obtained from all abnormal placentae and from all placentae where there was known to be some maternal illness. The histological findings have been extremely difficult to interpret but are referred to in the various sections where they appear to help towards an understanding of the situation.

The incidence of various lesions is summarised in Table AI.

TABLE AI.

ANOMALY	OVER-ALL INCIDENCE	INCIDENCE IN GROUP SHOWING PLACENTA EXTRACHORIALIS
PLACENTA EXTRACHORIALIS	587 (18.3 per cent)	-
VELAMENTOUS CORD ATTACHMENT	47 (1.5 per cent)	3 (0.5 per cent)
BATTLEDORE PLACENTA	62 (2 per cent)	8 (1.4 per cent)
SUCCENTURIATE LOBES	55 (1.7 per cent)	8 (1.2 per cent)
BIPARTITE PLACENTAE	25 (0.8 per cent)	-
BILOBULATE PLACENTAE	36 (1.1 per cent)	4 (0.7 per cent)
MECONIUM STAINING	169 (5.3 per cent)	22 (3.8 per cent)
SUB-CHORIONIC CYSTS	11 (0.3 per cent)	-
TWIN PLACENTAE	67 (2.1 per cent - 49 binovular	15 (2.6 per cent - all binovular)
AMNION NODOSUM	2 (0.07 per cent)	-
OLD BLOOD CLOT ON MEMBRANES	54 (1.7 per cent)	45 (7.8 per cent)
MEMBRANOUS FOLD TO UMBILICAL CORD	7 (0.2 per cent)	3 (0.5 per cent)
GROSS CHORIO-DECIDUAL INFARCTION	54 (1.4 per cent)	13 (2.2 per cent)
INFARCTIVE LESIONS DUE TO FOETAL THROMBOSIS	3 (0.1 per cent)	-
MASSIVE SUB-CHORIONIC FIBRIN DEPOSITION	11 (0.3 per cent)	-
EXTENSIVE RETICULAR CALCIFICATION	16 (0.5 per cent)	-
MARGINAL INFARCTION	23 (0.7 per cent)	-

Abnormalities Observed :-

1. Circumvallate and Marginate Placentae.

By far the commonest abnormality of placental form encountered was some degree of "placenta circumvallata" or "placenta marginata." Many of these placentae showed rings on their foetal surface with appearances which in part were typical of a "circumvallate" ring while elsewhere the ring was of the type commonly described as "marginate." Accordingly, as it appeared that these two types of ring were merely differing manifestations of the same placental anomaly - a chorionic plate smaller in area than the whole placenta - they have been grouped together under the term "PLACENTA EXTRACHORIALIS." The 578 (18.3 per cent) placentae which showed this abnormality are analysed and considered separately in Section B of the thesis.

Many of the placentae extrachorialis showed other anomalies and these are included in the subsequent analysis in this section.

2. Velamentous Cord Insertion.

The umbilical vessels became attached to the amniotic membrane outside the circumference of the placenta* forty-seven times - an incidence of 1.5 per cent of this anomaly.

The average distance of the attachment of the cord to the membrane from the circumference of the placenta was 3 inches - the maximum being 12 inches. Fig. A1. shows the placenta and membranes in this case (No. 1056) - the natural state having been restored by redistending the membrane sac with gelatine. The vessels in most cases of velamentous insertion divide in the membranes before reaching the placenta and this is well seen in the illustration.

In 5 cases the anomaly was found in association with twins - 4 times in 1 sac of binovular twins and once in one sac of uniovular twins.

In 6 the cord vessels sent separate supplies to bipartite placentae or succenturiate lobes.

In 3 placentae the abnormal cord insertion was associated with placenta praevia.

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* FOOTNOTE.
Cases in which the placenta was bipartite or had succenturiate lobes with vessels running in the membranes between the separate portions of the placenta were not included unless the primary attachment of the cord was to membrane rather than placenta.

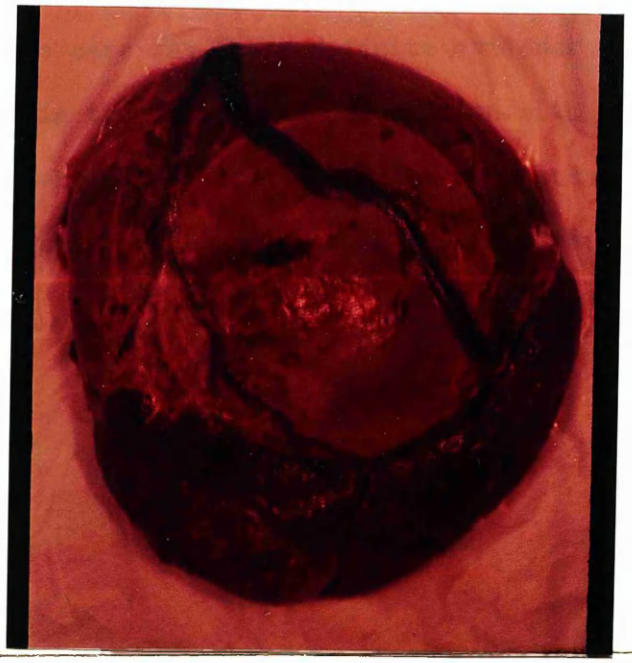

Fig. A.1.
Velamentous cord insertion. The sac has been redistended by filling with gelatin. The umbilical vessels can be seen running in the membranes and dividing before reaching the placental edge.

Fig. A.2.
Multilobulate placenta with multiple succenturiate lobes.

In no case was there definite evidence of haemorrhage from vasa praevia though once in association with 10 inches of velamentous vessel, there was blood clot on the membranes close to one branch of the umbilical vessel. It seemed possible the blood might have arisen from that vessel but there was no clinical evidence of foetal exsanguination.

There were 3 stillbirths in the velamentous cord group; 2 occurred in cases where the anomaly was associated with placenta praevia. The details were as follows :-

In case 1025 one sac of binovular twins showed the anomaly and both babies were stillborn when delivery was undertaken by Caesarean section for placenta praevia. Autopsy showed changes of asphyxia.

In case 1050, in which univolar twins were associated with placenta praevia, the first foetus, which was the one from the sac with the velamentous cord, was stillborn. The second foetus was alive and showed no evidence of having lost blood as would have been expected had the first succumbed from vasa praevia haemorrhage, for there was obvious communication of the two circulations; nor did the appearance of the membranes suggest that such haemorrhage had occurred. Again, on autopsy of the stillborn foetus the findings suggested an asphyxial death.

In case 1032 unexplained intra-uterine death occurred at term. The foetus weighed 9 pounds 13 ounces and autopsy showed signs of asphyxia.

3. Battledore Placenta.

Insertion of the cord at the perimeter of the placenta occurred in 62 instances, an incidence of 2 per cent. In no case did it appear to be of any clinical significance.

4. Succenturiate Lobes.

Areas of placental tissue separate from the main mass of placenta but not amounting to more than 1/3 of the placenta's area, were regarded as succenturiate lobes. In cases where the area exceeded 1/3 of the placental area the condition was regarded as a bipartite placenta.

Fifty-five placentae had succenturiate lobes - an incidence of 1.7 per cent. Multiple succenturiate lobes (Fig. A2.) were present

in 12 specimens - 2 lobes in 8; 3 lobes in 3 and 6 lobes in 1 specimen.

One showed a tiny isolated nodule of placental tissue ($\frac{1}{2}$ x $\frac{1}{2}$ inch) 3 inches outside the placental perimeter yet apparently without vascular connection to the main placenta.

Six examples were associated with binovular twin pregnancies. In one case manual removal of the placenta was necessary for morbid adherence of the succenturiate lobe. No other relevant complications occurred.

5. Bipartite Placentae.

Twenty-five placentæ were bipartite according to the definition given above - an incidence of 0.8 per cent. In 3 the anomaly was associated with the presence of succenturiate lobes. Three of the placentae were delivered from mothers who had suffered accidental ante-partum haemorrhages. In 2 of these cases the baby was stillborn. Both of these placentae showed in addition gross infarction involving approximately 40-50 per cent of the placental substance but it seems likely that the bipartite form of the placenta was merely incidental.

6. Bilobulate Placentae.

In this category were grouped placentae whose contour showed a constriction but this was not sufficient to separate the two portions. (Figs. A3 and 4). There were 36 anomalies of this type - an incidence of 1.1 per cent. One placenta had a trilobulate form while 2 others were quadrilobulate.

In one case (C.V. 505), associated with placenta extrachorialis, the extrachorial placental formation was entirely confined to one lobe of a bilobulate placenta.

There was one unexplained intrauterine death at term (No. 1032) but nothing suggested that the placental deformity was in any way responsible.

7. Meconium Staining.

The foetal surface of the amnion covering the placenta showed meconium staining in 169 specimens - (5.3 per cent). Twenty-two of these were in cases of placenta extrachorialis - an incidence in this group of 3.8 per cent. For the purposes of this study this was used as a rough indication of the extent, if any, of the asphyxiating

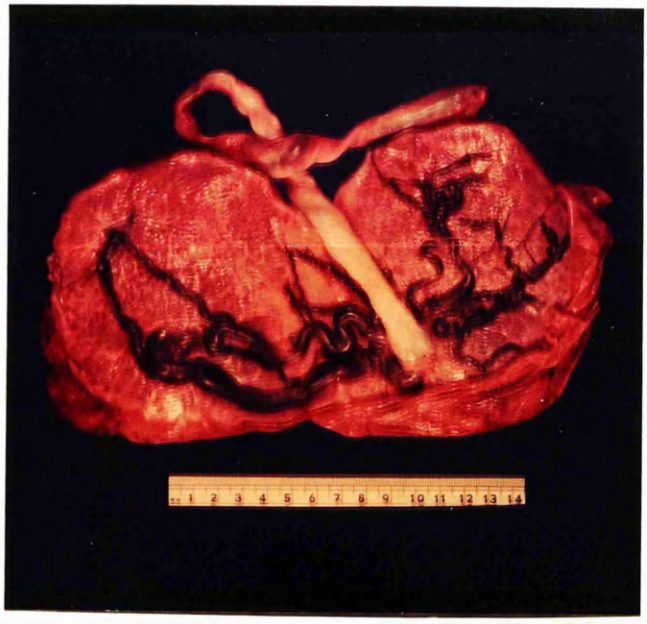

Fig. A.3.

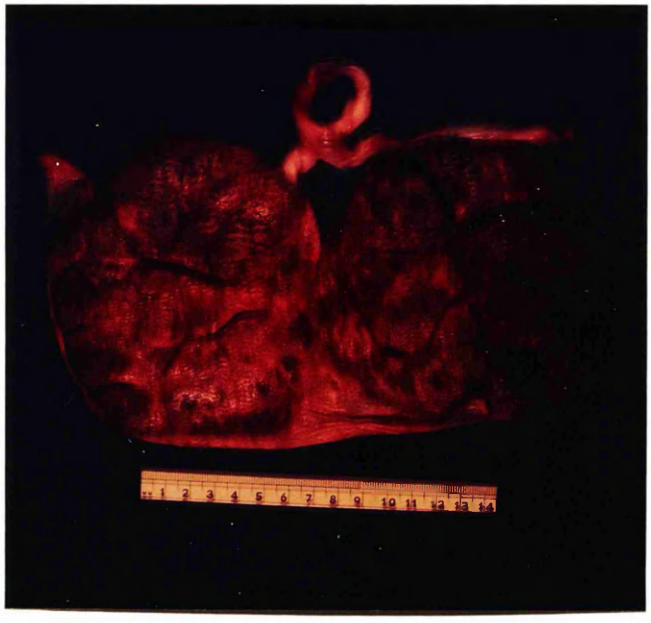

Fig. A.4.

Fig. A 3 and A 4 . Bilobulate placenta.

Although there is a strip of placental tissue connecting the two lobes, the main connecting vessel runs in the membrane. In the view of the decidual surface - the ahadow of the vessel can be seen through the membrane.

effect of placenta extrachorialis upon the foetus.

8. Subchorionic Cysts.

Eleven placentae showed cysts immediately beneath the membrane of the chorion - an incidence of 0.3 per cent. In two placentae these were multiple. In two cases only were the cysts associated with extensive multiple infarcts of the placental substance.

9. Multiple Pregnancy.

There were 67 sets of twins in the series - an incidence of 2.1 per cent. Of these 49 (or 73 per cent) were binovular. Uniovular placentae were distinguished by the presence of a single chorion and by evidence of communication of the two foetal circulations.

Fifteen of the twins were associated with placenta extrachorialis and all of these were binovular.

In one instance of uniovular twins (No. 975) the pregnancy was mono-amniotic and the two umbilical cords were knotted with each other.

There was one example of foetus papyraceous (No. 907).

10. Amnion Nodosum.

During the course of the survey 2 instances of this abnormality were observed affecting the amniotic membrane - especially that portion which covered the placenta. As far as can be ascertained the condition has not previously been recorded in this country. Since this initial finding a total of 12 examples of the condition have been collected and these are reviewed in detail and the full significance of the anomaly discussed in Section D of this thesis.

11. Old Blood Clot on the Membranes.

In cases other than those of frank ante-partum haemorrhage, blood clot in varying stages of organisation was found adherent to the maternal aspect of the chorionic membrane in 54 specimens - an incidence of 1.7 per cent. In 45 of these it was associated with placenta extrachorialis - giving an incidence of 7.8 per cent in the 578 placentae extrachorialis. The significance of the high incidence in this group is discussed in Section B.

In 4 of the cases not associated with placenta extrachorialis, there was extensive marginal infarction of the placenta, while in 2 the finding of blood clot covering a large area of the chorion was associated with oligohydramnios (Nos. 1148 and 1168). This is

considered in Section D.

12. Membranous Fold to the Umbilical Cord.

In 7 placentae (0.2 per cent) a membranous fold ran from the chorionic plate to the umbilical cord stretching 2-3 inches from its placental attachment. This gave a triangular or - in nautical parlance - "jib-like" fold (See Fig. A5).

13. Infarctive and Degenerative Placental Lesions.

It is probably because it is so difficult to describe, to classify and to comprehend the significance of that complex group of lesions - placental infarcts and other degenerative changes - that so few workers have attempted serious study of the placenta. These lesions have not been one of the subjects chosen for special investigation in this study for two reasons. Firstly, it would be impossible for one person

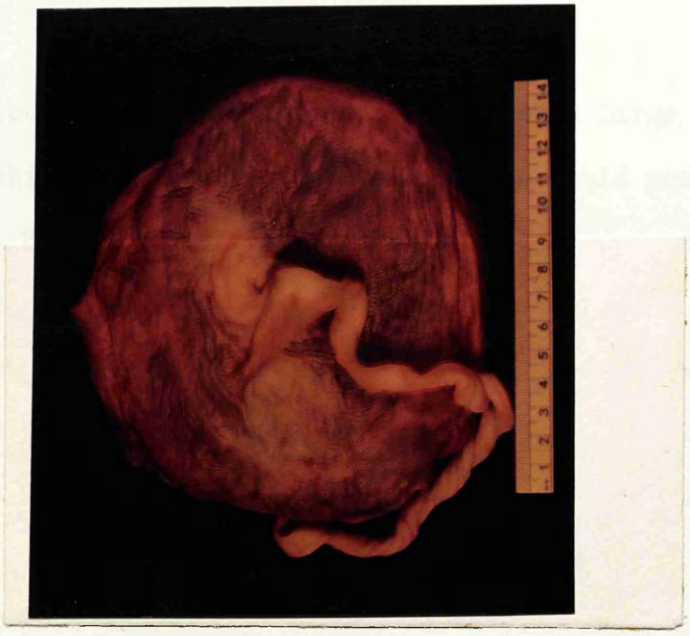

Fig. A5. Specimen showing triangular fold of membrane projecting from the placental surface to the umbilical cord. This placenta also shows a marginate ring, involving 2/3 of its circumference - with extrachorial placental tissue in this region.

to study in minute detail the infarcts from such a large series of placentae as this and a study of a small series would probably be of little value. Secondly, it seems probable that these changes, whatever their degree, are in most cases secondary phenomena and that they are rarely the primary factor in obstetric pathology. This suspicion may or may not prove correct but for the present it is sufficient to make the investigation of other aspects of placental pathology more attractive.

However, from this study several facts concerning infarctive and degenerative lesions of the placenta became evident which seem worthy of mention.

Infarctive lesions of the placenta are like ice-bergs - the large and presumably dangerous infarcts show little of their bulk on the surface. Conversely where there is fibrous deposition of considerable extent on either the foetal or the maternal surface of the placenta, this is often like an ice-flow and there is no significant involvement of the deep placental substance. Such deposits seem to have little effect on the efficiency of placental function. It is possible that superficial fibrin deposition on the decidual aspect of the placenta may be associated with an interference with the blood flow in the maternal vessels supplying the chorio-decidual space, but this is by no means inevitable. Fibrin deposited on the foetal surface of the

placenta (sub-chorionic), even if very extensive, rarely involves the placental substance and would appear to be of no importance whatever as it seems to interfere not at all with the foetal vessels supplying the cotyledons - the vessels, in fact, frequently lie deep to the fibrin plaques. Illustrations of these statements are given in Figs. A6, A7, A8, A9. and A.10.

These comments on the superficial appearances of a placenta with regard to fibrin deposition bearing little relationship to the situation existing deep in the substance of the organ, may seem so self-evident as to be unworthy of mention. Yet even in teaching hospitals in this country it is extremely rare for every placenta to be sliced routinely in order to assess the degree of infarction. Until such practice becomes routine in all maternity units, it seems unlikely that much progress will be made in assessing the significance of placental infarcts. A minimum standard of equipment for an obstetric unit should include the provision in each delivery room sluice of a bread-board and knife for this purpose.

From the macroscopic examination of the present series of placentae, infarctive or degenerative lesions have been differentiated into the following groups.

a. Infarctive lesions of the chorio-decidual space.

b. Infarctive lesions due to thrombosis in the foetal circulation.

c. Sub-chorionic fibrin deposition.

d. Reticular calcification.

e. Marginal infarction.

Fig. A6.

Fig. A7.

Figs. A6 and 7. Views of foetal surface and median section of the same placenta. Although there is extensive sub-chorionic fibrin deposition the chorio-decidual substance is practically unaffected. There is also some degree of placenta extrachorialis in this specimen.

Fig. A8.

Fig. A9.

Figs. A8 and 9. Views from the decidual and lateral aspects of a slice of placenta. Although a large pale infarct involving approximately 1/3 of the section is clearly seen on the lateral view, this is quite invisible on the decidual aspect.

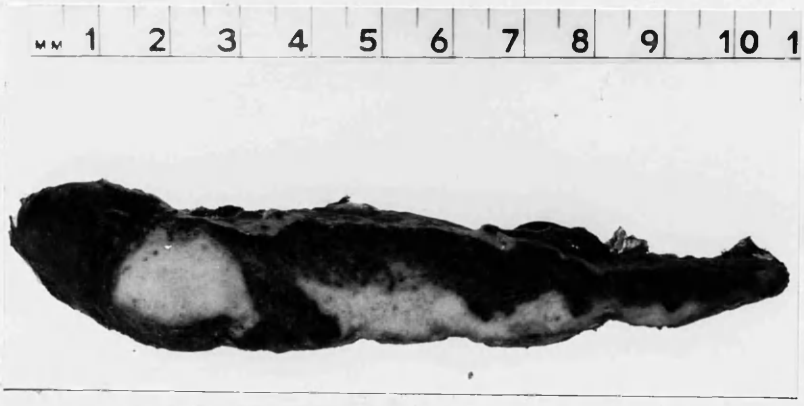

Fig. A.10.

Fig. A.10. Median section of a placenta (decidual surface at lower edge of picture) in which it will be seen that the fibrin deposition on the decidual aspect on the right side of the picture does not extend deeply to the chorio-decidual substance whereas a large infarct on the left side does not affect either the chorionic or the decidual plate.

a. Infarctive lesions of the choriodecidual space.

The majority of infarcts come into this category. They have been grouped together anatomically regardless of their appearance and apparent age - the red infarct of today is merely the white infarct of tomorrow and involves exactly the same portion of tissue. This classification is also adopted without regard to the debated question as to whether or not these infarcts originate primarily from arrest of the maternal or the foetal circulation in the area. During the survey a small number of placentae were seen in which the lesion was quite obviously a foetal thrombosis involving a large branch of the umbilical vessels - these are considered separately in group b.

In this group of chorio-decidual infarcts are included all placentae which on vertical slicing of the placenta, at approximately half inch intervals, more than 25 per cent of the chorio-decidual substance appeared to be involved in infarctive processes.

Fifty-four placentae came into this category - an incidence of 1.4 per cent. Of these 54 placentae showing gross chorio-decidual infarction, 13 were associated with intra-uterine death of the foetus - an incidence of 24 per cent. In the whole series of 3,161 placentae there were 92 intra-uterine deaths making an overall incidence only of 3 per cent. Likewise, in this group of grossly infarcted placentae there was a raised incidence of meconium staining (12 per cent) and

also of accidental ante-partum haemorrhage (10 per cent). In connection with the latter group, it was evident on 4 separate occasions in the course of this study, that accidental haemorrhages had arisen from haemorrhagic infarctions of the choriodecidual space which had lead to disruption of the decidua basalis. In the same placentae were to be seen other haemorrhagic infarcts of a similar age which had remained within the confines of the chorio-decidual space.

The history of the mother who delivered the most severely infarcted placenta seen (No. 927) is of some interest :-

Mrs M.M.

Age 23 years.

One previous pregnancy.

The first pregnancy was complicated by a severe accidental haemorrhage which produced renal cortical damage. During that pregnancy the blood pressure had been estimated twice before the occurrence of the haemorrhage. At 23 weeks it was 160/90 millimetres of mercury and at 27 weeks it was 140/90 millimetres of mercury. There was no albuminuria.

At 30 weeks she was admitted as an emergency with accidental haemorrhage. This was of extreme severity and subsequently anuria developed; this was followed by marked oliguria for 8 days before diuresis occurred. Treatment was by the Borst diet. The blood

urea reached a maximum of 215 mgm. per cent and the serum potassium a maximum of 30 mgm. per cent. Three months after delivery renal function tests were within normal limits except for the urea clearance which was sub-standard. No details of the placenta in this pregnancy were available.

Second Pregnancy.

The blood pressure in this pregnancy was 130/90 millimetres of mercury at 26 weeks and 140/90 mm. of mercury at 33 weeks when she was admitted to hospital. The blood pressure remained about this level and albuminuria of 0.5 - 1.0 gram per litre persisted until delivery occurred, following induction of labour, 6 weeks later. The baby weighed 3 pounds 10 ounces and survived.

The placenta weighed only 8 ounces and was extremely thin (chorio-decidual measurement 0.75 - 1.25 cms.) and gross infarction involved approximately 2/3rds of the placental substance. (Figs. A1and12).

It seems very likely that in this case placental damage was a secondary effect of the maternal hypertension and possibly to some extent related to the previous kidney damage.

Fig. A.11.

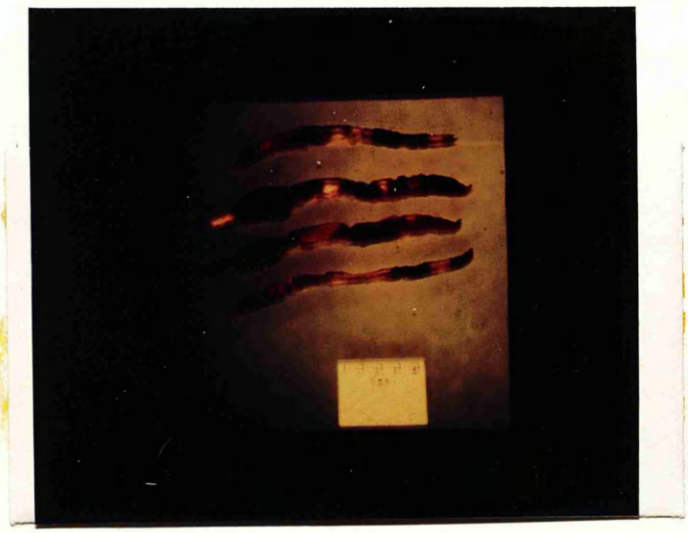

Fig. A.12.

Fig. A.11 and A.12. Placenta No.927 showing gross infarction. The mother had severe accidental antepartum haemorrhage in her last pregnancy, complicated by renal cortical damage. The remarkable feature of this pregnancy was that the foetus was able to survive despite infarction involving approximately two-thirds of the placenta - the total weight of which was only 8 ounces.

(See case summary - Mrs M.M.)

b. Infarctive Lesions due to Thrombosis in the Foetal Circulation.

On inspection of 3 placentae (Nos. 581, 682 and 942) it was quite evident that the distribution of the infarctive process involved a large branch of the umbilical vessels. It is quite possible that a considerable proportion of the lesions in the previous group were also primarily foetal in origin but only in these 3 could this be deduced with confidence on inspection of the placenta. Figure A13 shows the thrombosis of the foetal vessels in case 581 and the related distribution of the infarction.

In none of these cases were any untoward effects evident clinically.

c. Sub-chorionic Fibrin Deposition.

Small deposits of fibrin on the foetal surface of the placenta just beneath the chorion were found to be extremely common. In 11 specimens, however, this was on a relatively massive scale involving practically the whole of the chorionic plate - yet on section of the placenta in each of these instances it was found that the chorio-decidual space was quite free from infarction. There were no foetal deaths in this group nor any occurrence of meconium staining.

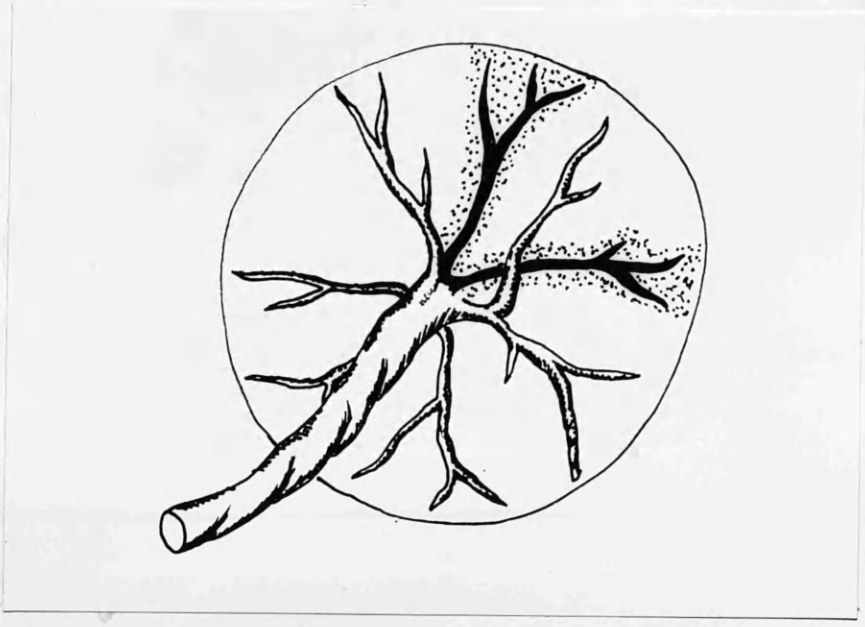

Fig. A.13. Placenta No.581 showing distribution of infarction corresponding to foetal vessel thrombosis. An area enclosed by the two branches of the thrombosed vessel was supplied by another vessel which crossed superficial to one of the infarcted branches. This portion of placenta was unaffected.

What is the mechanism of the formation of such sub-chorionic fibrin deposits? From observation of placentae numbers 1001 and 536 in this series it appears that they result from clotted blood which has escaped from the chorio-decidual space to lie beneath the chorionic plate. In the former specimen a thin layer of blood clot of sufficient age to be beginning to lose its colour was evident. This clot otherwise had all the appearances of a typical subchorionic fibrin plaque.

In No. 536 was encountered the most remakable placenta in the whole series. The maternal history was as follows :-

Mrs C.N.

Age 34 years.

Two previous pregnancies.

The first two pregnancies were normal and each resulted in the spontaneous delivery at term of 6 pounds 7 ounce babies. No note was made concerning any abnormality of the placenta on either occasion.

Third Pregnancy.

At 25 weeks the mother was first examined and the pregnancy seemed entirely normal. Blood taken at that time revealed a positive Wasserman reaction. There was no history of leuetic infection, nor any physical signs but as confirmatory serological tests were all positive, and her husband was an Arab seaman, an anti-syphilitic course of penicillin was given.

At 31 weeks she attended the clinic complaining of having lost a tea-spoonful of blood, associated with some abdominal discomfort, 24 hours previously. On examination the abdomen was rather tense and foetal parts hard to feel but the foetal heart was audible. No further developments occurred at this stage.

Two weeks later the foetus was lying transversely and at this examination the blood pressure was 140/100 mm. of mercury. There were no other toxaemic signs.

One week later at 34 weeks the patient was admitted in advanced labour with the breech presenting. Spontaneous delivery of a 2 pounds 14 ounce live female child took place in the admission room before the arrival of medical assistance. This was followed 10 minutes later by the spontaneous delivery of a large, abnormal looking placenta weighing 1 pound 15 ounces. The baby died at 5 days from prematurity.

The placenta was of remarkable depth, measuring 7.5 cms. from foetal to maternal surface. The other dimensions were 14 cms. x 16.5 cms. It appeared that blood had suffused beneath the foetal membranous surface of the placenta, stripping the chorionic plate from the rest of the chorio-decidual placental substance. The foetal vessels could be seen through the glistening distended chorionic membrane (Fig. A14).

Fig. A.14.

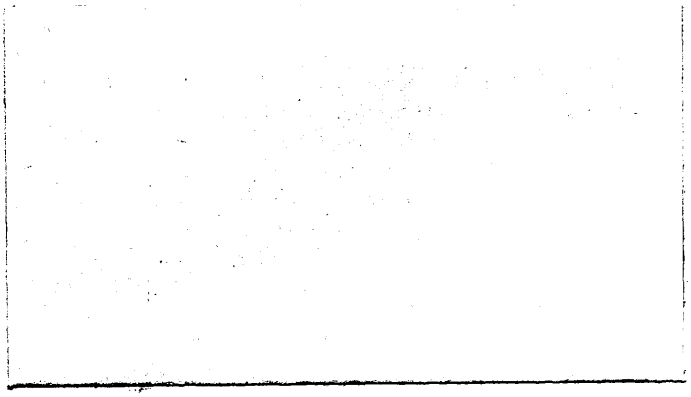

Fig. A.15.

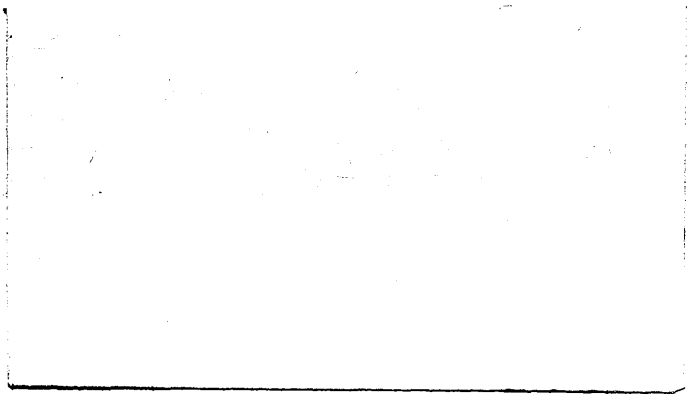

Fig. A.14 and A.15. Placenta No.536 showing foetal and maternal surfaces. The maternal surface appears normal except for a rim of blood clot involving two-thirds of the circumference. The foetal surface shows the membranes and vessels distended by underlying haematoma. The cord insertion is peripheral.

(See case history Mrs. C.N.)

The maternal surface (Fig. A.15) showed lush, red, healthy looking cotyledons for 4/5ths of its area, while the remaining 1/5th (a circumferential portion) showed blood clot that appeared to be approximately 2-3 weeks old. Viewed laterally (Fig. A.16) this clot appeared to extend right round the placenta and to be continuous with the blood clot lying beneath the chorionic plate. The appearance was rather suggestive of a turban with a mop of hair protruding from its top!

The placenta was fixed in formalin and vertical section two months later (Fig. A.17) confirmed the suspected anatomical arrangements. It was then shown that the sub-chorionic haemorrhage had lifted the chorionic plate 6.5 cms from the chorio-decidual labyrinth. It was estimated that only 13 ounces of the placenta's total weight was actually placental substance, the remainder being blood clot.

Staining of placental sections by Levaditi's method revealed no spirochaetes and the chorio-decidual substance was histologically normal. It seems unlikely that the placental lesion was in any way related to the positive serological tests for syphilis.

The remarkable feature of this case is that with this gross distortion of the placental anatomy, the foetus was able to survive in utero for a period which was probably of 3 weeks duration. The explanation of this can be seen in Fig. A.17. - where there are two large foetal vessels at one side (above 1 and 2 on the scale) running

Fig. A.16.

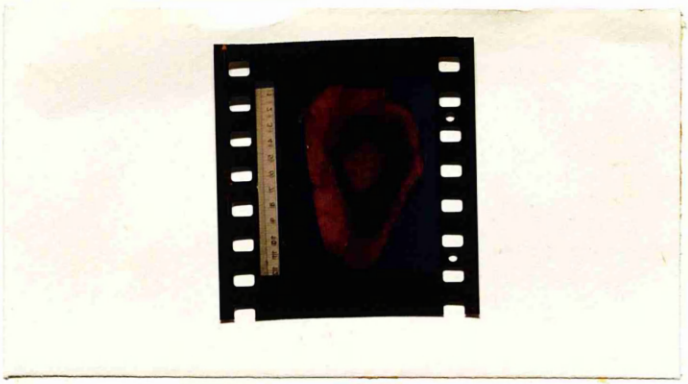

Fig. A.17.

Fig. A.16 and A.17. Placenta No.536 lateral view and medium sectional view. The large mass of clot lying between the chorionic membrane and the chorio-decidual placental substance can be seen. In the sectional view, foetal vessels can be seen running through the clot - from the chorionic plate to placental substance - on a level with "1" and "2" on the scale.

(See case history Mrs. C.N.)

down from the chorionic plate, through the mass of blood clot, to the functioning chorionic tissue.

This, would appear to represent the most severe form of sub-chorionic haemorrhage. In the majority of instances, it must be presumed that less extensive haemorrhages of this type produce no clinical effect and merely undergo gradual transformation to such innocuous sub-chorionic fibrin deposits as have been described.

d. Reticular Calcification.

There were 16 instances (0.5 per cent) in which there was gross reticular calcification of the maternal surface of the placenta. On multiple sectioning of these placentae, however, it was found that the calcification rarely extended deeply into the substance of the placenta and when it did, it was very much less intense than on the decidual surface.

This was well seen in specimen No. 958. Fig. A.18 is a photograph of the decidual aspect of the placenta showing extensive reticular calcification. Fig. A.19 is an X-ray taken from the same view-point which makes the calcification appear even more extensive. Fig. A.20.,

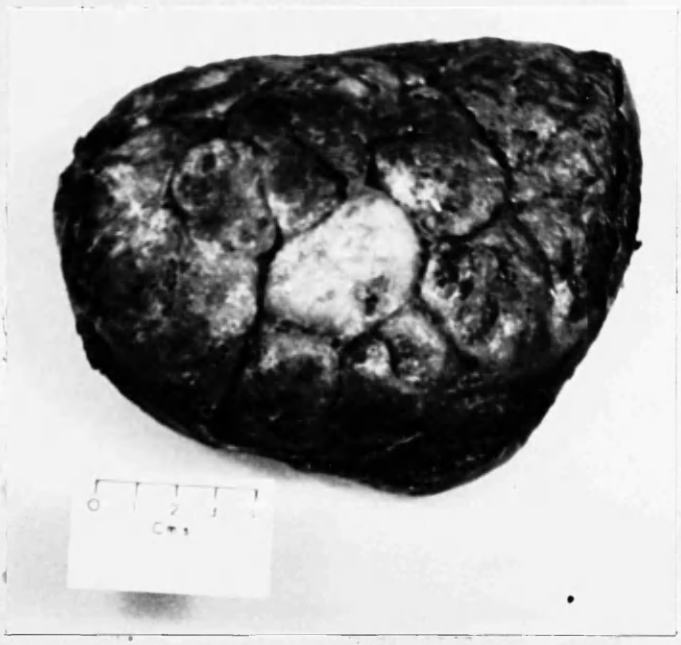

Fig. A.18. Photograph of the decidual aspect of a placenta showing gross calcification. (See Figs. A.19 and 20).

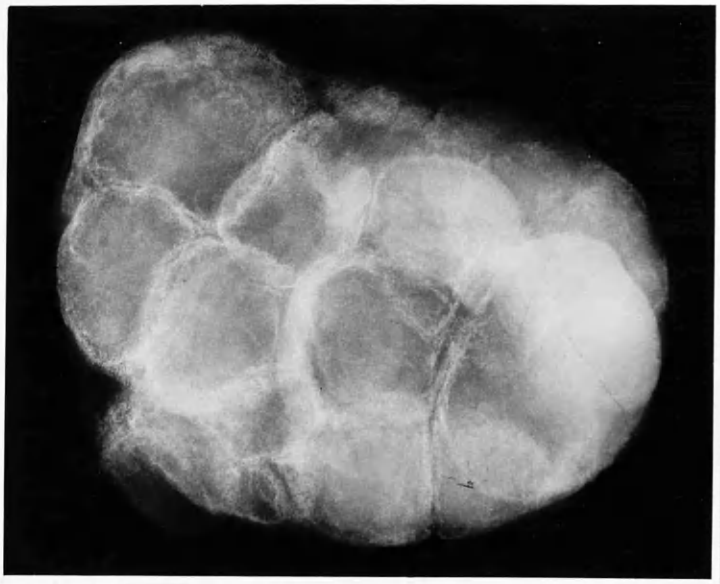

Fig. A.19.

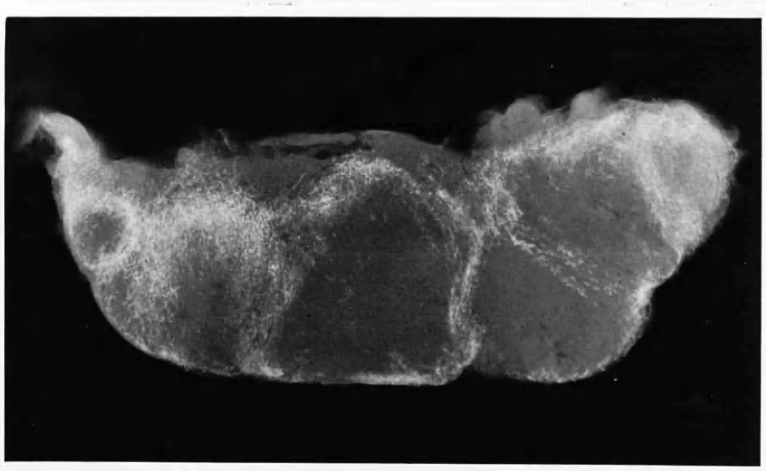

Fig. A.20.

Fig. A.19 and 20. X-rays of placenta showing gross calcification (See Fig. A.18). In Fig. A.20, an X-ray of a median section, it can be seen that this calcification is almost entirely confined to the periphery of the cotyledons - the placental substance being very little affected.

however, shows an X-ray of a $\frac{1}{2}$ inch section removed from the centre of the placenta. This shows quite clearly that the calcification is mainly confined to the superficial aspects of the placenta and of the individual cotyledons.

There were no intra-uterine foetal deaths in this group but in 5 out of the 16, the placenta was meconium stained.

e. Marginal Infarction.

Included in this group are placentae which showed infarction of the perimeter zone involving more than half the circumference. It does not include marginate and circumvallate placentae in which the area of the chorionic plate is restricted. They are together discussed in detail in Section B under the title "Placenta Extrachorialis" and the differentiation of the various types is discussed there also.

There were 23 examples of such infarction (0.7 per cent incidence) in the present series. None was accompanied by intra-uterine foetal death and only one by meconium staining of the placenta.

The importance of this lesion, apart from differentiating it from placenta extrachorialis, is theoretical and lies in its bearing

on the problem of the marginal sinus of the placenta. This topic also is discussed in greater detail in Section B but for the present it suffices to make two comments.

Firstly, marginal infarction rarely involves a regular strip round the periphery of the organ as one would expect if a sinus did run round the circumference; rather the infarction tends to be deep at one point and relatively shallow at the next. (Fig. A.21).

Secondly, if a marginal sinus did exist and if, as is claimed, it was mainly responsible for drainage of the maternal blood from the chorio-decidual space, thrombosis in this region would be expected to lead to considerable impairment of placental efficiency. This, however, does not seem to be the case. The present findings rather support the concept that the peripheral zone in the placenta contains functionally unimportant anchoring villi and furthermore that it is of little importance as far as the placental circulation is concerned. Such a concept is supported by other aspects of this study.

Fig. A.21. Median section from a placenta with marginal infarction. On the left side the infarct is relatively small and white, while on the right side it is much more extensive and is pale red.

14. "Abruptio Placentae."

The conditions of this investigation were unsuitable for a critical study of the placenta in accidental ante-partum haemorrhage. Any retroplacental clot was normally separated from the placenta by the attendant at the time of delivery. In only 26 specimens could it be ascertained from inspection that there had been haemorrhage from the decidual aspect of the placenta - of the type referred to by American writers as "abruptio placentae "- yet in the period of the study there were 80 cases classified as "accidental ante-partum haemorrhage" according to the criteria of the Royal College of Obstetricians and Gynaecologists standard Maternity Hospital report book.* As mentioned previously when discussing infarctive lesions of the chorio-decidual space, it was particularly evident in the study how close is the relationship between haemorrhagic infarcts and abruptio placentae. In 6 placentae were found fresh, haemorrhagic infarcts and abruptio placentae haemorrhage, in close relationship - giving the impression that in the region of the abruptio the infarctive lesion had broken the confines of the chorio-decidual space producing the accidental haemorrhage.

The incidence of ante-partum haemorrhage in association with

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* FOOTNOTE.
All ante-partum haemorrhages other than those proven to be due to placenta praevia by vaginal examination or at Caesarean section, are classified as "accidental."

placenta extrachorialis and its significance in this condition, is discussed in Section D.

15. Placentae Associated with Haemolytic Disease of the Foetus.

In the series of placentae examined were 35 known to be from cases of haemolytic disease of the foetus due to rhesus incompatibility - an incidence of 1.1 per cent. Seven of these were associated with placenta extrachorialis - an incidence in that group also of 1.1 per cent.

Attention centred on the placentae which were associated with hydrops foetalis, for in these definite macroscopic and histological changes were evident. Section C of the thesis is devoted to a study of these cases - together with others of the same type obtained from wider sources.

SECTION B.

PLACENTA EXTRACHORIALIS

The nature of this anomaly is described. Its associations and clinical effects, in particular its relationship to antepartum haemorrhage, are analysed. The mechanism and management of this is discussed together with the aetiology of placenta extrachorialis. The findings are then discussed in relation to the controversial "marginal sinus" of the placenta.

PLACENTA EXTRACHORIALIS

Description and Classification.

Placenta extrachorialis may be defined as one in which the membranous chorion is attached not to the periphery of the placenta but at a variable distance within the circumference. (See Fig. BI.) An alternative way of expressing this is to say that the chorionic plate (that portion of the chorion from which the placental villi have origin) is deficient in area and does not extend to the periphery of the placenta.

On naked eye examination this results in no evident abnormality other than a thin ring on the foetal surface of the placenta at the site of attachment of the chorionic membrane. This is found at variable distances from the circumferential edge. The ring may involve all or, as is frequently the case, only a portion of the circumference. In these circumstances the junction of the membranous and villous parts of the chorion, coincide with the placental edge for the remainder of the circumference.

Upon this basic pattern may be imposed a number of secondary variations :-

(i) At the site of the ring there may be an infolding of the membranes. This may take the form of :-

(a) A thin fold consisting of membrane only which is semi-transparent (Fig. B2.) or

(b) A thick fold containing a considerable amount of fibrin (Fig. B3). This gives a raised edge and a picture of a "projecting brim - - - which

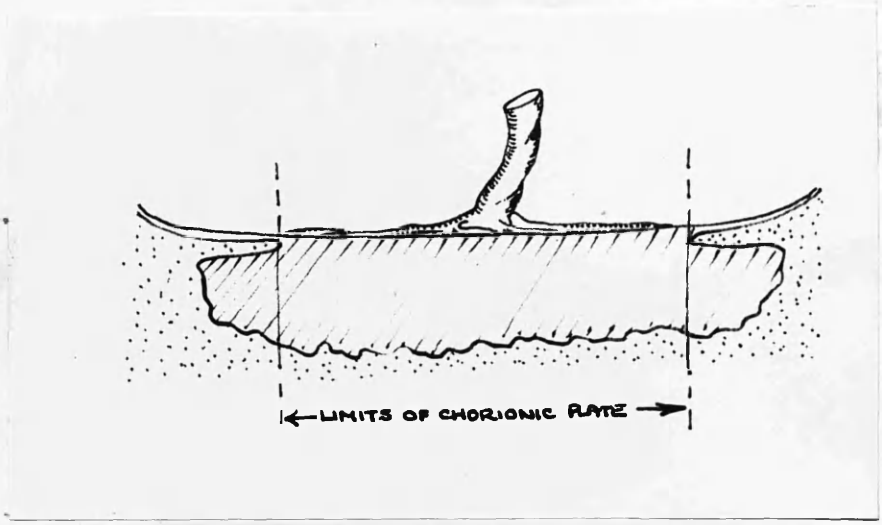

Fig. B1. Diagrammatic representation of the basic abnormality in placenta extrachorialis. This type of placenta has been frequently referred to as "placenta marginata."

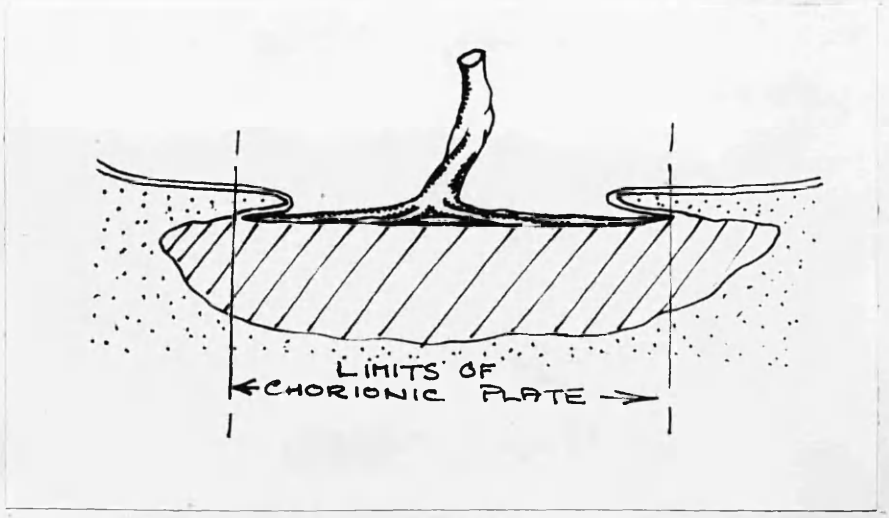

Fig. B2. Diagram of the type of placenta extrachorialis commonly referred to as "placenta circumvallata." It will be seen that the situation with regard to limitation of the chorionic plate and the presence of extrachorial placental tissue is the same as Fig. B1. The only difference is the presence of a fold of membrane overlying the edge of the chorionic plate.

Fig. B3. Photograph of foetal aspect of a placenta extrachorialis with a thick fold at the margin of the chorionic plate. The scale is in centimetres reading from 20 so it can be seen that the recess beneath the fold is 2 cms. deep.

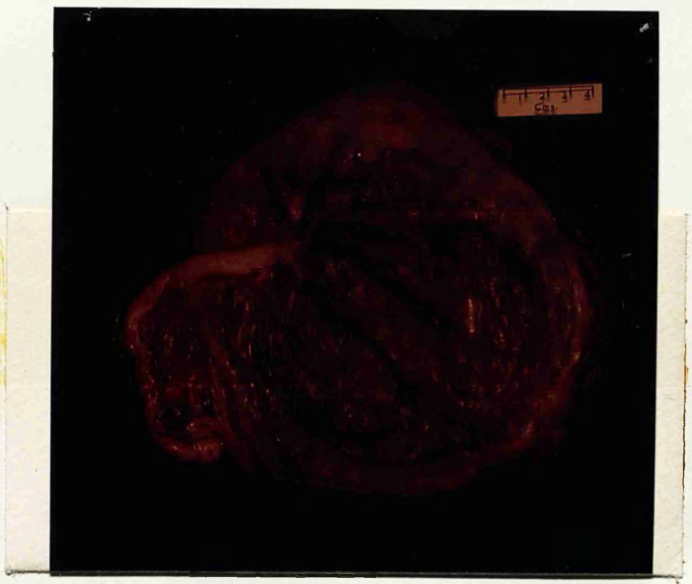

Fig. B4. Foetal aspect of placenta extrachorialis in which there is merely a thin sheet of fibrin at the region of the membranous fold.

gives a hollow dish-like appearance to the inside of the placenta" - to quote William Hunter.

(ii) There may be a considerable deposition of fibrin or blood clot outside the ring of attachment of the chorionic membrane. In some cases this is merely a thin sheet of fibrin (Fig. B4) while in others it may be a layer of obvious blood clot (Fig. B5). All grades between these two extremes may be seen.

(iii) The membranous fold, if present, may occasionally contain chorionic tissue rather than fibrin (Fig. B6). This was described by Pinkerton (1956) but he regarded <u>all</u> the folds as being of this nature. In the present series this was true in only a small number of the cases.

On transverse section of the placenta the appearances are remarkably unimpressive (Figs. B5, B7, B8 and B9). There is usually very little distortion of the anatomy of the chorio-decidual space. Even when there is an obvious fold containing a lot of fibrin or blood clot, the intrusion upon the chorio-decidual space is minimal.

If there is neither fibrinous deposition at the margin of the chorionic plate nor a membranous fold, the detection of placenta extrachorialis may be extremely difficult. In cases of doubt, confirmation may be obtained by separating the amniotic and chorionic membranes and

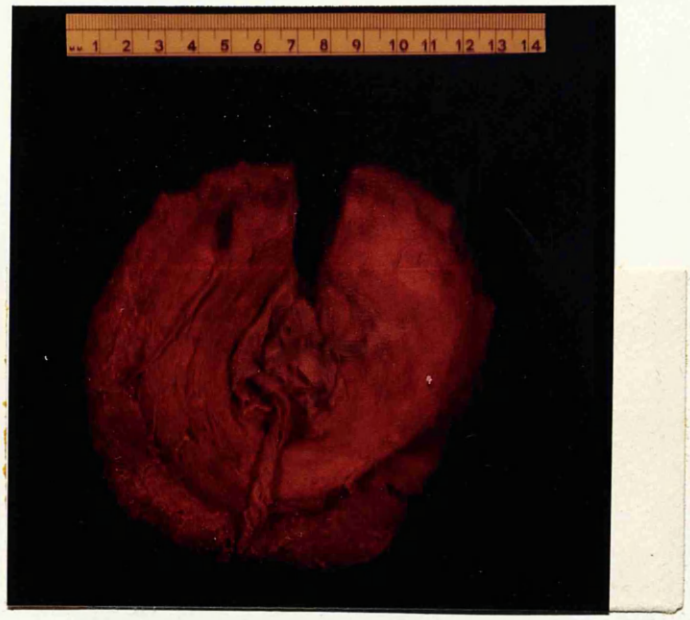

Fig. B5. Foetal aspect of placenta extrachorialis in which there is an extensive layer of clot encircling the placenta outside the edge of the small chorionic plate. (For cross-section view see Fig. B7).

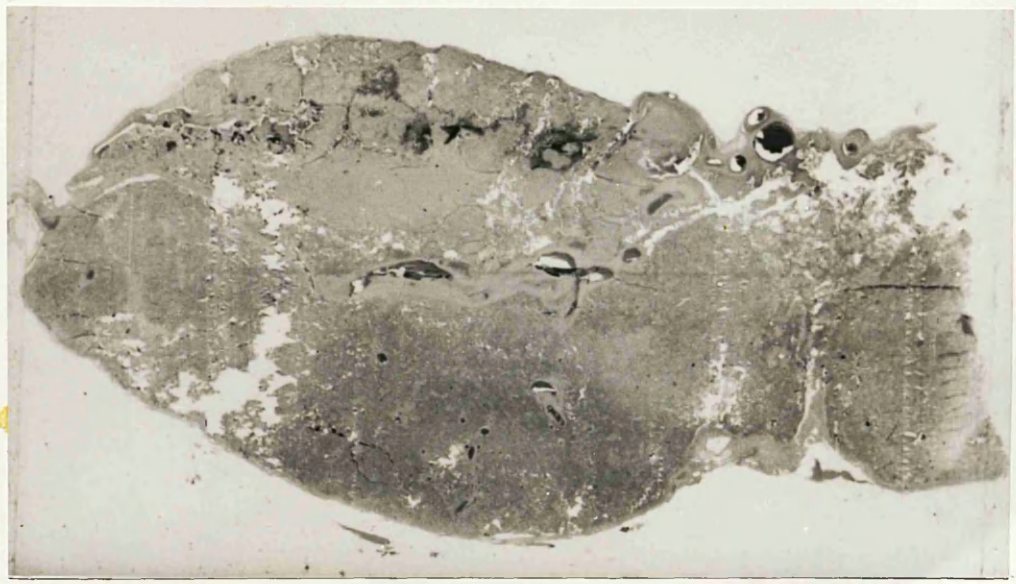

Fig. B6. Photograph of section of the circumference of placenta extrachorialis (magnified x2). The fold in this specimen contained chorionic tissue. The line of the recess formed by the fold can be seen extending from the largest vessel on the chorionic plate, downwards and to the left at an angle of 45 degrees with the surface. It is in this case partially occluded.

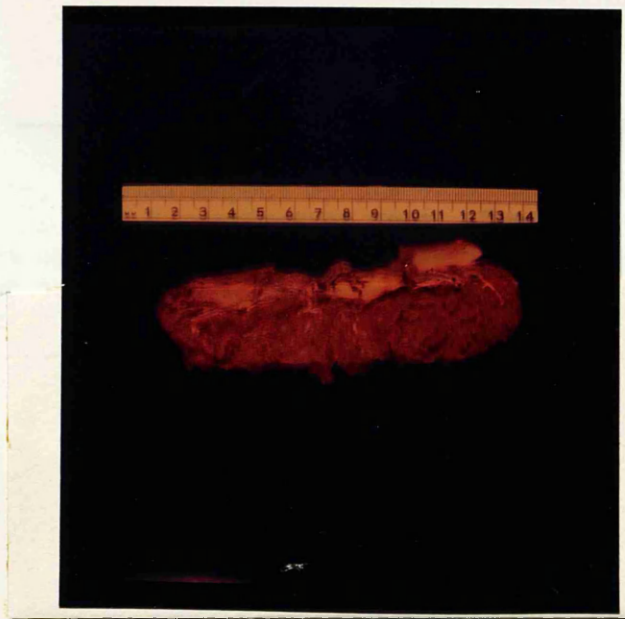

Fig. B7. Transverse section of the placenta shown in Fig. B5. Despite the extensive ring of old blood clot visible on the foetal aspect, there is little or no involvement of the inter-villous space.

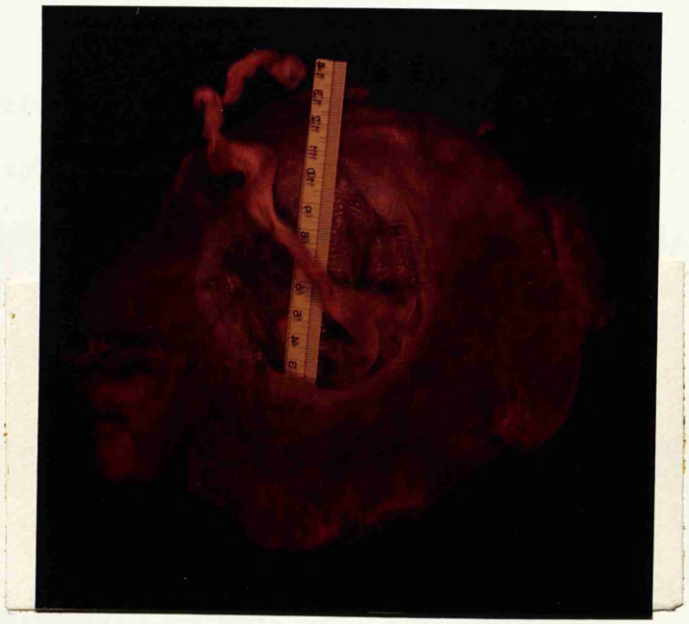

Fig. B8. Foetal aspect of placenta extrachorialis with a fold 2.5 centimetres deep. There is a large amount of blood clot covering the extrachorial placental tissue and lying in the fold. (See Fig. B9 and case history in appendix No. C.V. 544).

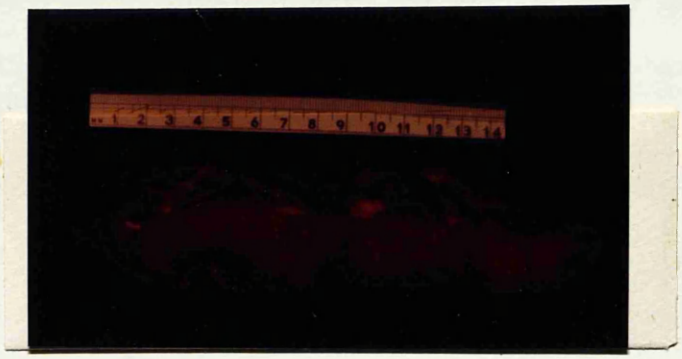

Fig. B9. Transverse section of placenta shown in Fig. B8. The fold overlying the edge of the chorionic plate and containing blood clot, can be seen beneath the figures 12-14 on the scale. There is little distortion of the chorio-decidual space. (See case history in appendix No. C.V. 544).

then tracing the chorionic membrane towards the placental edge. In a normal placenta attempts at separation cause tearing at the placental margin. Where there is extra-chorial placental tissue present, however, the membrane will quite readily strip from that part of the placenta which is outside the ring and tearing only occurs when the margin of the chorionic plate is reached. (Fig. B.10 and 11) Another feature of placenta extrachorialis is that, on its foetal surface, no foetal vessels can be seen peripheral to the ring marking the edge of the chorionic plate. (Fig. B.12)

From this study it appeared that those placentae in which there was gross naked-eye anatomical distortion - that is, those with peripheral rings of fibrin or blood clot on the foetal surface of the placenta, - were the most likely to be associated with clinical effects. This group included many, but not all, of those with membranous folds at the edge of the chorionic plate. When it came to statistical analysis, it seemed possible that the clinical effects, if any, of this grade of placenta extrachorialis, might be lost amongst the larger number which had little anatomical distortion. The placentae extrachorialis were accordingly divided into 2 grades :-

Grade A. Placentae with simple peripheral rings of extrachorionic tissue, with or without a membranous fold at the edge of the chorionic plate, were placed in this group. Examples of this type are shown in Figs. B.11, B.12, B.13 and B.14. It will be seen that although the

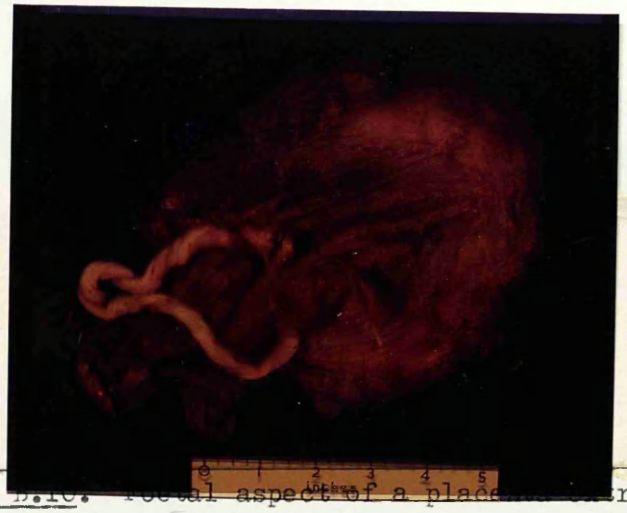

Fig. B.10. Foetal aspect of a placenta extrachorialis in which the chorionic membrane has been stripped back to the edge of the chorionic plate. There is a thick ring partially covering the foetal aspect of the extrachorial placental tissue. Near the scale this is recognisable as blood clot while at the other extreme it appears to be fibrin.

Fig. B.11. Partial placenta extrachorialis involving one third of the circumference. The chorionic membrane has been torn off and the edge of the chorionic plate can be clearly seen; the tissue outside this is devoid of membrane.

Fig. B.12. Complete placenta extrachorialis. No foetal blood vessels are visible beyond the limits of the chorionic plate.

Fig. B.13. Binovular twin placenta showing placenta extrachorialis with membranous fold involving one portion only of the placenta. The fold is held open by sticks.

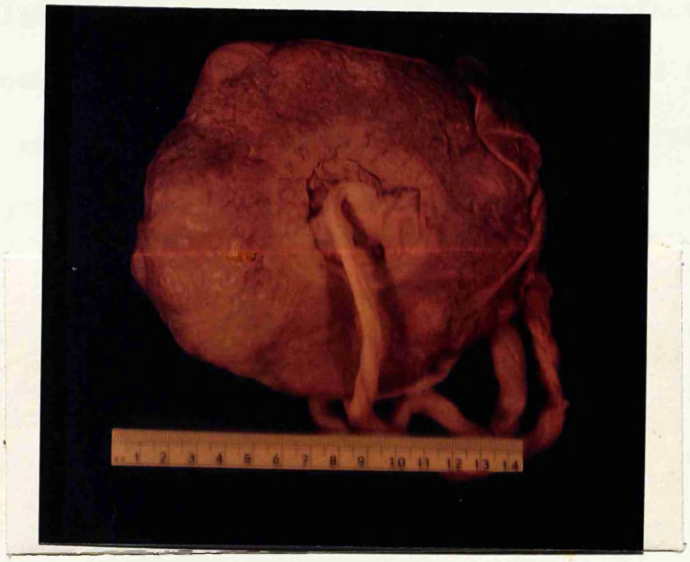

Fig. B.14. Placenta extrachorialis showing extreme limitation of the chorionic plate, with a thin membranous fold. There is no fibrin or blood clot evident.

ring may be associated with a considerable fold, and the chorionic plate be of less than half the diameter of the placenta, (Fig. B.14) there is little or no blood clot or fibrinous deposition and the general placental shape is normal.

Grade B. In this category were grouped placentae in which there was a ring of blood clot or fibrin round the foetal surface of the placenta. In some specimens this lay outside the edge of the chorionic plate Fig. B.15 and 16, but in others it lay in the membranous fold, therefore overlying the periphery of the chorionic plate (Fig. B9). The anatomical distortion in this group was extremely variable.

In considering certain possible clinical associations of placenta extrachorialis, figures will be given for the findings with regard to this group alone in addition to the figure for all the placentae extrachorialis.

Complimentary Terminology :-

Previous papers on placental anomalies of this type are confused by reason of the use of different terms to describe the same condition. The terminology deserves comment in order to clarify the relationship of the nomenclature used in this paper, to that employed by other workers.

1. Placenta marginata is the name most frequently given to describe the simplest form of placenta extrachorialis (as described above) - i.e. that in which there is merely a chorionic plate of area

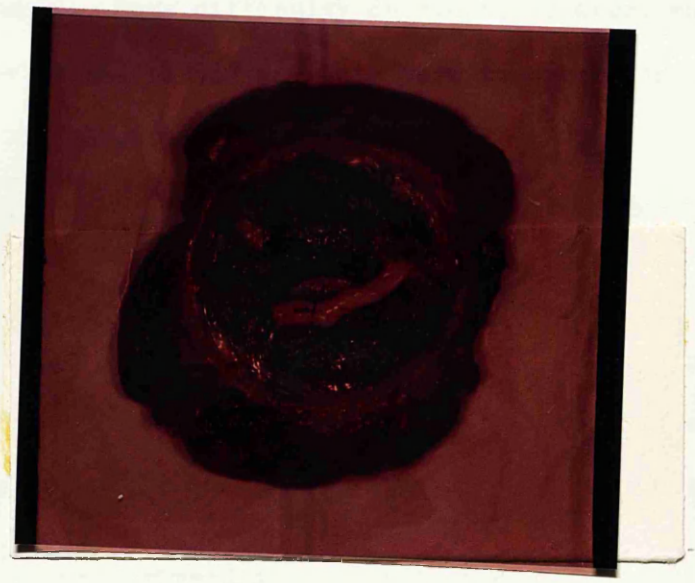

Fig. B.15. Placenta extrachorialis with a ring of blood clot outside the circumference of the chorionic plate. (See Fig. B.16 and case history in appendix No. C.V. 540).

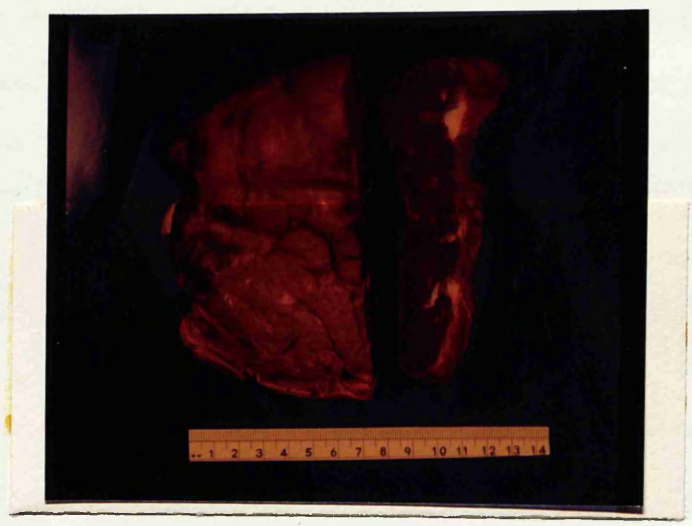

Fig. B.16. Transverse section and decidual view of placenta shown in Fig. B.15. The basal plate is healthy and there is very little involvement of the placental substance.

less than the placenta. Some difficulty develops, however, when writers such as Bartholomew et al. (1953) use this term to cover the quite unrelated condition of "marginal infarction."

2. Placenta circumvallata ("walled-around") is used to describe placentae which have a membranous fold or raised ridge at the edge of the restricted chorionic plate. The majority of the papers on the subject have this term in their title but some authors include placenta marginata under the same heading while others ignore the condition or regard it as unrelated.

Certain writers, notably Williams (1927) are at pains to differentiate the marginate from the circumvallate placenta. However, in the course of the present study it became clear that no such distinction could be made. Many of the placentae showed rings which were of simple marginate type in one region, while in another sector they showed typical circumvallate folds. This was also the conclusion of Torpin (1953) and Pinkerton (1956). It was for this reason that the present more comprehensive term was adopted.

3. Placenta extrachorialis was put forward to cover both the previously mentioned abnormalities by Robert Meyer, who wrote on these conditions in 1909 and 1912. Since then the term has lost favour. It is adopted here because it not only covers both placenta marginata and placenta circumvallata, conditions which are frequently found

simultaneously in the same organ, but it also describes the basic nature of the abnormality.

4. Circum-crescent placenta was used by Goodall (1934), apparently to refer to the marginate type of placenta.

5. Nappiform placenta ("turnip-like") is described by De Lee and Greenhill (1947) as being synonymous with placenta circumvallata. They confuse matters, however, by classifying these anomalies under "placental infarction."

Other placental adjectives encountered in the literature include "encollorata," "annulus fibrosus," "margine" "Brodé"and "collarette" but none of these are explained in detail.

Differential Diagnosis :-

Accepting that placenta marginata and placenta circumvallata are but different degrees of the same abnormality - placenta extrachorialis - the differential diagnosis from a pathologists angle becomes reduced to the problem of excluding one condition. This is the condition of marginal infarction of the placenta. In this there is no evidence of a primary anatomical abnormality in the chorionic plate; the placenta is normal except for infarction in the peripheral region. This change rarely involves the whole of the circumference and there

is usually some degree of irregularity of its inner limits. The ring of placenta extrachorialis, in contrast, is always a regular curve. On attempting to strip the membranes from a placenta with marginal infarction it will be found that the chorion is firmly attached to the edge of the placenta; efforts to strip it further than this merely result in tearing.

On transverse section of a placenta with marginal infarction it is obvious that the whole thickness of the placenta is involved in the process (Fig. B.17). In the placenta extrachorialis, on the other hand, any fibrin deposition is superficial and the underlying placental tissue is healthy. (Figs. B.15 and 16).

The differences between the two conditions are so obvious that it is hard to understand how they have become confused.

FINDINGS IN PRESENT STUDY

INCIDENCE

Out of the 3,161 consecutive placentae examined, 578 were classified as placentae extrachorialis - an incidence of 18 per cent. The diagnosis was only made when a strip of chorionic tissue, at least half an inch in thickness and involving at least a third of the circumference, lay outside the limit of the chorionic plate.

Of the 578 placentae, 307 were classified as Grade A and 271 as Grade B.

This incidence of placenta extrachorialis may appear remarkably high but it is in fact less than the incidence quoted by Torpin (1953 and 1955a) and Pinkerton (1956) (See Table BI). It is, however, a much higher incidence than had previously been suggested from the routine entries made in the records of the hospital concerned. On checking the delivery records in this series of 578 placentae extrachorialis it was found that in only 162 cases (28 per cent) had the anomaly been recorded by the attendant at delivery. The apparent low incidence in hospital statistics is therefore explained by failure to examine the placenta meticulously as a routine or by a failure to record the findings accurately.

PARITY DISTRIBUTION:-

The ratio of placentae delivered by primiparae to those delivered by multiparae was 1:1.4 in the whole series; in the group of placentae extrachorialis it was 1:1.9.

TABLE BI.

PERCENTAGE INCIDENCE OF PLACENTA EXTRACHORIALIS IN RECORDED SERIES

Author	No. of cases	Placenta Extrachorialis		
		Marginate	Circumvallate	Total
Bertkau (1912) (quoted by Williams)		14%	1.3%	15.3%
Williams (1927)	30		2%	
Hobbs & Price (1940)	150		0.7%	
Hunt et al. (1947)	47		0.5%	
Paalman and Veer (1953)	41		0.5%	
Torpin (1953)		23%	1-1.5 %	24-24.5%
Torpin (1955a)		36%	4%	40%
Pinkerton (1956)	50	22.5%	2.5%	25%
Scott (1958)	578			18%

ASSOCIATED PLACENTAL ANOMALIES:-

The incidence of other placental abnormalities found in association with placenta extrachorialis is shown in Table BII. In this the percentage incidence for each abnormality in the whole series is shown together with the incidence in the placenta extrachorialis group. It will be seen that there are no significant differences except in 2 respects. No example of a uniovular twin placenta was found in association with placenta extrachorialis but this is probably a chance finding. The other category in which there was a definite difference was in the finding of old blood-clot on the membranes. In the placenta extrachorialis group this was noted on 30 occasions (5.2 per cent) compared with a 1.3 per cent incidence in the whole series. The implications of this are discussed later.

MANIFESTATIONS OF FOETAL ASPHYXIA

a. Foetal Death "In-Utero."

Intra-uterine death of the foetus occurred on 22 occasions in the 578 cases of placenta extrachorialis. Allowing for twin births, this gives an incidence of 3.7 per cent. The comparable figure for the whole series of 3,161 confinements (3,228 babies born) is 101 or 3.1 per cent. In the Grade B placenta extrachorialis group there were 14 intra-uterine deaths (5.1 per cent). In only one case, however, did it seem at all likely that the placental anomaly had anything to do with the foetal death and even in that there was

TABLE BII.

ANOMALY	OVER-ALL INCIDENCE	INCIDENCE IN GROUP SHOWING PLACENTA EXTRACHORIALIS
PLACENTA EXTRACHORIALIS	587 (18.3 per cent)	-
VELAMENTOUS CORD ATTACHMENT	47 (1.5 per cent)	3(0.5 per cent)
BATTLEDORE PLACENTA	62 (2 per cent)	8(1.4 per cent)
SUCCENTURIATE LOBES	55 (1.7 per cent)	8(1.2 per cent)
BIPARTITE PLACENTAE	25 (0.8 per cent)	-
BILOBULATE PLACENTAE	36 (1.1 per cent)	4(0.7 per cent)
MECONIUM STAINING	169 (5.3 per cent)	22(3.8 per cent)
SUB-CHORIONIC CYSTS	11 (0.3 per cent)	-
TWIN PLACENTAE	67 (2.1 per cent - 49 binovular)	15(2.6 per cent - all binovular)
AMNION NODOSUM	2 (0.07 per cent)	-
OLD BLOOD CLOT ON MEMBRANES	54 (1.7 per cent)	45(7.8 per cent)
MEMBRANOUS FOLD TO UMBILICAL CORD	7 (0.2 per cent)	3(0.5 per cent)
GROSS CHORIO-DECIDUAL INFARCTION	54 (1.4 per cent)	13(2.2 per cent)
INFARCTIVE LESIONS DUE TO FOETAL THROMBOSIS	3 (0.1 per cent)	-
MASSIVE SUB-CHORIONIC FIBRIN DEPOSITION	11 (0.3 per cent)	-
EXTENSIVE RETICULAR CALCIFICATION	16 (0.5 per cent)	-
MARGINAL INFARCTION	23 (0.7 per cent)	-

reason for doubt. (This case is described in the section on "Antepartum Haemorrhage in Association with Placenta Extrachorialis.")

b. Other Signs of Foetal Asphyxia.

Meconium staining of the amniotic surface was observed in 22 placentae extrachorialis (3.8 per cent). This compares with an incidence of 169 (5.3 per cent) for the whole series. In Grade B placentae extrachorialis the incidence was 9 (3.3 per cent).

A clinical diagnosis of foetal asphyxia from auscultation of the foetal heart in labour was made in 21 (3.7 per cent) cases of placenta extrachorialis and in 111 (3.5 per cent) of the whole series.

From the analysis of the comparative incidence of intra-uterine foetal death and of the occurrence of signs of foetal asphyxia, it would appear that placenta extrachorialis does not interfere with foetal oxygenation. This is perhaps surprising when it is recalled that inspection of the chorionic surface of the placenta reveals that the foetal vessels do not extend beyond the limits of the chorionic plate, and that the latter may be 2 or more inches within the placental margin. Moreover, there is often considerable fibrin deposition around the edge of the chorionic plate.

Radiological studies of placentae in which the foetal vascular tree was injected with radio-opaque medium, make it clear, however, that although vessels are not evident on the surface of the placenta beyond the chorionic plate, the chorionic tissue which lies outside

this is just as well supplied with foetal vessels as elsewhere. It seems therefore that the foetal vessels merely pass from view at the edge of the chorionic plate and their course is uninterrupted. (Figs. B.18, B.19, B.20, B.21, B.22 and B.23).

The placentae were prepared for injection in the manner described by Bacsich and Smout (1938); the umbilical vessels were then injected with barium sulphate suspension* using an injecting apparatus with attached manometer at a maximum pressure of 80 millimetres of mercury.

Maturity and Birth Weight.

The average duration of pregnancy in the cases with placenta extrachorialis was 39.5 weeks, compared with 40.2 weeks in the control series. In Grade B placentae extrachorialis the figure was 39.2 weeks. None of the differences is statistically significant.

The incidence of premature delivery by dates was calculated on the number of pregnancies which terminated in the 36th week or earlier. The figure of 5 per cent was obtained for the placenta extrachorialis group and also for the controls.**

Immaturity by weight was taken as a birth weight of 5 pounds 8 ounces or less. The incidence was 10.7 per cent in the placenta

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* FOOTNOTE.
"Micropaque" (Damancy and Co.Ltd.) was used. This contains one ounce by weight of a stabilised micro-dispension of barium sulphate in each fluid ounce. This standard preparation was mixed with an equal volume of water before use.

** FOOTNOTE.
The control series is that referred to in Section A, in which 200 women with normal placentae were questioned personally as to their health in pregnancy and their case-notes scrutinised in the same manner as those with abnormal placentae.

Fig. B.17. Transverse section of placenta with marginal infarction. The infarcts involve the whole thickness of the placental substance.

Fig. B.18. Placenta extrachorialis after injection of the foetal vascular tree with "Micropaque." (See Fig. B.19).

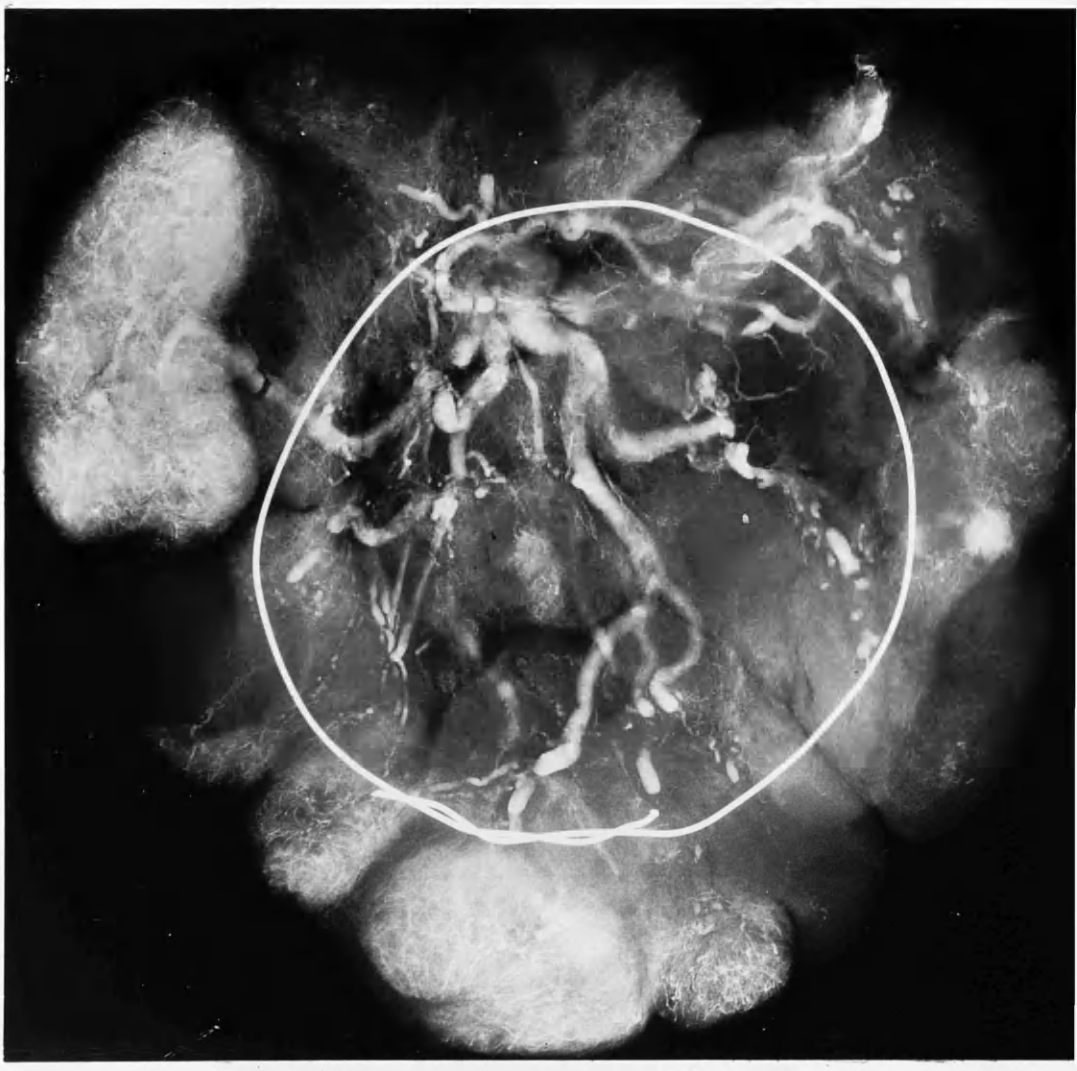

Fig. B.19. X-ray of the injected placenta extrachorialis shown in Fig. B.18. A wire was laid on the placenta at the margin of the chorionic plate and it can be seen that cotyledons situated outside this are well vascularised.

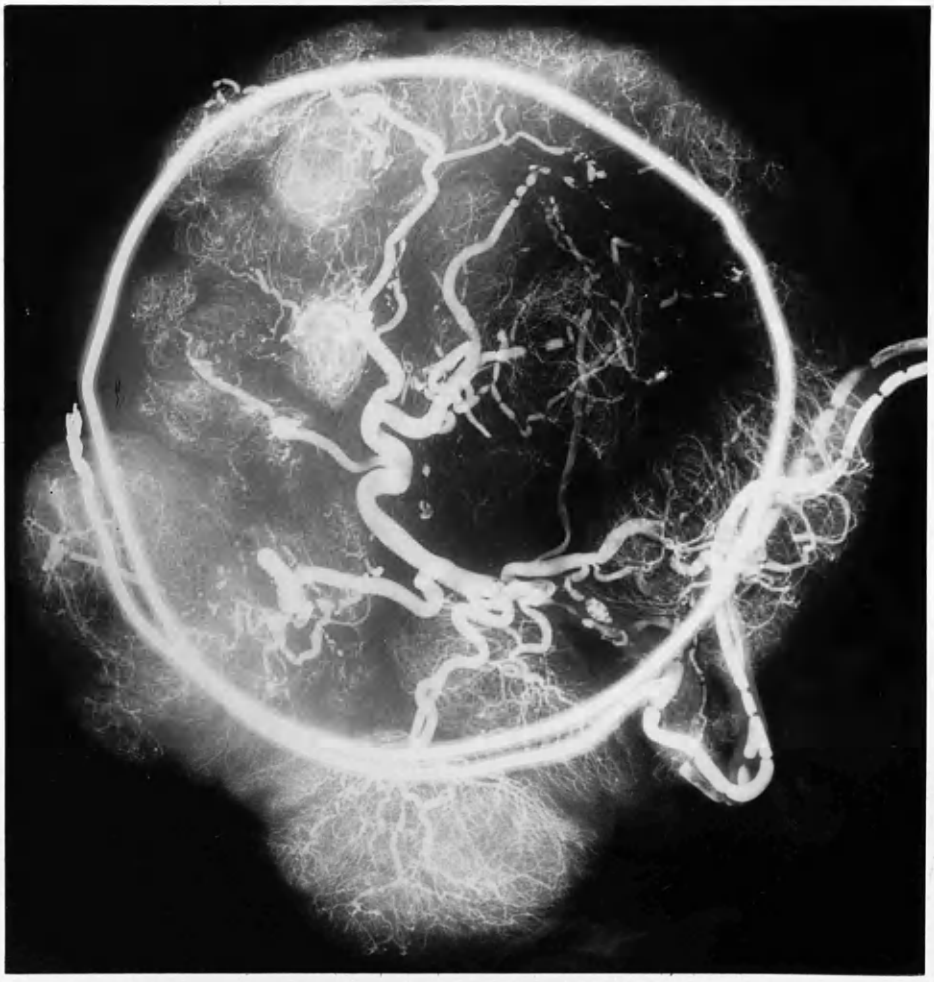

Fig. B.20. X-ray of another similarly injected placenta extrachorialis. There is again evidence of good foetal vascular supply to the extrachorial placental tissue.

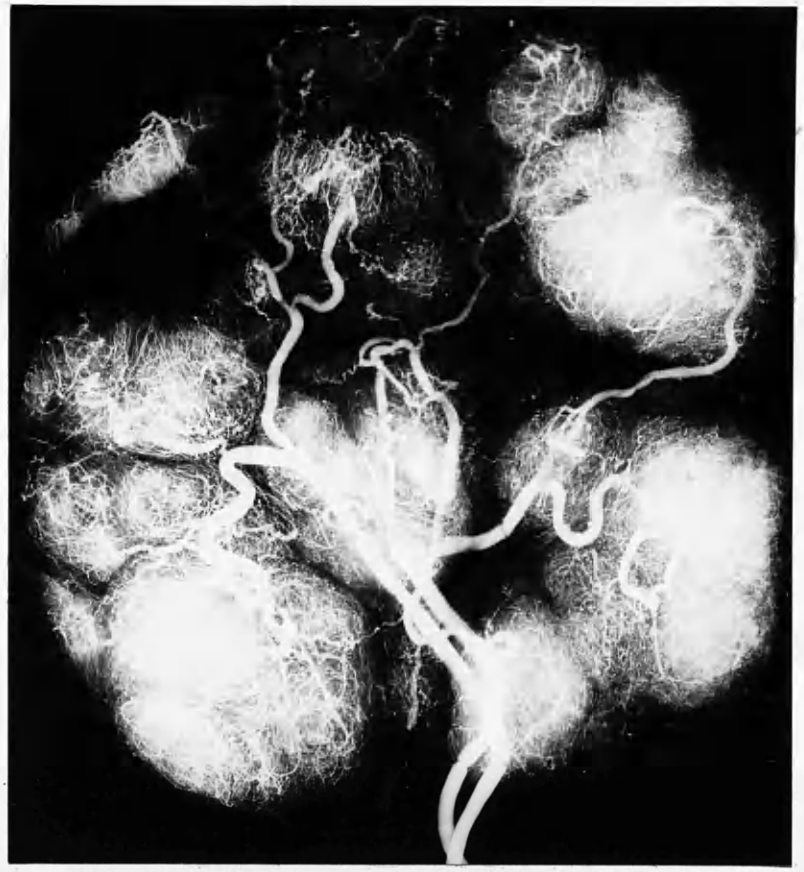

Fig. B.21. Normal placenta injected in a similar manner. In this and the previous X-ray, constrictions of the vessels can be seen presumably due to the sphincters described by Spanner (1935) and Bartholomew et al. (1953).

Figs. B.22 and B.23. Placenta extrachorialis showing absence of vessels outside the chorionic plate on the foetal surface view. In the transverse section it can be seen that there are vessels present in this region but they lie at a deeper level.

extrachorialis series and 11.5 per cent in the Grade B placentae extrachorialis. The overall hospital incidence for immaturity by this standard was 9.5 per cent. These differences are, again, not statistically significant.

The average birth weight of the babies who had placentae extrachorialis was 7 pounds 0 ounces and in the Grade B placentae extrachorialis group 6 pounds 14 ounces. In the control series it was 7 pounds 5 ounces.

Post-partum haemorrhage.

Post-partum haemorrhage occurred in 27 cases in which placenta extrachorialis was found - an incidence of 4.7 per cent. In association with Grade B placenta extrachorialis, post-partum haemorrhage occurred in 20 cases an incidence of 7.4 per cent. This compares with an overall incidence of 4.4 per cent in all the women delivered during the period of the investigation.

Manual Removal of the Placenta.

This was necessary in 4 of the cases of placenta extrachorialis (0.7 per cent). The hospital overall incidence of manual removal was 0.9 per cent.

Toxaemia of Pregnancy.

Pregnancy toxaemia occurred in association with placenta extrachorialis in 24 cases - an incidence of 4.2 per cent. In the Grade B

placenta extrachorialis group the incidence was 4.1 per cent (11 cases). This is less than the overall toxaemia incidence which was 6 per cent at the time this investigation was being conducted.

The standards adopted for the diagnosis of toxaemia are detailed in full in Section C of the thesis, where the problem is discussed in greater detail.

Leakage of Liquor during Pregnancy.

In 2 cases, women who eventually delivered Grade B placentae extrachorialis drained "per vaginam", fluid which was presumed to be liquor, for 14 and 8 weeks respectively before delivery.

Neither of these patients were seen personally during the ante-natal period and they were not investigated in any detail. They are of some interest, however, in view of the remarkably high incidence of so-called "hydrorrhoea gravidarum" recorded in association with placenta circumvallata by writers such as Hunt et al. (1947) and Paalman and Veer (1953) (See Table BIII).

Hydramnios with Placenta Extrachorialis.

In only 3 pregnancies, out of the 578 which were associated with placentae extrachorialis, was hydramnios an ante-natal complication. (0.5 per cent incidence). This compares with an over-all incidence for hydramnios of 0.8 per cent for all the patients delivered in the period of the survey. The standards adopted for making the diagnosis

of hydramnios were those of Scott and Wilson (1957).

Mention is made of these facts merely because it has been claimed (Plentl and Gray, 1957) that placenta circumvallata is a cause of hydramnios. Various aspects of liquor production and disposal are discussed in Section D.

Placenta Extrachorialis in Relation to Abortion.

It is difficult to come to definite conclusions as to the association of placenta extrachorialis with abortion. Abortion placentae of from 12-28 weeks maturity are hard to obtain in good condition. Patients at this stage of pregnancy are rarely delivered in maternity units. During the period of the study, only 17 abortion placentae of this maturity were obtained suitable for study. Four of these showed evidence of placenta extrachorialis (23.5 per cent), though in some placentae early in this period it was extremely difficult to decide whether they were examples of placenta extrachorialis or not. (Fig. B.24)

McKay and Hertig (1957) state that placenta circumvallata is the one anatomical finding of any frequency in placentae from second trimester abortion. This was also so in the present series with regard to placenta extrachorialis but the incidence was not significantly higher than in the mature placentae examined. The fact that the incidence appears to be approximately the same in abortion as in last trimester placentae has bearing on the aetiological theories concerning placenta extrachorialis.

Recurrent Placenta Extrachorialis.

In the course of this study 4 cases were discovered of recurrent placenta extrachorialis. In 3 of these cases the previous abnormal placentae had been seen personally but before the present study was commenced. The details of 2 of these cases are given in full in the appendix for they serve as good examples of the sort of complications which may arise in the ante-natal period as a result of the presence of placenta extrachorialis.

Whatever the mechanism of aetiology of the condition, with an incidence as high as 18 per cent there is clearly a considerable chance of encountering recurrent cases in a series of this size. The personal series studied extended over 13 months, however, and only 12 women were delivered twice in this period. It is impossible to allow for the percentage of cases of the anomaly which were correctly diagnosed and recorded in pregnancies occurring outside this study.

There is no evidence from this study to show that the occurrence of placenta extrachorialis is other than a chance one. In this respect the aetiology of the condition would appear to be on a similar basis to that of placenta praevia.

Ante-partum Haemorrhage in Association with Placenta Extrachorialis.

Signs of Haemorrhage.

It is difficult to assess the exact incidence of haemorrhage in association with placenta extrachorialis - either clinically or from inspection of the delivered placenta. Definite evidence of old blood clot on the membranes was present in 45 specimens of placenta extrachorialis (7.8 per cent). In association with Grade B placentae extrachorialis there were 38 specimens showing clot on the membranes, an incidence of 14 per cent in this group. As shown in Table BII the overall incidence in the whole series was only 1.7 per cent.

In addition, however, very many of the placentae showed haemorrhage on the foetal surface of the extrachorial placental tissue which did not extend beyond the placental edge. In some cases the blood was relatively fresh, while in others it was pale pink and obviously of some weeks standing, while in a third group it was yet older, consisting simply of a fibrous ring. In some specimens there was evidence of layers of blood clot and fibrin at all these various stages visible in the same placenta.

From the examination of these 578 placentae extrachorialis it became evident that the fibrous ring seen in so many of the placentae was merely the end result of circumferential haemorrhage. If this is accepted, it can then be said that all the Grade B placentae extrachorialis showed evidence of haemorrhage - in the shape of this fibrous ring.

A feature of these haemorrhages at the edge of the chorionic plate was that in the great majority of cases the escaped blood spread circumferentially, round the foetal surface of the extra-chorial placental tissue, beneath the membranes. (Fig. B.15 and 16). In some cases the blood extended round only part of the perimeter zone but in many it covered the entire circumference. No such tendency towards circumferential spread of escaped blood was noted in normal placentae (i.e. in placenta in which the edges of the chorionic and basal plates coincided). In these, any blood escaping from the placental edge appeared to track initially in the direction of the cervix. In the placenta extrachorialis group tracking in this direction usually only occurred secondarily, if at all, after circumferential spread. This different method of spread of escaped blood is shown diagramatically in Figs. B.25 and 26. This means that the high incidence of blood clot on the membranes in association with placenta extrachorialis, is even more significant than the statistics show.

Another feature which was evident from the examination of these 578 placentae extrachorialis, was that when peripheral haemorrhage did occur in such placentae it <u>always</u> occurred from the edge of the chorionic plate - <u>not</u> from the edge of the placenta - which in these placentae was the edge of the basal (or decidual) plate. This fact has bearing on the question of so-called "marginal sinus haemorrhage" - which is discussed later.

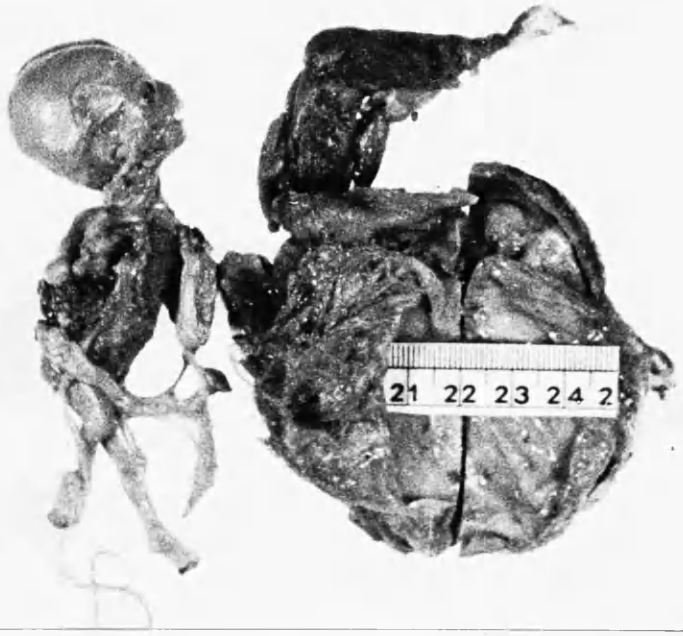

Fig. B.24. Abortion placenta from a 14 weeks pregnancy, probably an example of placenta extrachorialis with a 0.6 cm. recess (Scale in centimetres reading from 20). The diagnosis of placenta extrachorialis is difficult at this stage of pregnancy.

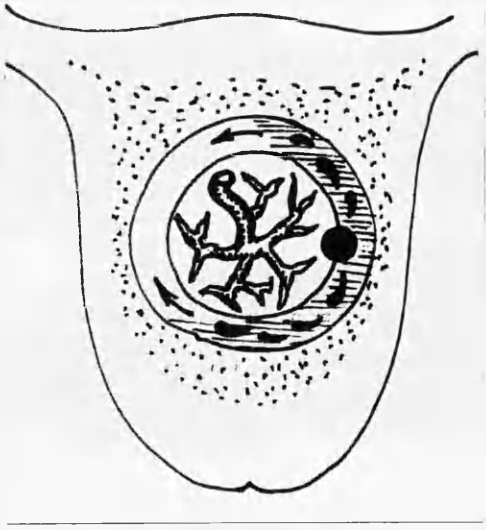

Fig. B.25.

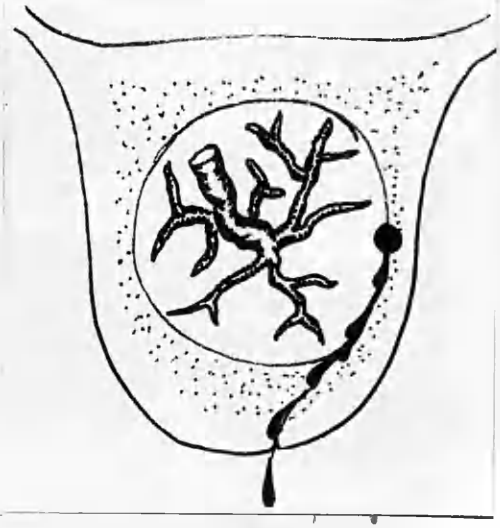

Fig. B.26.

Figs. B.25 and B.26. Sketches to show the different routes of spread when haemorrhage occurs from the edge of the chorionic plate in placenta extrachorialis. (Fig. B.25) and in the normal placenta (Fig. B.26).

Revealed Ante-partum Bleeding in Placenta Extrachorialis

Early Pregnancy.

Vaginal bleeding occurred before the 28th week in 47 pregnancies from which placentae extrachorialis were obtained - an incidence of 8.1 per cent. In the Grade B placenta extrachorialis group the incidence was 10.3 per cent. The haemorrhages varied from slight "shows" to a loss of over a pint of blood in 2 cases. The incidence of early pregnancy haemorrhage in the 200 control patients * with normal placentae was 15 (7.5 per cent). None of these 15 haemorrhages was a major one.

Late Pregnancy.

Vaginal haemorrhage occurred after the 28th week of pregnancy in 40 of the cases of placenta extrachorialis (6.8 per cent). In the control series questioned the comparable incidence was 3 per cent. There was a preponderance of late pregnancy haemorrhage in association with Grade B placentae extrachorialis - 32 cases (11.8 per cent).

The severity of the haemorrhage was as varied as in early pregnancy. On analysis the cases could be divided into the following

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* FOOTNOTE

The figure for this control series rather than the overall figure for the hospital must be used for comparison in this matter as only these controls were subjected to the same personal questioning with regard to ante-partum blood loss as were those women who had delivered placentae extrachorialis.

groups :-

Haemorrhage due to placenta praevia.	4 cases
Haemorrhage of "abruptio placentae" type, with classical signs of concealed haemorrhage.	7 cases
Trivial "shows".	11 cases
Haemorrhage of a type suspicious of placenta praevia but not associated with a low-lying placenta.	18 cases

This last group of 18 cases would appear to constitute the one clinically important association of placenta extrachorialis. In all of these the type of painless ante-partum haemorrhage was sufficient to raise a suspicion of placenta praevia. In some the presence of placenta praevia was eventually excluded with reasonable confidence by the physical signs but in others this was not possible and the cases were managed as ones of placenta praevia. This involved 8 of the 18 patients in varying periods of hospital stay - the longest being 9 and 11 weeks. Five of the patients had to be examined under anaesthesia to exclude placenta praevia with certainty, while 4 required blood transfusion.

There was one foetal death in this group of 18 cases. A haemorrhage of 6 ounces occurred at the onset of labour, the foetal heart sounds disappeared and a fresh stillborn infant was delivered. There

was a complete placenta extrachorialis ring with a slight membranous fold at the limit of the chorionic plate. There was a considerable amount of fibrin in the fold and this was seen to arise from organising blood clot. There was approximately a further 6 ounces of relatively fresh blood clot apparently arising from the edge of the chorionic plate.

One foetal death in-utero occurred in association with a trivial ante-partum haemorrhage. It appeared, however, that the death was unrelated to the haemorrhage.

Recognition and Management of Placenta Extrachorialis Haemorrhage

This group of 18 cases, in which ante-partum haemorrhage occurred resembling that of placenta praevia, constitute a problem of some magnitude. In the first place can they be differentiated from placenta praevia? The symptomatology is usually almost identical - painless, vaginal haemorrhage. Though recurrent losses are perhaps not as frequent as in placenta praevia, 10 out of these 18 cases had recurrent haemorrhages. The physical and radiological signs of placenta praevia are, however, usually absent. This is, of course, only of any value as a differential feature once the pregnancy has reached a stage of maturity of approximately 34-36 weeks when these signs can be elicited with some confidence. On 3 occasions during the course of the present survey the presence of placenta extrachorialis was correctly suspected during the ante-natal period.

Even when placenta praevia had been excluded with some degree of certainty, such as in the case of Mrs. J.S. (C.V. 544 - see appendix), there was a natural hesitancy to discharge such patients from hospital while yet undelivered if the initial haemorrhage had been very severe. Three other cases out of the 18 also presented with relatively heavy haemorrhages early in the third trimester, so the question of the safety of allowing these patients to return home undelivered is of some importance.

Although the haemorrhage in placenta extrachorialis may recur and may be quite considerable, it appears that it carries a very small risk to the life of the child nor does it tend to jeopardise the mother's life suddenly as in placenta praevia. It would appear that in these cases of haemorrhage from a placenta extrachorialis, early in the third trimester, a prolonged ante-natal stay in hospital can be avoided with safety, once placenta praevia has been excluded.

Mechanism of Bleeding in Placenta Extrachorialis

From this study it appears that peripheral haemorrhage in placenta extrachorialis follows a different pattern from haemorrhage occurring at the edge of a normal placenta. Firstly, the bleeding in placenta extrachorialis occurs from the edge of the chorionic plate not from the

actual circumference of the placenta. Secondly, as previously mentioned, the escaped blood tends to spread circumferentially round the foetal surface of the extra-chorial placental tissue. This is shown diagrammatically in Figs. B.25 and 26.

The evidence obtained in this study suggests that there is little, if any initial increase in risk of revealed haemorrhage occurring in early pregnancy in association with placenta extrachorialis - but, if it be accepted that every fibrinous ring is the end result of such haemorrhage, then there is a considerably increased risk of concealed haemorrhage. Once, such a haemorrhage has occurred - and if it has been of sufficient extent to form a complete, thick ring of clotted blood, - the process of contraction and organisation of that clot, may lead to further haemorrhage. The way in which the contraction of such a ring of clot (or fibrin) is liable to produce peripheral tension with subsequent haemorrhage is shown diagrammatically in Figs. B.27 and 28.

This would appear to be the mechanism of many of the haemorrhages from placenta extrachorialis in late pregnancy which constitute a definite clinical problem. In this series, in all the cases where the haemorrhage was severe and caused clinical concern, it was found at delivery that there was a considerable ring of clot or fibrin at the edge of the chorionic plate. This also seems to account for the high incidence of haemorrhage in association with Grade B placenta extrachorialis.

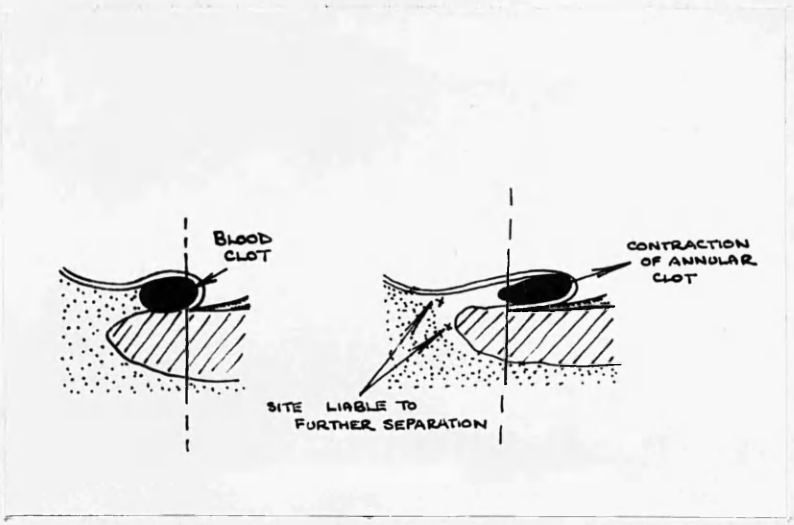

Fig. B.27. Fig. B.28.

Figs. B.27 and B.28. Sketches to show how contraction of a ring of blood clot at the edge of the chorionic plate, might lead to further haemorrhage. The vertical lines indicate the edge of the chorionic plate.

Another feature of placenta extrachorialis haemorrhage is that it rarely if ever causes signs of foetal asphyxia or leads to foetal death, nor does it commonly result in critical maternal exsanguination. In these respects it differs from both placenta praevia and accidental haemorrhage of "abruptio placentae" type. This can be explained on a purely mechanical basis. In placenta praevia, haemorrhage is associated with a shearing tear of the peripheral utero-placental attachments - caused by uterine contraction. If further uterine contractions occur - especially when the lower segment is being "taken-up" in late pregnancy or in labour - they will tend to cause further haemorrhage which, if untreated, will lead in many cases to maternal exsanguination. In "abruptio placentae," the haemorrhage commences from a central area of the basal plate of the placenta. This involves tearing of the basal arterioles and the subsequent arterial haemorrhage collects under pressure and must lead to further placental separation, until it spreads to the placental edge. This, of course, produces foetal asphyxia and often death, while at the same time causing considerable maternal disturbance.

In placenta extrachorialis haemorrhage, however, the blood loss occurs from the foetal surface of the placenta at the edge of the chorionic plate. The circumferential spread of this blood over the foetal aspects of the extrachorionic placental tissue interferes not at all with normal placental function. In this respect it differs

from placenta praevia haemorrhage in that, provided the membranes are intact, uterine contraction - by increasing the intra-amniotic pressure - will tend to control the bleeding, without at the same time tending to produce further separation of the placental edge - as does happen in placenta praevia.

In most cases, the placenta extrachorialis haemorrhage is self-limiting. If the blood loss is sufficient to spread beyond the limits of the extrachorial placental tissue and comes to lie between the membranes and the uterine wall, it will tend to induce uterine contraction by irritation. As described above, the contractions will tend to control the haemorrhage. Haemorrhage from placenta extrachorialis is thus relatively innocuous to both mother and baby.

There is no reason, of course, why "abruptio placentae" type of haemorrhage or placenta praevia haemorrhage should not occur in association with placenta extrachorialis - but in these circumstances the placental anomaly is purely an incidental finding. In this series the combined incidence of placenta praevia and "abruptio placentae" haemorrhage in association with placenta extrachorialis was 12 (this includes one case of placenta praevia in which no bleeding occurred). This gives a percentage figure of 2.1 while the comparable figure for such conditions in the normal placenta group was 2.3 per cent.

Discussion :-

The modern English literature on the subject of placenta extrachorialis starts with Whitridge Williams' comprehensive and comprehensible paper on placenta circumvallata in 1927. Prior to this, in the late 19th and early 20th century there had been a number of papers by German authors on and around the subject. These, however, tend to be unintelligible - even allowing for language difficulties. Their terminology is so confused that it is impossible to discover exactly the type of anomaly to which they refer. The condition had, however, been described long before this. Williams mentioned that other writers had attributed the first description to William Hunter, although he himself had been unable to trace this.

"An Anatomical Description of the Human Gravid Uterus and its Contents" - was published in 1794, after Hunter's death edited by his nephew Mathew Baillie. This volume was intended as a companion to his earlier and better known volume of plates on the same subject which had merely brief explanatory notes.

On p.38-39 of the verbal descriptive volume is to be found this :-

"The following peculiarity I have often observed in the placenta. Upon its inner surface,at more or less distance from the extreme border, there is a projecting brim, of the whitish colour of pleuritic blood, which gives a hollow dish-like appearance to the inside of the placenta. The membranes go off from this brim and the

circumference of the placenta is remarkably thick, forming a convex surface (part of the outer surface of the placenta) instead of a thin edge.

"In considering such a placenta, it would be natural to suppose that there had been a cell or recess in the uterus corresponding to the outward convexity of the placenta. I will not attempt to explain this peculiarity because it never occurred in any instance where I saw the placenta still adhering to the uterus. Perhaps it will be found to happen when the ovum attaches itself near one of the Fallopian tubes, in those women who have the uterus divided at its fundus into a right and left sinuosity, corresponding to the horns of that organ in a quadruped. I have observed that such placentae part from the uterus after labour with more difficulty, requiring a good deal of patience and cautious assistance; and frequently after all, the chorion and decidua are found to be torn from the placenta all around, and left, or a portion of them at least, adhering to the uterus."

Though he does not use the term there is no doubt that the condition he is describing is the same as that labelled "circumvallate" by Williams. For clarity and simplicity the description compares more than favourably with any to be found in the modern literature.

For 150 years following this, until Whitridge Williams' paper in 1927 the condition appears to have been ignored by writers in the English language.

Williams came to the conclusion that the condition had no clinical significance. In the 30 years since his paper, however, there have been a series of reports in which statistical analysis has related the placental anomaly to various clinical conditions - the one most frequently noted being ante-partum haemorrhage. The findings in these series are shown in tabular form in Table BIII.

Normal Placental Development

It is perhaps worthwhile to review the normal development of the placenta before considering the possible mechanisms of development of placenta extrachorialis. It will be recalled that the entire surface of the embedded sac is at first covered with villi. These, however, tend to be more luxuriant in their growth on the aspect which is most deeply embedded. Villous growth in this area persists ("chorion frondosum") while over the rest of the surface the villi fail to flourish and atrophy ("chorion laeve") - this differentiation occurring from 8-12 weeks.

The area of persistant chorionic villi ("chorion frondosum") develops, by subtle integration with the decidua in the region, into the definitive placenta. Its foetal surface remains smooth glistening and membranous - this is the "chorionic plate." The chorionic plate normally corresponds in area to the finite placenta and, at the placental edge where it meets the "basal (or decidual) plate,"

TABLE BIII.

PERCENTAGE INCIDENCE OF CLINICAL COMPLICATIONS RECORDED IN ASSOCIATION WITH PLACENTA CIRCUMVALLATA

	Hobbs and Rollins (1934)	Hobbs and Price (1940)	Hunt et al. (1947)	Paalman and Veer (1953)	Morgan (1955)	Pinkerton (1956)
Number of cases	79	150	47	41	204	50
Abortion	43%	22%	17%			6%
Ante-partum Haemorrhage	11%	22%	19%	51%	14%	2%
Premature Births		16%	21%		14%	10%
Hydrorrhoea Gravidarum		2.6%	15%	26.8%		
Foetal Survival	57%	67%	76%	71%	96%	92%
Post-partum Haemorrhage				14.6%	22%	22%
Manual Removal of Placenta		8%			7%	2%

the chorionic plate becomes continuous with the membranous chorion. There is at the line of demarcation between villous and membranous chorion a fine, fibrous ring, which exactly corresponds to the circumference of the normal placenta and is therefore not usually conspicuous. Attempting to strip the chorionic membrane beyond this line will result in tearing of the membrane.

The question of circumferential growth of the placenta in the second half of pregnancy is of some importance as certain concepts of the aetiology of placenta extrachorialis are based on the assumption that this does not normally occur. However, Stieve (1940) and Hamilton and Boyd (1951), gave it as their opinion from the study of both "in-situ" and delivered placentae, that the placenta continues to grow in circumference throughout pregnancy.

Aetiology of Placenta Extrachorialis

The theories of aetiology of the condition are almost as numerous as the publications on the subject, but many of these can now be excluded in the light of knowledge obtained since they were first put forward. Several still remain which are extremely difficult to prove or disprove but there seems to be no single one which is entirely acceptable.

1. Implantation in the cornual region of the uterus.

Hunter suggested that the explanation of the placental abnormality was that the ovum had been implanted near one of the Fallopian tubes. He made it clear, however, that this was purely speculative as he had never had the opportunity to examine such a placenta still attached to the uterus.

Bayer (1910) advanced the same explanation as his "Tubenecke Placenta" theory. Torpin (1932) originally supported this idea but in more recent papers (1953 and 1955) he has expressed the view that it is incorrect. His reasons for changing his view were two fold. Firstly he personally found circumvallate placentae "in-situ" on the anterior or posterior uterine walls. Dees-Mattingly (1939) also described such a case. Torpin (1953) also recorded an investigation of "5,000 odd" placental sites of attachment by his amniotic sac distension method.* He found that 25 per cent of those attached to the anterior or posterior uterine walls were placentae extrachorialis.

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* FOOTNOTE
The amniotic sac is redistended by fluid after delivery. From the shape it assumes the position of the placenta in utero is deduced (Torpin 1938).

During the present study it was possible to obtain 2 specimens of extrachorial placentae "in-situ" and neither of these (Figs. B.29, B.30, B.31 and B.32) were attached at the uterine cornu. Furthermore, if cornual implantation were an important factor in the aetiology of the condition, it would be expected that a high incidence of breech presentations would occur, if the views of Whitehead (1953) on the relationship of cornual placentation to breech presentation are accepted. In fact there was only a 3.1 per cent incidence (18 cases) of breech presentation in the series reviewed. The hospital breech incidence was 4.2 per cent.

There seems no doubt that this idea, superficially attractive though it may be, is not the correct explanation of this placental anomaly.

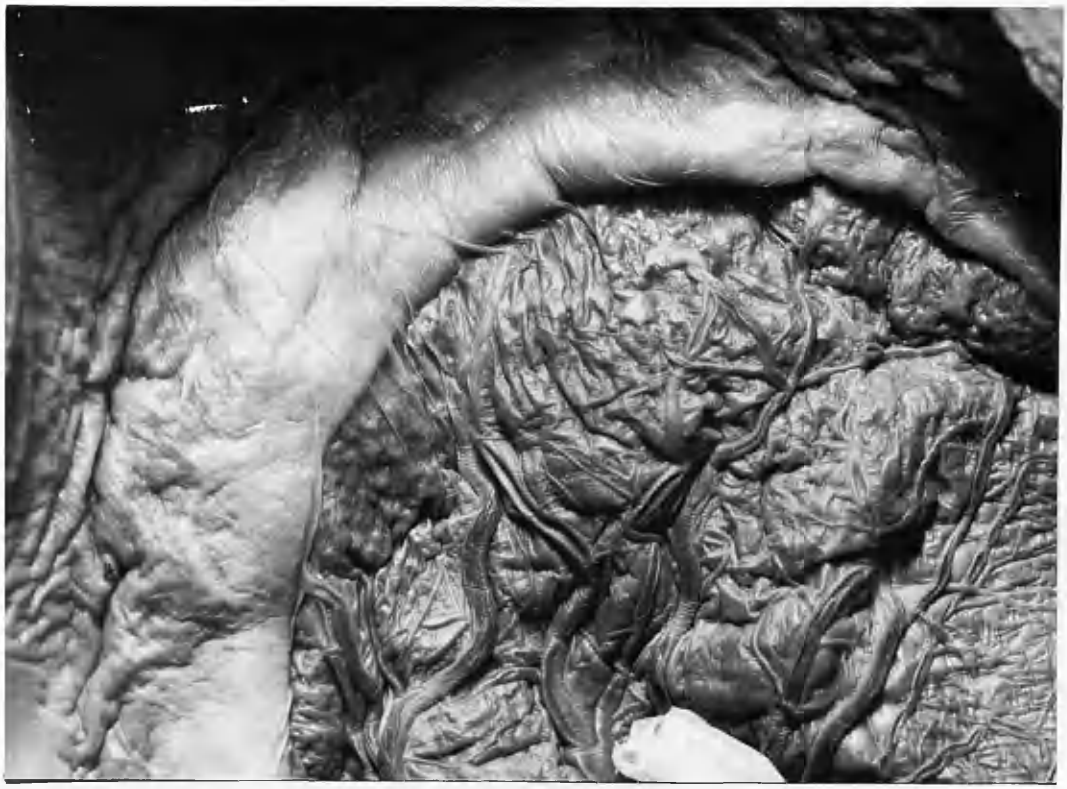
2. Endometritial inflammation theory.

This theory, initially propounded by Veit (1885), is now outmoded by the realisation that true inflammation of the endometrium is rare. Inflammatory changes are not found histologically.

3. Excessive Resistance of the decidua to trophoblastic invasion.

The successful establishment of placentation by the human embryo is dependent upon a proper balance being established

Fig. B.29. Placenta extrachorialis "in-situ". It is situated on the posterior uterine wall. (See Fig. B.30 and B.31).



Figs. B.30 and B.31. Close up views of the placental edge from Fig. B.29 which show the rolled edge of the membrane fold and the foetal vessels disappearing at this level.

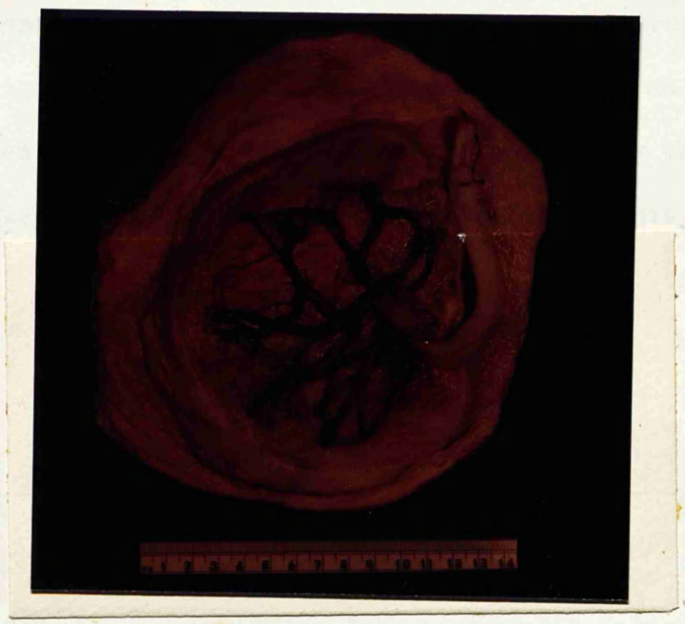


Fig. B.32. Placenta extrachorialis still attached to the uterine wall. This was taken from a specimen in which the maternal uterine circulation was injected in the intact uterus. The position of the placenta was on the posterior uterine wall.

between the actively proliferating, invasive chorionic villous tissue and the protective, cushioning decidual tissue. It would seem not unlikely that this delicate mechanism should sometimes break down and that if the fault were one of excessive resistance to the trophoblast by the decidua round the placental margin, this might result in an intrusion on the chorionic plate, restricting its area. Such an idea was postulated by Schwab (1895). It was supported by the finding of decidual tissue in the circumvallate fold. This is not always present, however, and as Pinkerton (1956) pointed out, and has been confirmed in this study, some of the folds are composed of chorionic tissue.

4. Folding of the foetal membranes due to excessive mobility.

Liepmann (1906) described four uteri with the placentae still attached, in which there were crescentic folds of membrane overlapping the margin of the placenta. He ascribed these folds to variation in the amniotic fluid pressure relative to the growth or motility of the uterine wall. If this were the case one would expect the condition to be associated with abnormality of the liquor amnii volume. As is pointed out elsewhere, there would appear to be no such relationship. Furthermore, such an explanation would only account for partial degrees of placenta circumvallata, but not those involving the whole circumference; nor does it

explain the facts that the fold consists of more than mere membranes and that restriction of the chorionic plate may occur without the presence of a membranous fold.

5. Incoordination of placental and uterine growth.

This idea is to some extent similar to the previous one. It was advocated by Sfameni (1908) and taken up in a modified form by Drosin (1935). One would expect such a shearing effect at the placental edge to result simply in separation with haemorrhage and, while haemorrhage is a feature of many of these case, in others there is no evidence of bleeding even on detailed examination of the placenta.

6. Compensatory Reduction of the Area of Chorion Frondosum.

Funck (1910) suggested that if the area of placental chorion (chorion frondosum) was excessive after the original atrophy of the chorion laeve at 8-12 weeks, a secondary atrophy of the peripheral part of the chorion frondosum might occur and produce the anomaly. This is quite incompatible with the facts - especially the finding of active chorionic villi outside the ring and the fact that the ring may on some occasions (Fig. B.14) only enclose a very small area - only 6 cms. in diameter in the placenta illustrated.

7. Deep Implantation of the Ovum in the Decidua.

This idea has been given prominence as the result of the writings of Torpin. Torpin has devoted his life to a study of the circumvallate placenta. In his early papers he favoured the theory of cornual implantation or of normal implantation followed by compensatory reduction of an excessive area of chorion frondosum - "an effort of nature to convert excess placental tissue into passive membrane."

In recent years, however, he has advocated the deep implantation theory to the exclusion of all others - and has championed it with a zeal which at times verges on the fanatic. While he must be credited with having kept the circumvallate placenta in the attention of the obstetric world, his statements on the subject of aetiology can hardly be accepted without considerable reservations.

Torpin's statistical data tend to be presented in terms of approximations, and this is particularly unfortunate for his theory is in contradiction of modern views of implantation and placentation. His thesis is that if the ovum is deeply embedded in the decidua the original placenta covers more than half of the early ovular sac, a ring forms, and the chorionic and amniotic membranes herniate through this to give the circumvallate placenta. If the implantation is

rather less deep a marginate placenta will result. (Torpin 1955a and 1955c). Despite its opposition to modern concepts of early embryology, this theory does deserve consideration. If it were true one would expect it to operate in cases with a thick, hyperplastic decidua. Torpin (1953) shows a picture of an early circumvallate placenta in utero, where the decidua is apparently extremely hyperplastic.

It seems probable that the type of patient likely to present such a thick, hyperplastic decidua for the implantation of the ovum, would be one who normally develops a hyperplastic type of endometrium with menstruation. Accordingly, in the course of this study the patients who produced extrachorial placentae were all questioned personally as to their menstrual history.

The results were as follows :-

Normal menstrual history..... 497 (86 per cent)

History of heavy menstrual losses (over 12 pads per period) or history of irregular menses - sometimes associated with heavy losses .....81 (14 per cent)

A control series of 200 women whose placentae were normal were also interviewed individually and the results were as follows :-

Normal menstrual history .....155 (78 per cent)

Abnormal menstrual history as above .....44 (22 per cent)

It will be seen that the incidence of excessive menstrual loss is higher in the control group. This study, therefore, provides no support for the concept that implantation in a hyperplastic type of endometrium is likely to lead to placenta extrachorialis. This fact, however, should not be used as an argument against this theory being correct, for it is a study of an indirect nature. The negative result may be due to a wrong assumption that thick, hyperplastic endometrium is necessarily associated with a heavy menstrual loss.

Torpin's theory must, then, be regarded as ingenious but unsupported by controlled scientific observations.

8. Splitting of the decidua vera.

Herff (1896) suggested that splitting of the decidua vera by the peripheral chorionic villi, resulted in the anomaly. Whitridge Williams favoured a combination of this idea and the next. Hamilton and Boyd (1951) state that such decidual splitting at the placental edge occurs normally, though to a variable extent.

9. Initial Formation of an excessively small chorionic plate.

William's idea was that if there was initially excessive chorionic atrophy, giving a small chorionic plate, the villi at the periphery later grew laterally when the foetus required a greater villous area for survival. They would grow into the decidua vera - splitting it and producing the anomaly. This idea is at variance with our present knowledge of placental growth. The placenta does normally grow by increase in area of the chorionic plate after mid pregnancy, according to Stieve (1940) and Hamilton and Boyd (1951). In special circumstances where excessive placental growth occurs, such as hydrops foetalis (Crawford, 1958 and Section C of this thesis) there is no particular tendency for the development of placenta extrachorialis.

Both this theory and that of "Compensatory reduction of the chorion frondosum" is made unlikely by the finding in this investigation of an approximately equal incidence of placenta extrachorialis in 12-28 week abortion placentae as in placentae of the last trimester.

10. Haemorrhage at the placental edge.

Pinkerton (1956) favours the view that the condition is the result of haemorrhage round the placental edge, occurring at an early stage of pregnancy. That such circumferential haemorrhages occur in extrachorial placentae and that they

have a profound affect on the picture, has been confirmed in the present study but they cannot be of primary aetiological importance for very many of the rings, especially those of the marginate type, show no evidence of haemorrhage whatever.

11. Rupture of the decidua capsularis.

This idea was put forward by Lahm in 1924. He suggested that if this happened the ruptured decidua capsularis then contracted down forming a collar which restricted the chorionic plate (placenta marginata) and might actually lead to infolding of the membranes (placenta circumvallata). Williams dismisses this theory on the grounds that remnants of decidual tissue may be found outside the chorion laeve and separating it from that part of the placenta which is extra-chorionic. This would not seem a valid objection and, of all the theories, it appears the most attractive, though there is no scientific proof of its correctness.

Subsequent Development.

Whatever the explanation of the initial restriction of the chorionic plate, there seems no doubt that the subsequent changes are the result of haemorrhage occurring at its circumference. In the normal placenta, the outer edge of the placenta and the limits of both chorionic and decidual

plates coincide. This is the region from which bleeding commonly occurs. In the extrachorial placentae, however, the edge of the chorionic plate is a variable distance within the placental edge and it is from the margin of the chorionic plate rather than the placental edge from which bleeding tends to occur in these placentae. This aspect of the problem is discussed in the section on "Mechanism of Bleeding in Placenta Extrachorialis."

Placenta Extrachorialis and the Marginal Sinus

There is both a practical and a theoretical connection between placenta extrachorialis and the marginal sinus. From a clinical point of view it is a striking feature that the type of ante-partum haemorrhage which occurs in relation to placenta extrachorialis is identical to that described in the American literature by writers such as Sexton et al. (1950), Fish et al. (1951), Harris (1952), Bartholomew et al. (1953), Fish (1955), Ferguson (1955) and Schneider (1958) as occurring in association with rupture of the marginal sinus. This might be summarised in a sentence as - painless ante-partum bleeding without the signs of placenta praevia.

In practice the clinical differentiation of marginal sinus and placenta extrachorialis haemorrhage is of no importance and, indeed, impossible. The real clinical problem with both conditions is the same - to exclude placenta praevia.

From a theoretical point of view, the study of placenta extrachorialis offers some indirect evidence on the question of the existence and function of the marginal sinus of the placenta. With regard to this matter, a complete difference of opinion has developed in recent years between workers in this country and the United States. Hamilton and Boyd (1951) in a concise and well illustrated paper, gave it as their view that "it seems unlikely that the marginal sinus is a feature of the normal placenta." This work has, however, been virtually ignored by the American writers. Ferguson (1955) said of the marginal

sinus that there was "no need to defend its existence" while Fish (1953) in his monograph which is mainly concerned with marginal sinus haemorrhage, fails to mention Hamilton and Boyd's work. They accept Spanner's (1935) concept of the maternal placental blood flow being from the centre of the decidual plate outwards towards the marginal sinus from which most of the venous drainage is said to occur. Harris (1952) shows illustrations of injection studies in 3 placentae "in-situ." One of these was a placenta circumvallata and it is implied that in this case the sinus lies at the level of the circumvallate ring and extends from chorial to decidual surfaces of the placenta. The illustrations are, however, extremely unconvincing. Neither this nor any other of the American papers have illustrations which show clearly what is described in the text - as does Hamilton and Boyd's (1951) paper. Marginal sinus rupture, as described by the American writers has been taken to account for up to 50 per cent of ante-partum haemorrhages and this has apparently become generally accepted in American teaching.

The position of the marginal sinus is said to be at the junction of chorion laeve and chorion frondosum (Fish 1955) - that is, the site of the marginata or circumvallata rings in placentae extrachorialis. In the cases where this lies far from the circumference of the placenta (e.g. Figs. B8 and B.14), it is inconceivable that a vessel in this situation could be the main channel of venous drainage. None of the

placentae examined in this series showed naked-eye or histological evidence of substantial venous connections between this region and the decidua. That this is not the main collection channel for venous drainage is also supported by the fact that considerable fibrous deposition can occur in this region without any clinical effects.

In Section A the condition of "Marginal Infarction," in which the region where the chorionic and basal plates meet at the circumference of the normal placenta is considerably infarcted, was discussed. It is apparently not accompanied by any clinical effects. This is strong evidence that the marginal sinus, if it exists, is not an important route of drainage from the inter-villous space.

This concept was further supported by injection experiments carried out on the maternal circulation of three intact uteri removed at autopsy from women who had died in the last half of pregnancy. This was carried out with radio-opaque medium. The technique used was similar to that described for injection of the foetal circulation except that the maximum pressure used was 120 millimetres of mercury. Cannulae were tied into both uterine arteries and the ovarian vessels were ligated.

The injection was carried out under the control of a fluorescent X-ray screen and serial X-ray photographs were obtained. In none was there any evidence of the venous drainage from the placenta being concentrated in the marginal region. X-ray illustrations (Figs. B.33, B.34, B.35, B36, B.37 and B.38) were taken at a stage when free return flow

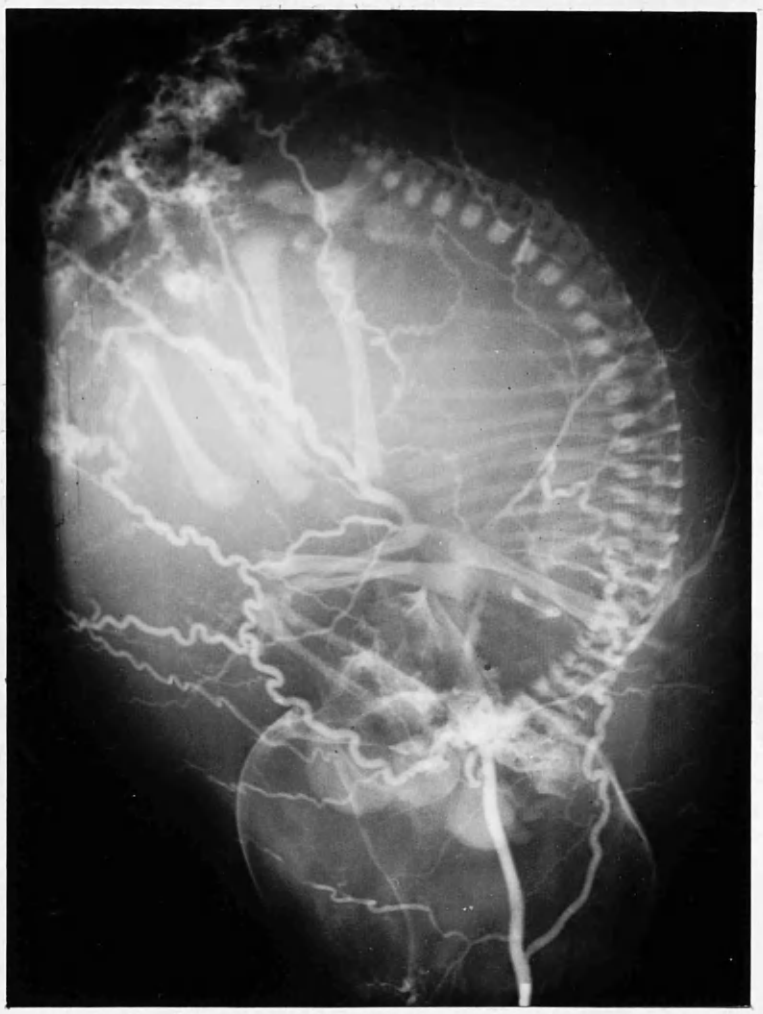


Fig. B.33. Intact gravid uterus injected with 35 ml. of radio-opaque medium; the cotyledons are beginning to fill.

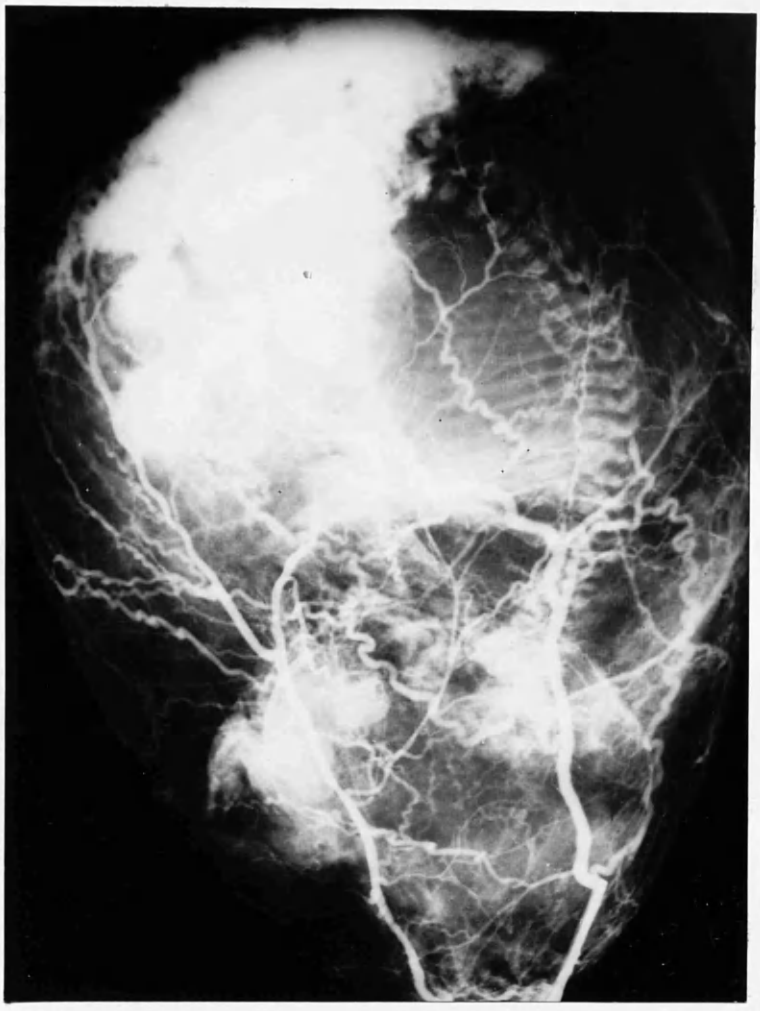


Fig. B.34. Same specimen as Fig. B.33. 80 ml. injected.

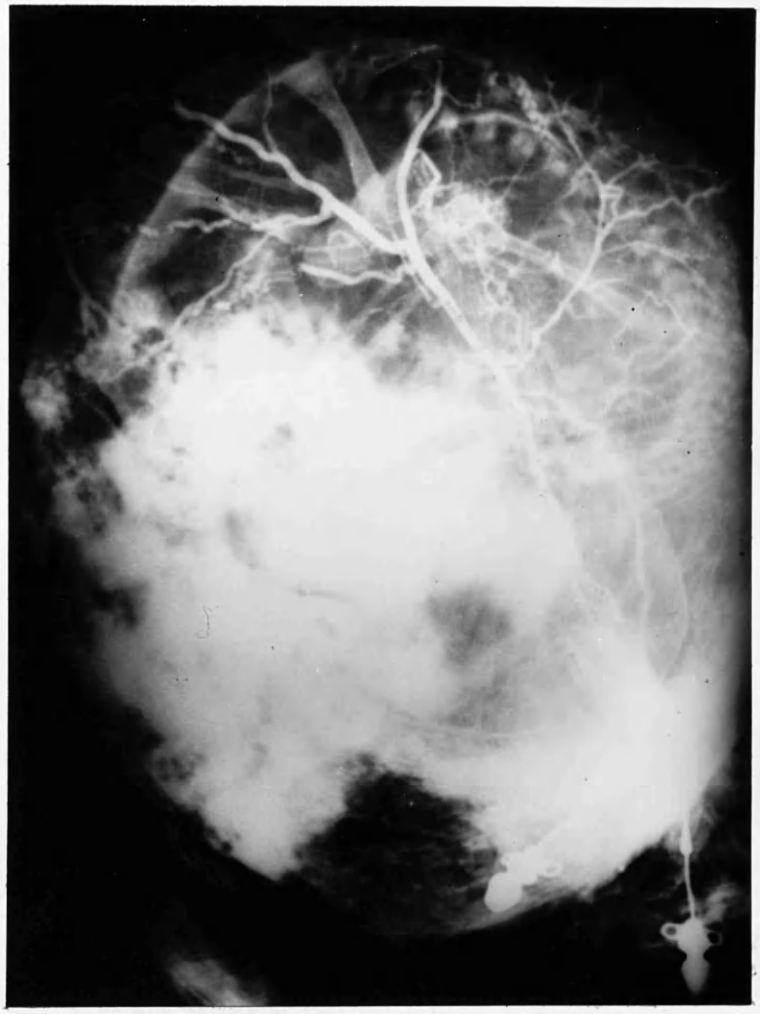


Fig. B.35. Same specimen as Figs. B.33 and B.34. 160 ml. injected; specimen rotated to obtain improved view of placenta. Free venous drainage was occurring at this stage. There is no suggestion of any sinus round the placental circumference.

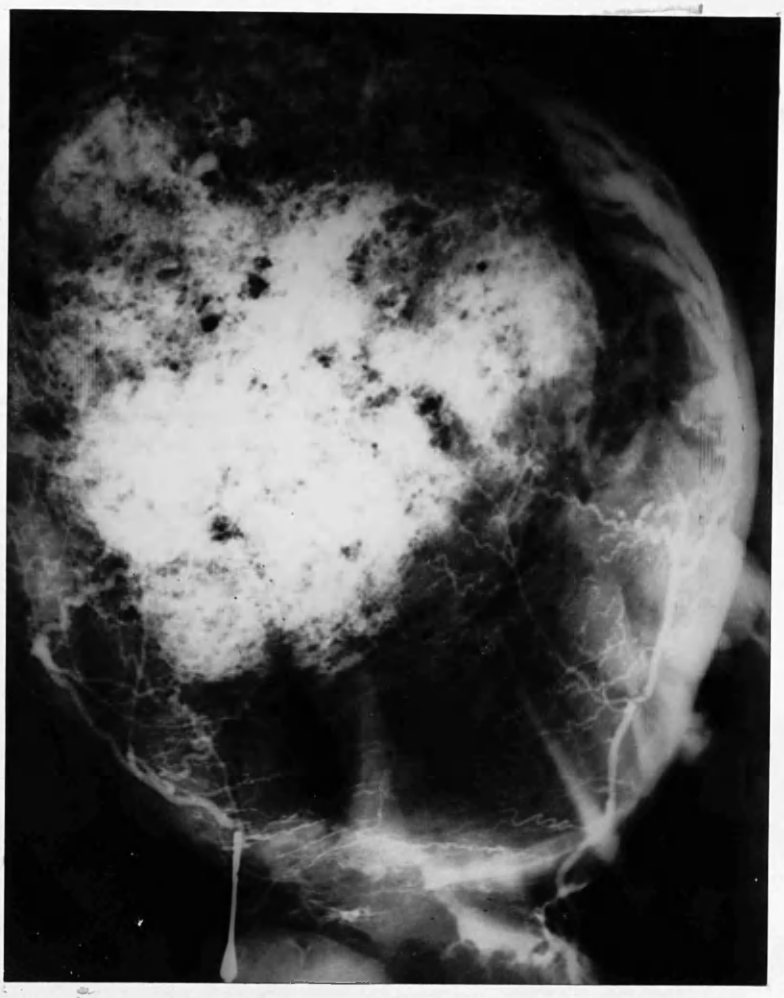


Fig. B.36. Injection of maternal circulation after delivery of foetus through a small incision in the anterior wall of the uterus. The incision was firmly sutured to control oozing. 200 ml. of medium injected. It can be seen that there is no evidence of a sinus round the circumference of the placenta although the uterine veins are visible on the right side of the picture and are obviously well filled.

Fig. B.37. Intact gravid uterus; 50 ml. of medium injected; - a few cotyledons beginning to fill.

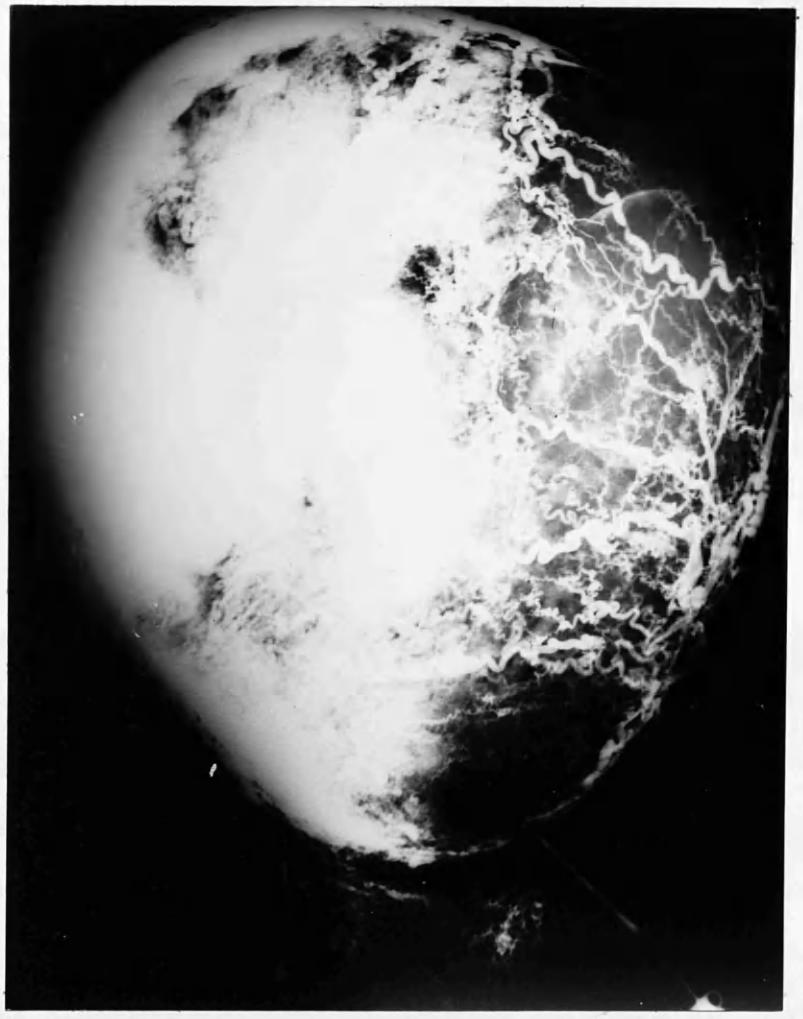


Fig. B.38. Same specimen as Fig. B.37; 250 ml. of medium injected; free drainage occurring through uterine veins; no evidence of marginal sinus.

of the injected medium was being obtained via the uterine veins. This medium presumably was passing through the intervillous space as in each experiment, free venous drainage did not occur until filling of the inter-villous space was evident on the screen. All the pictures in fact give an impression that the maternal placental circulation generally maintains a cotyledonary distribution, without peripheral spread for venous draining.

With one exception, none of the 3,161 placentae examined (and including all the placentae extrachorialis from which marginal sections were taken for histology) showed any structure which appeared to resemble a marginal sinus. The single exception was a section from the margin of the placenta in specimen "X" which was a circumvallate placenta "in-situ" (Fig. B.29) . This section shows (Fig. B.39) a discrete area which has the appearance of a circular sinus filled with blood. This lies near the margin of the basal plate, not of the chorionic plate which is approximately $\frac{3}{4}$ inch nearer the centre. On microscopic view, however, this is seen to be merely an area of organising blood clot and not a definitive sinus (Fig. B.40). (Fig. B.41 is a view of the circumvallate fold in the same section - old chorionic villi can be seen embedded in fibrin).

The findings in the present studies give support to Hamilton and Boyd's view that the marginal sinus does not exist as an entity and that the marginal region of the placenta is of little importance in the maternal venous drainage.

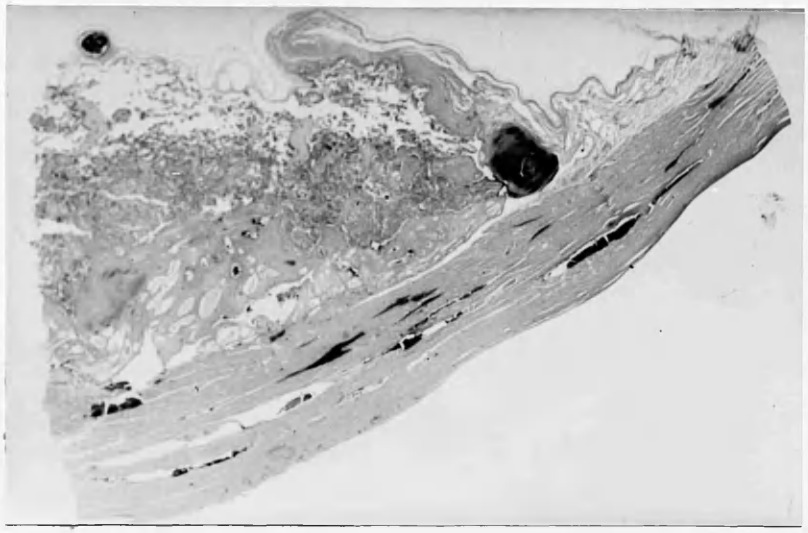


Fig. B.39. Section from margin of placenta extra-chorialis "in-situ". (See Figs. B.29, B.30 and B.31). At the edge of the placenta a structure can be seen which could possibly be a marginal sinus.
(Magnification x2)

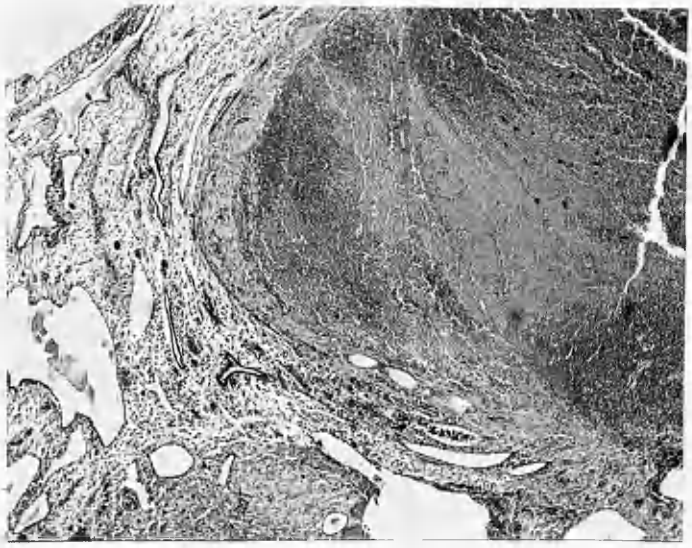


Fig. B.40. Microscopic view of the structure seen in Fig. B.39 which resembled a marginal sinus. It is a mass of organising thrombus with no definite wall.
(Magnification x37)

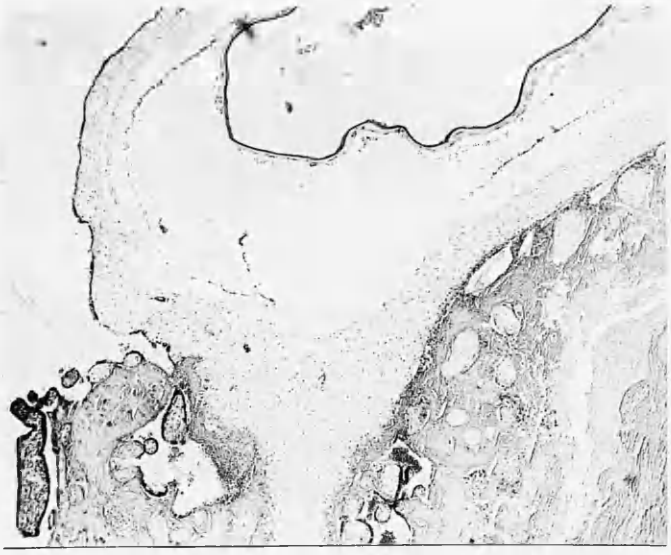


Fig. B.41. Microscopic view of part of the fold seen in Figs.B.29, B.30, B.31 and B.39. Degenerate chorionic villi can be seen.
(Magnification x37)

This is not to say that the syndrome described by the American writers under the title of "marginal sinus rupture" does not exist. There is strong evidence that haemorrhage from the edge of a placenta which lies in the upper segment does occur not infrequently and greater appreciation of this might lead to an improvement in the management of ante-partum haemorrhage. It is unfortunate that a clinical entity should fall into disregard through being labelled in terms of an anatomical structure which is non-existent. In this study it has been found that all haemorrhages of this nature do arise at the edge of the chorionic plate. It would seem that "haemorrhage from the edge of the chorionic plate", though cumbersome, offers a correct anatomical description for these cases.

Summary :-

1. Placenta extrachorialis is a condition in which the chorionic plate of the placenta is deficient in area. This description covers both "placenta marginata" and "placenta circumvallata." These latter terms do not cover specific entities.

2. The one condition which may be confused with placenta extrachorialis on examination of the placenta is "marginal infarction." This condition involves the whole thickness of the placental substance, which is not the case in placenta extrachorialis.

3. There were 578 examples of placenta extrachorialis in the 3,161 placentae examined consecutively in this study.

4. From a detailed analysis of the pregnancies in these cases it appears that ante-partum bleeding from the edge of the chorionic plate is the only complication which occurs with increased frequency in association with placenta extrachorialis. This haemorrhage may be revealed or concealed; it may be recurrent and severe. A diagnosis of placenta praevia is often wrongly suspected. Eight patients in this series were detained in hospital on this account, five were examined under anaesthesia because of the suspicion of placenta praevia and four required blood transfusion. The clinical presentation may be summarised as - painless ante-partum haemorrhage, without the physical signs suggestive of placenta praevia. These haemorrhages seem to be associated with negligible foetal or maternal risk. Once placenta praevia has been excluded, it would probably be safe to allow patients

with haemorrhage of this type to be discharged from hospital while yet undelivered because a self-limiting mechanism operates.

5. The mechanism of recurrent haemorrhage in placenta extrachorialis appears to be related to the contraction of the ring of blood clot or fibrin which tends to form round these placentae.

6. Radiological studies of injected placentae extrachorialis show no evidence of impaired foetal vascularisation of the extrachorial placental tissue.

7. In the present study no evidence was found to support the existence of a "marginal sinus" in the placenta. In placentae extrachorialis, such a sinus would be situated at the edge of the chorionic plate and it would not be possible for venous drainage to occur from there. Neither in placenta extrachorialis nor in the condition of marginal infarction of the placenta,does the placental function appear to be impeded, which it would certainly be if venous drainage occurred by a marginal sinus.

8. Radiological studies of injection of the maternal circulation in gravid uteri from women who had died in late pregnancy support the idea that the marginal sinus plays no significant part in the maternal venous return from the placenta.

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APPENDIX TO SECTION B.

Specimen case histories of patients who suffered clinical complications apparently related to placenta extrachorialis.

No. C.V. 226.

Mrs J.M.

Age 30 years. Five previous pregnancies.

First pregnancy 1950. Normal pregnancy and delivery at term of a live child. No record of the placenta available.

Second pregnancy 1951. Abortion at 10 weeks, followed by curettage in hospital.

Third pregnancy 1952. At 36 weeks she was admitted to hospital as an emergency with an ante-partum haemorrhage. Signs of toxaemia were present and there were signs of concealed bleeding; the foetal heart could not be heard. A 4 pound 3 ounce fresh still-born foetus was delivered followed by a 15 ounce placenta which was described as "unhealthy." There was estimated to be 14 ounces of concealed haemorrhage.

Fourth pregnancy 1954. This pregnancy was entirely uneventful. Strict ante-natal observation was carried out at hospital and there were no signs of toxaemia. Normal delivery occurred at term of a 7 pound 13 ounce live child. The placenta weighed 1 pound 9 ounces and the only feature recorded about it was the presence of some areas of calcification.

Fifth pregnancy 1955. In this pregnancy the patient was again admitted as an emergency on account of ante-partum bleeding - on this occasion at 33 weeks. She gave a history of sudden loss per-vaginam

of approximately half a pint of bright red blood. This had been associated with some abdominal discomfort but no significant pain. She was pale and slightly shocked; there were no signs of toxaemia and the only suggestion of concealed bleeding was some slight tenderness on the left side of the uterus. The head was at the pelvic brim; the foetal heart was audible.

Steady blood loss continued and blood transfusion was begun. A note was made at the time :- "hard to say whether this is accidental haemorrhage or placenta praevia." X-ray placentography showed the placenta on the anterior uterine wall with the lower margin possibly extending onto the lower segment. In view of the continued blood loss, examination under anaesthesia was performed; no placental tissue was felt and the membranes were ruptured artifically. An oxytocin intravenous drip was set up and delivery followed of a live 4 pound 15 ounce male child. The baby died in the neonatal period from prematurity. The placental weight was recorded as 1 pound 14 ounces, - but this included approximately 6 ounces of old blood clot adherent to the circumference of the placenta and apparently arising from the edge of the chorionic plate which was approximately 1 inch within the circumference of the placenta. The blood clot covered the foetal aspect of the extra-chorial placental tissue.

Sixth pregnancy 1957. The pregnancy was uneventful in the early months and regular ante-natal examinations revealed no signs of toxaemia. At 32 weeks the patient was admitted following a painless

vaginal haemorrhage of approximately 2 ounces. There were no signs of toxaemia or of concealed haemorrhage. The vertex was presenting and was high above the pelvic brim; the foetal heart was heard.

Conservative management, was instituted on the assumption that this was a case of placenta praevia. No further loss occurred though the patient was in hospital for 9 weeks. The possible presence of placenta praevia was supported by continued instability of the foetal lie in this period. At term vaginal examination under anaesthesia was performed but no placental tissue could be felt. The membranes were not ruptured artifically at this time, as the head was free above the brim. Spontaneous onset of labour occurred a week later followed by normal delivery of an 8 pound live child. The placenta weighed 1 pound 13 ounces and showed extrachorionic placental tissue involving 2/3rds of its circumference to a maximum width of 1 inch. There was a membranous fold of circumvallate type at the margin and this contained a considerable amount of fibrin.

Comment:-

The ante-partum haemorrhage in the third pregnancy was associated with toxaemia and clinically was of typical abruptio placentae type. In the fifth and sixth pregnancies, however, it was of a type suggestive of placenta praevia - in both, examination under anaesthesia was required. In the fifth pregnancy the baby succumbed to prematurity

and this foetal death might be attributed to placenta extrachorialis. (This delivery did not occur during the period of the placental s tudy). In the sixth pregnancy the suspicion that the condition was one of placenta praevia resulted in the patient being in hospital for 9 weeks prior to delivery.

No. C.V. 510.

Mrs G.K.

Age 30 years. Two previous pregnancies.

First pregnancy 1952. This resulted in a forceps delivery at term of a stillborn foetus weighing 6 pounds 12 ounces. The exact details of the foetal death were unknown nor was any information available concerning the placenta.

Second pregnancy 1954. This resulted in the delivery of a healthy 7 pound 10 ounce child following induction of labour for post-maturity. The placenta was normal.

Third pregnancy 1957. The pregnancy was uneventful until the 32nd week when she was admitted to hospital on account of painless vaginal bleeding. There was no evidence of concealed haemorrhage and the foetal head was free above the pelvic brim.

Bleeding continued and transfusion had to be instituted. When approximately 30 ounces had been lost, examination under anaesthesia was performed and excluded placenta praevia. The membranes were then ruptured artifically.

Thirty-six hours later a male child weighing 4 pounds 3 ounces was delivered, followed by a placenta weighing 1 pound 1 ounce.

There was approximately 9 ounces of old blood clot at one edge of the placenta. This part of the placenta showed extrachorial placental tissue - involving 2/3rds of the circumference, there was

a slight membranous fold and a moderate amount of fibrin in the fold. The placental edge in this region was considerably disrupted by the blood clot which extended onto the membranes.

Comment:-

The clinical presentation in this case so resembled placenta praevia that examination under anaesthesia had to be performed.

No. C.V. 540

Mrs A.A.

Age 29 years. One previous pregnancy.

First pregnancy 1954. Miscarriage at 6 months; no notes available concerning the placenta.

Second pregnancy 1956. Early months of pregnancy entirely normal. Admitted to hospital at 32 weeks on account of painless ante-partum haemorrhage of 3-4 ounces. The uterus was not tense or tender; the head was in the mid-line at the pelvic brim.

Placenta praevia was diagnosed and conservative management as an in-patient instituted. At 36 weeks the membranes ruptured and 5 days later spontaneous vaginal delivery occurred without there being any further bleeding. The child, a male, weighed 6 pound 10 ounces.

The placenta weighed 1 pound 7 ounces and showed a complete ring of extrachorial tissue. The chorionic plate circumference was a maximum of $1\frac{1}{2}$ inches from the placental edge and was associated with a well marked fold which contained a considerable amount of fibrin. There was blood clot covering the foetal surface of the extrachorial placental tissue and it appeared that the edge of the chorionic plate had been the source of the ante-partum bleeding (See Figs. B.15 and 16). The site of rupture of the membranes was several inches from the placental edge at the nearest point.

Comment:-

This case also illustrates how placenta extrachorialis haemorrhages may resemble placenta praevia, leading to a long period of stay in hospital. The illustrations show well the mode of spread of haemorrhage in placenta extrachorialis.

No. C.V. 544.

Mrs J.S.

Age 21 years. One previous pregnancy.

First pregnancy 1954. Uneventful pregnancy; normal delivery at term of an 8 pound 14 ounce baby; normal placenta.

Second pregnancy 1956. The patient was first seen at 15 weeks when she appeared to have a normal intra-uterine pregnancy. At 30 weeks she was admitted as an emergency on account of painless ante-partum haemorrhage. She had suddenly lost approximately one and a half pints of fresh blood. There was no evidence of concealed bleeding and although it was too early to elicit the physical signs of placenta praevia, this diagnosis was made with confidence on the history. Two pints of blood were transfused and following this the haemoglobin was 72 per cent. Conservative management as for placenta praevia was continued in hospital until the 37th week.

At this time examination under anaesthesia revealed that there was no evidence of placenta in the lower uterine segment.

The spontaneous onset of labour was then awaited, and this occurred at 41 weeks, resulting in a 9 pound 15 ounce live child and a placenta which weighed 2 pounds 15 ounces.

The placenta showed a grossly restricted chorionic plate, the edge of which was $2\frac{1}{2}$ inches within the circumference of the placenta. There was a thick ring of old, organising clot running right round the

foetal surface of the placenta in this region and from this ring, clot extended out to the periphery of the placenta. There was a membranous fold $\frac{3}{4}$ inch deep enclosing a layer of old blood clot. (See Figs. B8 and B9).

Comment:-

This case again illustrates how closely placenta extrachorialis haemorrhage may simulate placenta praevia and how much this may involve in terms of stay in hospital.

No. C.V. 571.

Mrs T.M.

Age 30 years. Five previous pregnancies.

First pregnancy 1947. Normal pregnancy; no ante-partum bleeding; forceps delivery at term of a 9 pound boy; baby died at 9 months from "Pink Disease."

Second pregnancy 1949. Several minor haemorrhages occurred during the early months of pregnancy; normal delivery at term of a 9 pound 7 ounce boy; child alive and well.

Third pregnancy 1951. Repeated haemorrhages occurred during the early months and bleeding eventually became severe at 5½ months. The haemorrhage was of sufficient severity to require the transfusion of 2 pints of blood and to cause the diagnosis of placenta praevia to be suspected. Despite the fact that the foetus was not yet viable, examination under anaesthesia was performed and having excluded a low-lying placenta, the membranes were ruptured. Delivery followed rapidly but unfortunately no record was made of the appearance of the placenta.

Fourth pregnancy 1954. Several painless haemorrhages again occurred in the early months of pregnancy, starting at the 6th week. At 28 weeks there was a heavier loss and liquor started to drain per vaginam. Liquor continued to leak for the next 2 weeks till labour occurred resulting in a 3 pound 8 ounce male child, which survived. No specific note was made concerning the placenta.

Fifth pregnancy 1955. The early part of the pregnancy was normal but she was admitted to hospital in premature labour at 35 weeks. On admission some blood stained liquor was draining but there was nothing suggestive of concealed haemorrhage except backache between contractions, nor were there any physical signs of placenta praevia. On vaginal examination the cervix was almost fully dilated and the forewaters were found to be intact. On rupturing the membranes, liquor drained which was stained with old blood. A 6 pound 5 ounce male child was soon delivered, followed by a placenta weighing 1 pound 5 ounces.

The placenta showed a complete ring of extrachorial tissue with a membranous fold 1 inch from the placental circumference containing a thick fibrinous ring. From the ring of fibrin, clot extended out over the extrachorionic placenta and, in several regions, on to the membranes. The total amount of clot was estimated as 6 ounces. Some of this clot was fresh and some old, in varying stages of organisation. The membranes showed two separate sites of rupture - one large rupture - through which the child had been delivered - and one small rupture close to the edge of the chorionic plate. Through this rupture, the haemorrhage from the edge of the chorionic plate appeared to have escaped into the amniotic sac. This presumably occurred some considerable time before delivery because at birth it was noted that the baby was passing melaena stools.

From the inspection of the placenta and membranes it was quite evident that there had been several haemorrhages earlier in pregnancy,

though with none of these had there been any revealed loss.

Sixth pregnancy 1956. The early months of this pregnancy were again complicated by haemorrhages - at 8, 12, 15, 17 and 18 weeks. Further slight loss occurred at 24 and 25 weeks.

At this stage a circumvallate placenta was suspected and a note made to this effect. No further losses occurred till 37 weeks when she had two slight "shows." At 39 weeks labour commenced and was associated with blood loss which was more than a normal "show" - 6 diapers have been stained prior to her admission to the labour ward.

A 7 pound 12 ounce girl was delivered and followed by a placenta weighing 1 pound 15 ounces. The placenta showed a thick fibrinous ring with a membrane fold extending round the placenta at a maximum distance of 2 inches from the circumference. (See Fig. B.10). The ring was seen to consist of organising blood clot of varying age. There were also traces of organising blood on the membranes - again obviously of varying age - presumably resulting from the minor ante-partum haemorrhages which had occurred.

Comment:-

The opportunity to examine the placenta personally only occurred in the last two pregnancies. In both of these there was a definite placenta extrachorialis - and both pregnancies were associated with ante-partum bleeding. The suspicion naturally occurred that the second, third and fourth pregnancies - all of which were complicated

by ante-partum haemorrhage of a similar type - might have been associated with the same anomaly. Unfortunately, despite writing to the institutions in which these confinements took place, no information about the placentae could be obtained.

The photograph of this placenta (Fig. B.10) shows clearly how the chorionic membrane can be stripped from the extrachorial placental tissue.

SECTION C.

THE PLACENTA IN HYDROPS FOETALIS

The placental changes in hydrops foetalis are described. The alterations in the trophoblast are shown to be related to a high incidence of toxaemia of pregnancy and raised excretion of gonadotrophins. The mechanism of the changes and their effects is discussed and the aetiology of the pre-eclamptic syndrome is considered in the light of the information derived from this study.

THE PLACENTA IN HYDROPS FOETALIS

ANATOMICAL CHANGES IN THE PLACENTA

During the course of this placental study, placentae from cases of hydrops foetalis attracted special interest. On macroscopic examination they are made notable by their massive bulk, pale colour and deep fissuring between cotyledons. (Fig. C1.) In some cases the placenta seemed to be disproportionately large even compared with the hydropic foetus. This impression was confirmed by studying the weight of the placenta in relation to the weight of the foetus - the so-called "placental co-efficient." In the normal case this co-efficient is approximately 1/5th or 0.2. In a series of 52 cases of hydrops foetalis the average placental co-efficient was found to be 0.5.

On histological examination it was found that the placental substance showed changes other than the passive oedema which might be expected. The villi, in addition to being blown out by oedema, showed clear histological evidence of over-activity of the trophoblast with, in some areas,a well developed Langhans layer which is not normally visible in late pregnancy. (Figs. C2, C3, C4 and C5). The degree of syncitial degeneration is usually less than in a normal placenta of comparable maturity while both trophoblastic layers show increased vacuolisation. Although the vascularity of the villi is deficient, the stroma is often distinctly hyperplastic. Indeed, the overall

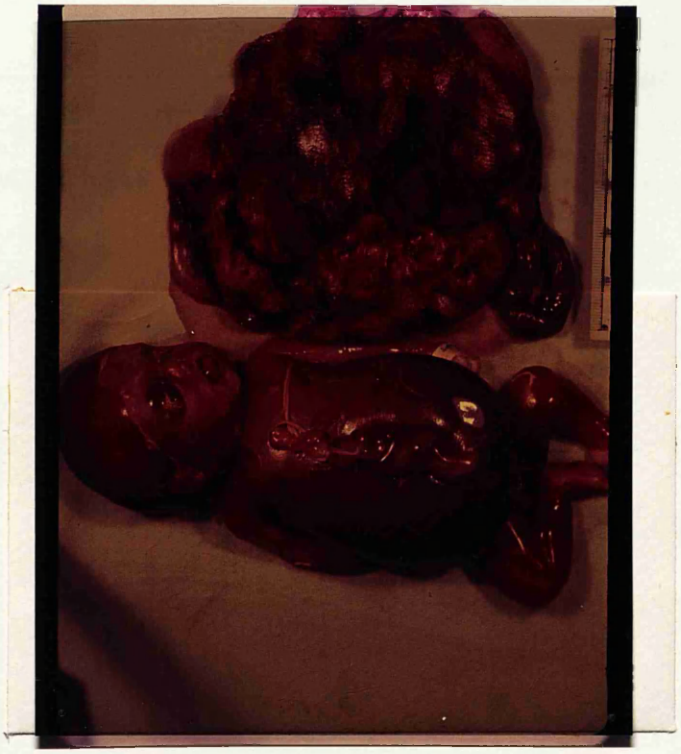

Fig. C1. Placenta and foetus from case of hydrops foetalis showing the massive bulk of the placenta relative to the foetus, areas of pallor and deep fissuring between some of the cotyledons.

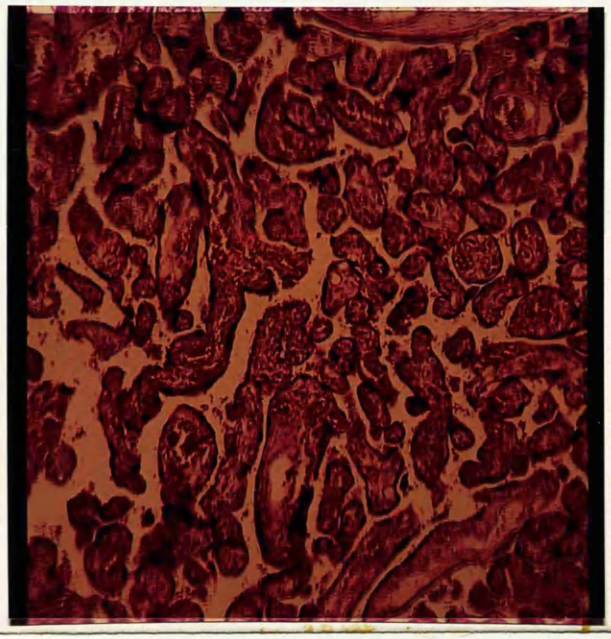

Fig. C2. Photo-micrograph of normal placenta of third trimester showing well vascularised villi with single layered trophoblastic covering (x 70)

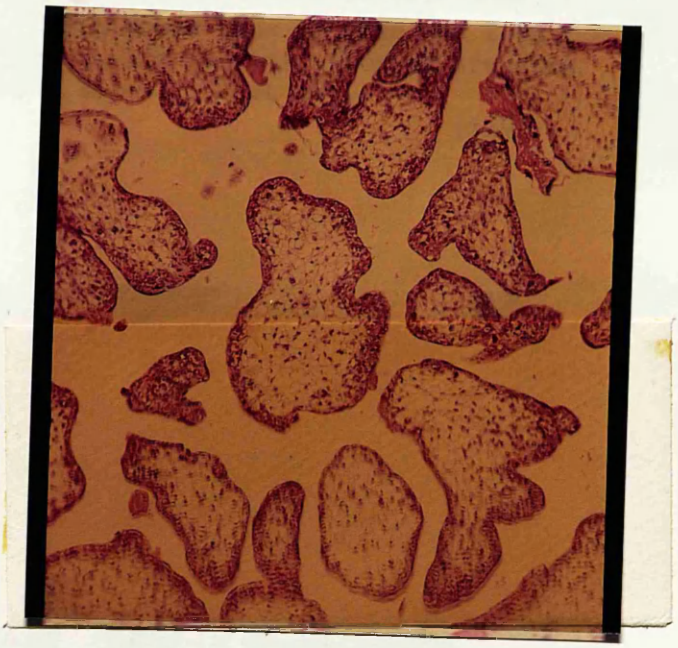

Fig. C3. Hydrops foetalis placenta at 34 weeks showing oedema of villi and double-layered trophoblast.

(x70)

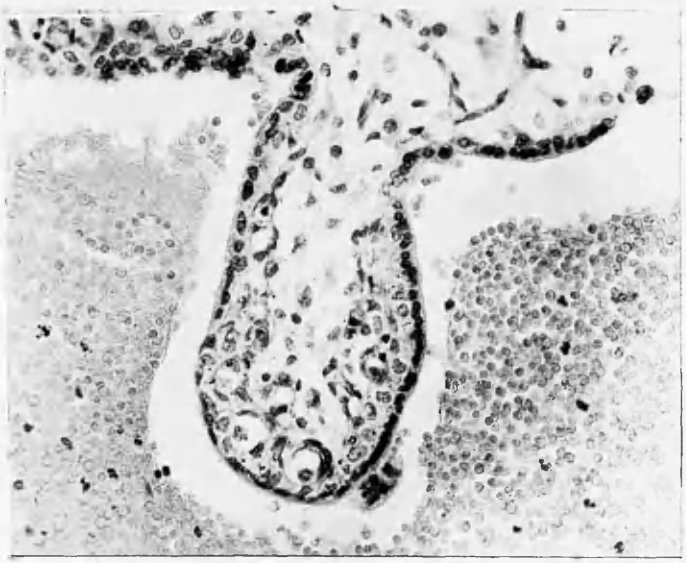

Fig. C4. High power view of placenta from haemolytic disease hydrops, showing presence of Langhans layer. (Case 49).

(x290)

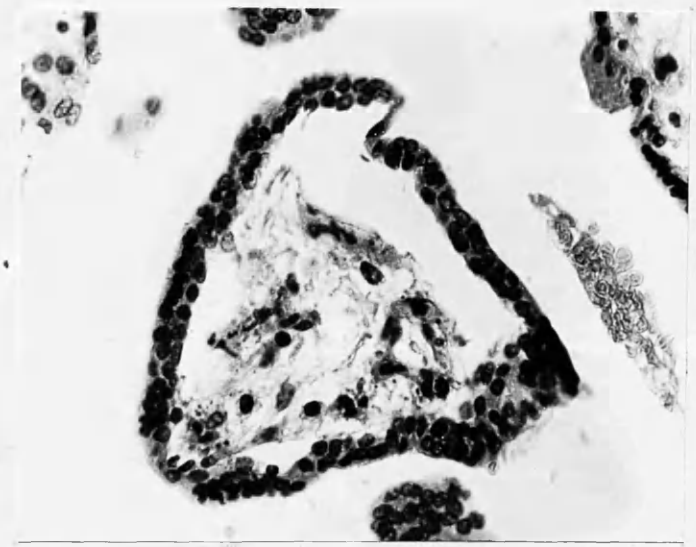

Fig. C5. Villous from hydrops foetalis placenta of 32 weeks maturity, showing clearly the presence of Langhans layer.

(x290)

appearance of the placenta of the hydropic foetus suggests unusual activity and an absence of the degenerative changes usually associated with advancing maturity.

The presence of Langhans layer was first pointed out by Hellman and Hertig (1938) and since then it has usually been referred to as "persistence" of the layer. It seems more than probable, however, that it represents a regeneration of tissue which has atrophied in the normal way in mid-pregnancy. The idea that this can occur is supported by two sets of recent observations. Amoroso (1957) by using an electron microscope was able to demonstrate that the cytotrophoblast does not, as is generally supposed, disappear completely in the second half of normal pregnancy. It persists to term as a very fine membranous layer. This, presumably, is capable of reactivation. In addition Crawford (1958) has shown by digestion studies on placentae from cases of severe haemolytic disease that fresh sprouting of chorionic villi occurs at about the time the foetus develops the hydropic state.

Further interest in these placental changes and their effects was stimulated by the observation of several women carrying hydropic foetuses who developed illnesses closely resembling pregnancy toxaemia but which appeared to be in some way related to the hydropic condition of the conceptus. Accordingly, a detailed study of the problem of maternal reactions in cases of rhesus haemolytic disease was undertaken.

MATERNAL REACTIONS TO RHESUS FACTOR ISO-IMMUNISATION

Following the discovery of the Rhesus factor it was for long believed that pregnancy associated with a state of iso-immunisation carried no special hazards for the mother except in the event of an incompatible blood transfusion. Later it was recognised that, when the foetus dies *in utero* as a result of haemolytic disease, the mother can sometimes develop fibrinogen depletion or other haematological change which leads to blood coagulation failure. This condition, however, is not peculiar to Rhesus iso-immunisation and can arise whenever a dead foetus is retained long in utero - irrespective of the cause of death.

The literature does, however, contain reference to cases in which there has been quite serious maternal illness associated with the carrying of a foetus severely affected by haemolytic disease. From a study of these cases it would appear that the maternal reactions fall into two groups :- (i) those which suggest a haemolytic process and (ii) those presenting a picture similar to, or identical with, that of pre-eclampsia.*

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* In view of a doubt as to whether pre-eclampsia is a specific disease or a syndrome which may be produced by more than one disease, the loose term "toxaemia" is generally preferred in this thesis.

(i) This type of reaction varies. In an acute form it may be manifested by rigors and vomiting, followed by evidence of haemolysis having occurred. The onset may, however, be insidious, and is then characterised by jaundice appearing in association with malaise and raised levels of bilirubin and bile acids in the blood. Early reports on this condition were by Rolleston (1910, 1920) who, writing on "grave familial jaundice of the new born", noted maternal jaundice in 15 out of 130 pregnancies. His description of the cases leaves little doubt that he was dealing with babies severely affected by haemolytic disease. Kaiser (1952) described 2 cases of maternal illness associated with hydrops foetalis, a feature of the illness being generalised pruritus associated with a high level of bile acids in the blood. Velez Orozco et al. (1950) claimed, in this connection, that the severity of foetal haemolytic disease can be assessed by estimation of the level of haemolytic products in the maternal serum. Chown (1954 and 1957) and recently Goodall, Graham, Miller and Cameron (1958) of Dundee recounted cases in which they suspected that a maternal disturbance resulted from foetal haemorrhage into the maternal blood stream. Javert and Reiss (1952) described histological changes in the placenta which they attributed to such haemorrhages.

It would seem therefore that whereas certain of these maternal reactions, especially those with an acute onset, may be caused by incompatible foetal blood crossing the placenta and resulting in lysis in the maternal blood, others are the result of the products of haemolysis within the foetus entering the maternal circulation. There is nothing in the case records, however, to suggest that these illnesses are in any way related to the "toxaemia" which the mother sometimes develops and with which this communication is mainly concerned.

(ii) The maternal toxaemia described in association with severe foetal haemolytic disease is characterised by oedema, hypertension and albuminuria; some writers regarding it as true pre-eclampsia, others as something different. As with toxaemia in other circumstances, not all the three signs are necessarily present in one case. Rolleston (1920), Kaiser (1952), O'Driscoll and Lavelle (1955) and Goodlin (1957) all reported cases of toxaemia associated with severe haemolytic disease of the foetus, while McGaughey (1952) commented that the association is "well-known." Potter (1947) described a maternal syndrome, occurring about the time of intra-uterine death of severely affected babies, which was characterised by albuminuria and oedema; this she regarded as being

different from pre-eclampsia because the systolic blood pressure did not rise above 140 mm.Hg. Walker et al. (1957) observed that the incidence of pre-eclampsia was doubled in mothers of stillbirths due to haemolytic disease and increased four fold when the foetus was hydropic. However, Dieckmann (1952), quoting Hurst et al. (1946) and also Potter's review of 190 cases of haemolytic disease of all types, stated that the incidence of toxaemia is not increased in cases of Rhesus sensitisation. Greenhill (1955) also declared that there is not an overall increase in the likelihood of toxaemia of pregnancy when a state of Rhesus iso-immunisation arises. He went on to say, however, that when it does occur, the foetus is usually hydropic. Here would appear to be the crux of the matter. Is toxaemia likely to occur in any case of foetal haemolytic disease or only when the foetus is dropsical ?

In an attempt to answer this question the records of the Liverpool Maternity Hospital and Mill Road Maternity Hospital for 4 years 1953 - 1956 were examined.

The criteria used for the diagnosis of toxaemia in this and other studies reported here were the same as those used by Gemmell and others (1954) in their survey of all the 15,364 births in Liverpool

during 1951. Toxaemia was diagnosed on the presence of any two of the following :-

(i) A blood pressure of 140/90 or more.

(ii) Oedema.

(iii) Albuminuria without local cause.

Eclampsia was included as the most severe form. In regard to the interpretation of blood pressure readings, isolated rises during labour were ignored; blood pressures in which either the systolic was more than 140 or the diastolic was more than 90 mm. of mercury, were included but not those where only systolic or diastolic equalled the critical figure when the other reading was normal. (Gemmell, 1957). No attempt was made to distinguish between pre-eclampsia and essential hypertension in their study and the same is true of this one: both are included in the term toxaemia.

During this time 172 babies affected by haemolytic disease but not showing hydrops, were born. All the mothers were multiparous and only 8 of the pregnancies were complicated by toxaemia. This gives an incidence of 4.6 per cent which is not significantly higher than the 4.2 per cent expected incidence in the unselected Liverpool multiparous patients (Gemmell et al, 1954). These findings lend support to the statements quoted above which go to show that Rhesus incompatibility in itself does not cause toxaemia of late pregnancy. It remains to be decided, however, whether hydrops foetalis is an aetiological factor.

TOXAEMIC REACTIONS TO HYDROPS FOETALIS

1. Literature.

The many references in the European Continental literature to an association between hydrops foetalis and toxaemia of pregnancy are reviewed by Jann (1954). He goes on to comment that prior to the elucidation of the relationship of hydrops foetalis to other forms of haemolytic disease, and to the discovery of the Rhesus factor, the common occurrence of toxaemia in cases of hydrops foetalis was often recorded and was generally recognised. Recent knowledge, however, has obscured the situation and the grouping together of all cases of Rhesus incompatibility has led to the neglect of older clinical observations. In this respect it is of interest to note that Burger (1947), being deprived by war conditions of knowledge of the Rhesus factor, was enabled to develop the theoretical implications of the maternal effects of hydrops foetalis beyond the stage reached by other writers before or since.

That hydrops foetalis had some connection with maternal oedema and albuminuria was also well known in this country in the past. Ballantyne in 1902 gave a complete account of it and his, as well as other contemporary writings, were probably responsible for the statement that hydrops foetalis may be complicated by toxaemia of late pregnancy which has appeared in some British textbooks on Obstetrics throughout this century.

Of the many authors who have written on the subject however, few have attempted to state statistically the incidence of toxaemia in cases of hydrops foetalis. The exceptions are Kloosterman (1947, 1954) who found toxaemia in 23 out of 35 mothers (65 per cent) who gave birth to a hydropic infant, and Jann (1954) who reckoned the incidence as being more than 70 per cent in the cases recorded in the literature. In these papers, however, and in those of other authors who describe individual cases there is much confusion over terms such as "toxaemia" and "pre-eclampsia." The standards used are not stated nor is any attempt made to compare the findings with controls. It was therefore decided to re-investigate the matter on a statistical basis.

2. Material.

The patients reviewed were those delivered of a hydropic foetus in the Liverpool Maternity Hospital, Mill Road Maternity Hospital and the Birmingham Maternity Hospital during 8 years 1950 to 1957. There were 52 such cases and the diagnosis of hydrops was beyond doubt in all. Forty-six babies were still-born; the remaining six lived for no longer than a few hours. All but three of the mothers had had previous pregnancies.

3. Findings.

(a) Jaundice.

One of the mothers of a hydropic foetus developed jaundice without any other significant signs. Jaundice in a second patient was accompanied

by signs of toxaemia and by accidental antepartum haemorrhage followed by severe oliguria. Neither of these two cases was fully investigated so the cause of the jaundice remains uncertain.

(b) Toxaemia.

Twenty-six out of the 52 women in the series (50 per cent) developed signs which fulfilled the previously stated criteria for the diagnosis of toxaemia. This high figure tallies reasonably with the collected figures of Jann (1954) and those of Kloosterman (1947) mentioned earlier. Addition of the 3 series together gives a total of 166 cases of toxaemia in 249 cases of hydrops foetalis (66 per cent). (Fig. C6.)

For statistical purposes, it would be unwarranted to assume that the over-all toxaemia incidence was the same in Birmingham as Liverpool. If, however, the 32 Liverpool cases are considered alone (30 multiparous) the incidence of toxaemia is found to be 15 whereas the expected incidence according to the figures of Gemmell and others (1954) is 1.5 cases - a highly significant difference statistically. The high incidence of toxaemia is even more significant than the figures show for it frequently occurred in pregnancies which terminated as early as 28 - 32 weeks. (Fig. C7.)

In the present series, the appearance of signs of the maternal illness very often coincided with the making of a firm or tentative diagnosis of hydrops foetalis. Moreover, they became manifest

TOXAEMIA INCIDENCE IN ASSOCIACIATION WITH HYDROPS FOETALIS

	Number of cases	Number with toxaemia	Percentage
Present series	52	26	50
Kloosterman (1947)	35	23	65
Jann (1954)	162	117	72
Total	249	166	66

Fig. C6. Toxaemia incidence in association with hydrops foetalis - collected series.

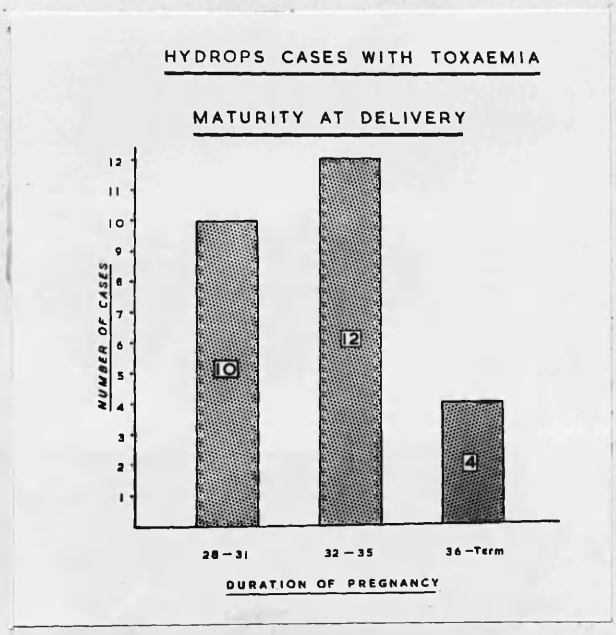

Fig. C7. Maturity at delivery of 26 cases of hydrops foetalis associated with toxaemia.

relatively early in pregnancy. The toxaemia was generally of severe degree (Table CI.); one woman died from the disease and another 8 were critically ill, - 2 having to be delivered abdominally on account of the toxaemia.

The details of the fatal case were as follows :-

> Case 23. Mrs F.D. Aged 43, was an 8-gravida whose blood group was O. Rh.negative with antibodies present. Her first 4 pregnancies were uneventful and resulted in the delivery of healthy babies. The fifth baby was macerated at birth and the sixth, although born alive, died in the neonatal period from haemolytic disease; the seventh was healthy. During this woman's last and fatal pregnancy, at the 37th week she developed oedema and slight hypertension (150/90, 140/100 mm.Hg.). There had been no evidence of toxaemia in any of her previous pregnancies. Labour at term had to be assisted in the second stage with forceps because of the large foetal trunk. An 8-lb.12-oz.fresh stillborn hydropic infant was delivered, followed by a large, pale, oedematous looking placenta and a blood loss of 15 ounces. The operation was carried out under local anaesthesia and immediately after delivery the patient complained of pain in the epigastrium and chest; a state of shock developed and she died 3 hours later despite resuscitative measures. Examination of a blood sample revealed afibrinogenaemia but excessive haemorrhage was not a feature.

The signs of pre-eclampsia having been of the mildest, the maternal death was regarded as possibly due to amniotic or fibrin embolism. Post-mortem examination, however, showed macroscopic liver haemorrhages similar to those seen in eclampsia. Histologically these proved to have a periportal distribution and to be of the "lake" type. The kidneys showed intracapillary fibrils in the majority of the glomeruli; congestion of the capillary loops; glomerular thrombi; and

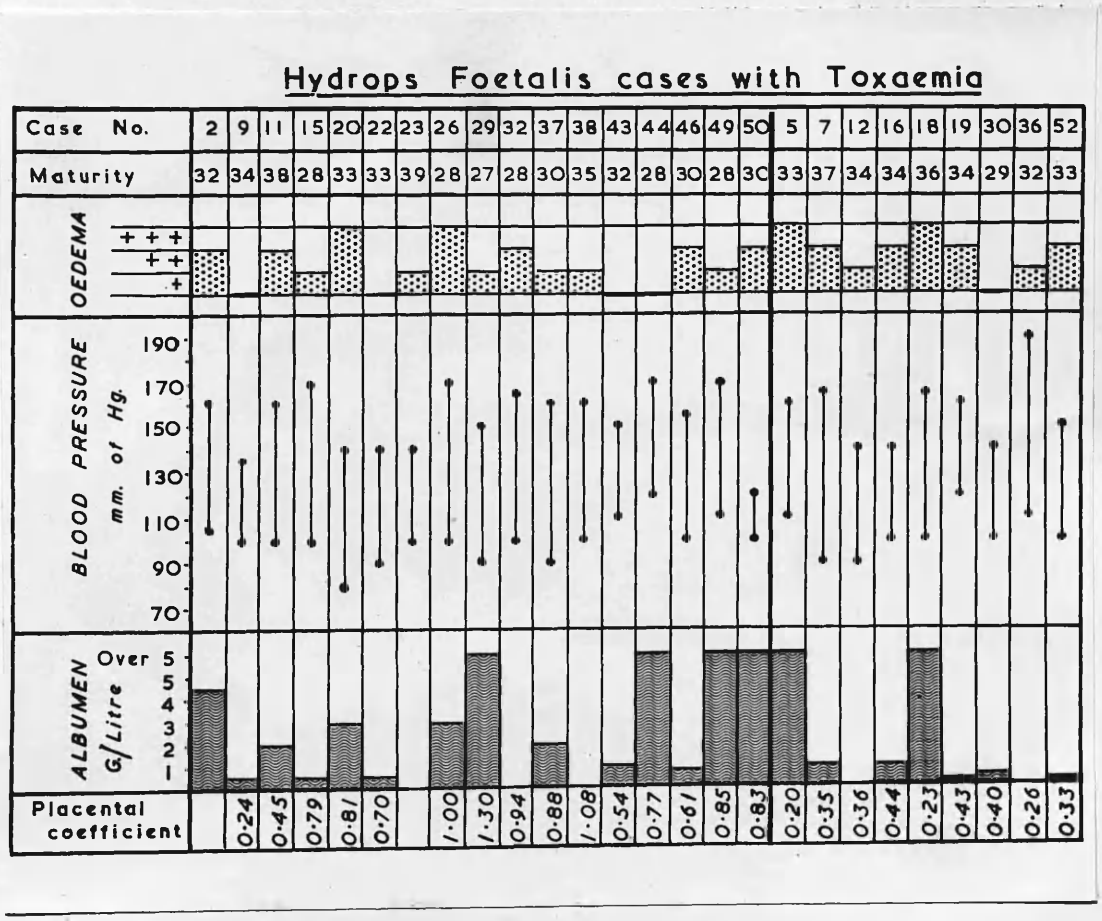

Table CI. Twenty-six cases of hydrops foetalis with toxaemia (50 per cent of total). The average placental coefficient in these cases was 0.62 whereas in the non-toxaemic cases the average placental coefficient was 0.38. The 9 cases (Number 5-52) to the right hand side of the heavy vertical line were cases of hydrops not due to erythroblastosis.

hyaline droplets in the cells of some of the proximal tubules. These changes were considered to be typical of hypertensive toxaemia of eclamptic type.

(c) Accidental Antepartum Haemorrhage (Abruptio Placentae).

Accidental antepartum haemorrhages occurred in 13 cases (25 per cent). In 5 of these there were also signs of toxaemia and they are included in group (b) above. In one patient the placenta was praevia but concealed haemorrhage had also occurred above the level of the lower segment attachment. Although its severity varied (Table CII), the bleeding was always sufficient to have real clinical significance; trivial shows (so-called minor accidental haemorrhages) were not included.

Counting only once cases with both accidental haemorrhage and toxaemia, the combined incidence of the two conditions was 34 (65 per cent).

The frequent occurrence of antepartum haemorrhage is of considerable interest. A figure for the expected incidence of this condition is not readily available for comparison but, in the annual statistics of the hospitals in question, the percentage of the total deliveries complicated by accidental haemorrhage ranges from 1.5 to 5 per cent. Many of these cases are emergency admissions to the hospitals, having been booked for delivery elsewhere, so it is

HYDROPS FOETALIS CASES WITH ACCIDENTAL ANTE-PARTUM HAEMORRHAGE

Case Number	Estimated blood loss (in ounces)		Toxaemia
	Revealed	Concealed	
Case 3	20	—	—
Case 6	Slight	8	—
Case 9	2	Slight	Present
Case 15	20 +	20	Present
Case 17	20	—	—
Case 24	Slight	Moderate	—
Case 31	50	10	—
Case 32	—	10	Present
Case 37	20	10	Present
Case 43	10	12	Present
Case 45	6	8	—
Case 47	30	10	—
Case 48	Moderate	—	—

Table C.II. Cases of accidental ante-partum haemorrhage complicating hydrops foetalis showing the estimated blood loss. The total of 13 cases gives an incidence of 25 per cent in the series. Five of the cases had toxaemia.

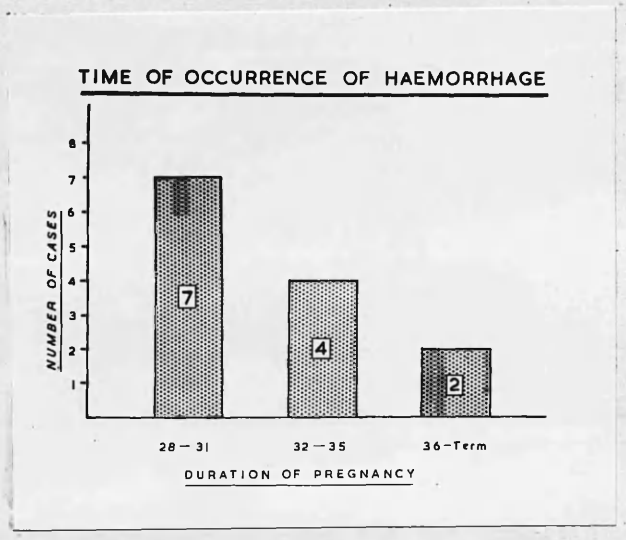

Fig. C8. Time of occurrence of haemorrhage in the 13 cases of hydrops foetalis complicated by accidental ante-partum haemorrhage.

probable that the overall incidence of this abnormality in the total obstetric population is less than this; textbooks put it at 0.5 per cent or less. However, even if the highest figure of 5.0 per cent be taken for comparison, the incidence of 25 per cent in association with hydrops foetalis is significantly raised (possibility of a chance finding = 0.000004).

Like the signs of toxaemia, antepartum haemorrhage in these cases tended to occur at an unusually early stage in pregnancy (Fig. C8). Often the clinician noted at the time that the uterus was larger than expected for the period of gestation and that it had a 'doughy' consistency on palpation. Indeed, in 2 patients a provisional diagnosis of hydatidiform mole was made and, in one this was still considered a possibility after radiological demonstration of a foetal skeleton. In another 2 cases it was recorded at the time of delivery that the placenta had appearances which resembled those of a hydatidiform mole (Fig. C9). This observation is by no means unique; Ballantyne (1902) quotes Jakesh (1878) who described the delivery of the placenta in these cases as being comparable to "the slow rolling forth of wool from an over-filled torn woolsack," a graphic description which could apply equally to the passage of a hydatidiform mole (Fig. C.10). Herrnberger (1940) studying case records in the literature also noted the difficulty in distinguishing between the two conditions.

Fig. C9. Enlarged view of hydropic placenta, showing bulky villi in upper part of picture which might be mistaken for early hydatidiform change.

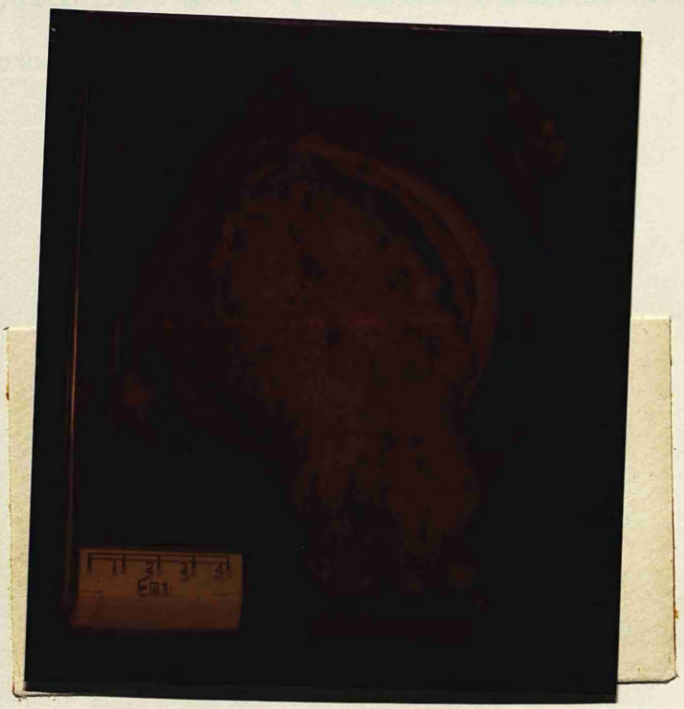

Fig. C.10. Like "The slow rolling forth of wool from an over-filled torn woolsack," is a description that could equally apply to the hydatidiform mole shown above.

As always with accidental antepartum haemorrhage, the problem occurs as to whether it is caused by toxaemia of pregnancy. In this connection it will be noted (Table CII) that signs of toxaemia were present in less than half the cases of haemorrhage yet the toxaemia incidence in the whole series was 50 per cent. It is therefore tempting to look for another cause. It seems possible, if not probable, that the separation of the placenta is a mechanical response to the bulk of the hydropic placenta and that the mechanism of haemorrhage is similar to that in hydatidiform mole - a condition which, as will be seen later, has yet other similarities.

THE CAUSE OF TOXAEMIA IN CASES OF HYDROPS FOETALIS

Since there seems no doubt that pregnancy toxaemia of quite severe degree is commonly seen when the foetus is hydropic, the question arises as to the cause and effect relationship. Older writers, as discussed by Ballantyne (1902) for example, considered that the oedema of the foetus and placenta was secondary to, and caused by, the maternal illness. This view is no longer tenable, if only because the foetus is not affected in the common type of pre-eclampsia seen in primigravidae and in other states when the mother becomes grossly oedematous. Modern knowledge makes it necessary to regard the foetal condition as causing the maternal disturbance and it might so operate by one of three mechanisms :-

(i) A relatively massive transfer of foetal blood (or its breakdown products) into the maternal circulation, or the side effects of the antigen - antibody disorder association with Rhesus incompatibility, might in themselves cause the toxaemia in the mother. In this connection, Jann (1954) went so far as to suggest that the maternal signs are caused by a pressor substance liberated by the foetal kidneys in response to haemolysis.

(ii) Excessive distension of the uterus, caused partly by the bulk of the foetus and the placenta and partly by hydramnios which sometimes complicates hydrops foetalis, could be responsible, according to one present day theory of the aetiology of pre-eclampsia.

(iii) Abnormal activity of the placenta itself might cause a maternal upset - as in the case of hydatidiform mole.

These three mechanisms are discussed in turn.

1. An antigen-antibody reaction.

Although there is a certain amount of inconclusive evidence that a sudden transfusion of foetal blood into the maternal circulation does sometimes occur, producing a serious and dramatic reaction, the signs, as emphasized earlier, are quite different from those of pre-eclampsia. The complication is, moreover, rare. It may be added that in 3 of our cases in which foetal hydrops was complicated by severe toxaemia, the maternal blood was examined for foetal haemoglobin with negative results.

The toxaemia-like response of so many mothers is very unlikely to be the result of iso-immunisation because it is fairly clearly established that the signs are only found when the foetus is hydropic. Blood destruction is equally extensive in other severe forms of erythroblastosis but it does not cause toxaemia.

It is not always realised that some 25 per cent cases of hydrops foetalis are not caused by haemolytic disease - although Ballantyne (1898 and 1902) expressed the belief that the condition, like dropsy arising after birth, could have several causes. In one of Seeger's (1670) cases he attributed the disease to the mother drinking large quantities of beer! This sort of aetiology may not now be accepted but it remains necessary to recognise that hydrops foetalis not resulting from iso-immunisation is by no means uncommon. There are 11 such cases among the 52 reported here and toxaemia complicated 9 of these pregnancies. In each case the foetal and maternal bloods were exhaustively examined to exclude all forms of iso-immunisation. The number of cases is small but the findings, when taken in conjunction with other evidence, offer strong support for the view that the cause of toxaemia is not the haemolytic disease but something connected with the hydropic change in the foetus and placenta (Figs. C.11 and 12).

2. Over-distension of the uterus by hydramnios and bulky products of conception.

For this to be considered as the operative mechanism in the production of the toxaemia three questions require to be answered :- (a) Does hydrops foetalis cause hydramnios? (b) Does hydramnios 'per se' predispose to toxaemia? (c) Does over-distension of the uterus predispose to toxaemia?

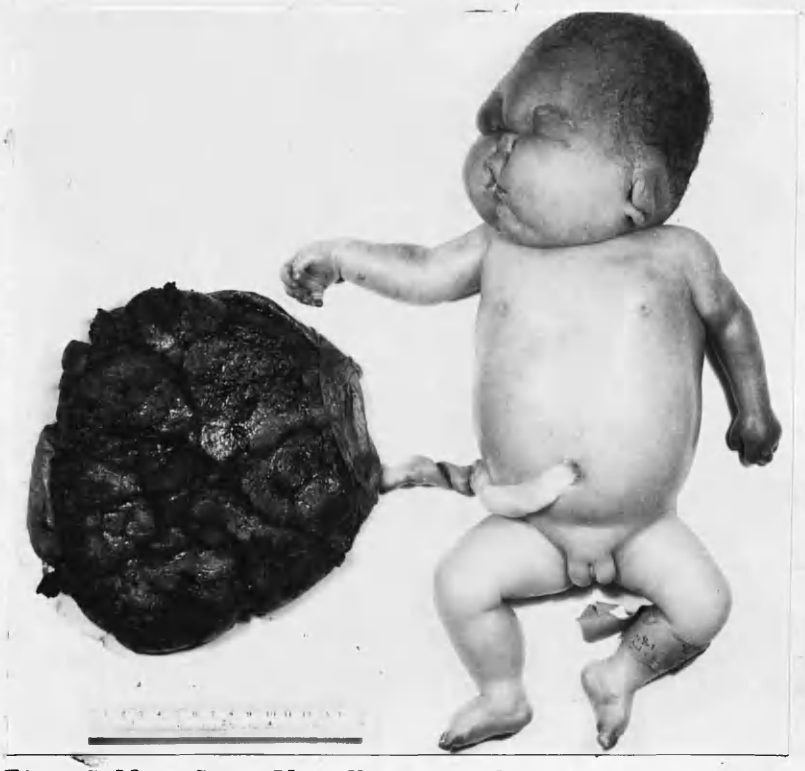

Fig. C.11. Case 51. Hydropic foetus and placenta not due to haemolytic disease. (Baby 5 lbs. 15 ozs. Placenta 1 lb. 14 ozs. Placental coefficient 0.37).

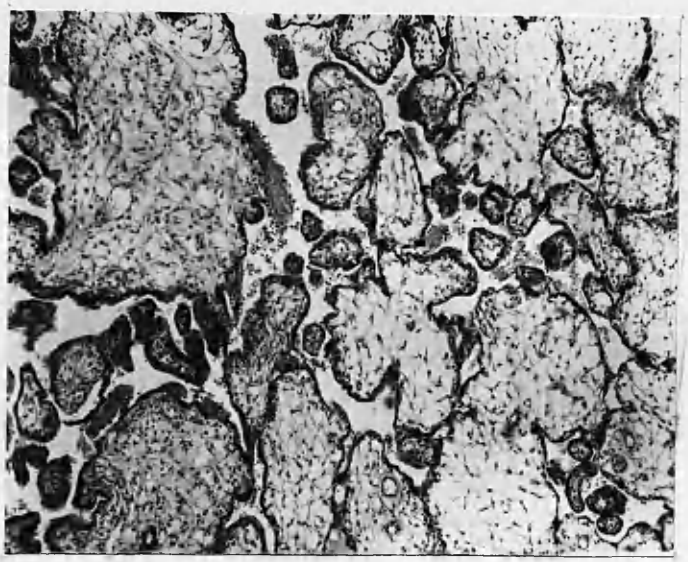

Fig. C.12. Section from placenta of case of hydrops foetalis not due to haemolytic disease (Case 36).

(x70)

(a) The increased incidence of hydramnios in association with hydrops foetalis is recorded by Ballantyne (1902) and by Henderson (1942) but the latter and Macafee (1950) both point out that the grossly oedematous foetus with its large placenta may lead to a mistaken diagnosis of hydramnios. Personal experience confirms that this is a real problem and that it can be extremely difficult to say on clinical examination whether hydramnios is present or not. Nevertheless, in 3 cases of this series measured quantities of more than 3 pints of liquor were removed at amniotomy while in 4 others a clinical impression of hydramnios was supported by a torrential gush of liquor when the membranes ruptured. The mechanism causing the hydramnios is almost certainly the inability of the foetus to swallow owing to the gross oedema of its cheeks, lips and fauces; unless circumoral oedema is gross the amount of liquor is usually normal (Scott and Wilson, 1957) (Figs. C.13 and 14). It can be concluded that hydrops foetalis can under certain circumstances cause hydramnios and that, even in those cases where it does not, the increased bulk of the foetus and placenta is likely to lead to excessive uterine distension.

(b) It is commonly assumed that hydramnios <u>per se</u> can cause, or favour the development of, pre-eclampsia. Theobald (1955), however, is critical of this view and emphasises the remarkable lack of statistically acceptable evidence. He points out that hydramnios is often

Fig. C.13. (From Ballantyne) Such gross facial oedema would clearly interfere with swallowing. (By courtesy of the publishers. Green Edinburgh).

Fig. C.14. Case 49. of the present series showing the same facies as Ballantyne's case.

secondary to factors which in themselves may determine the occurrence of toxaemia by some mechanism other than uterine over-distension.

Macafee (1950) in a review of 147 cases of hydramnios reports a 24 per cent incidence of toxaemia but in his original paper he does not mention which of the cases occurred in association with other factors which, in themselves, are known to predispose to pre-eclampsia. This point, however, he elaborated later in a personal communication quoted by Theoblad (1955).

At Mill Road Maternity Hospital, Liverpool, during the 8 years 1948 - 1955, there were 169 cases of hydramnios, 144 amongst women booked for hospital delivery for other reasons and therefore under continual observation. The criteria used for diagnosing hydramnios were those reported previously (Scott and Wilson, 1957):- (i) the recording of clinical evidence of an excessive amount of liquor by two independent observers on at least two separate occasions during late pregnancy, or (ii) the recovery of more than 1,500 ml. of liquor at amniotomy.

The total number of cases of toxaemia in this series was 27 (16 per cent) in comparison with Macafee's 24 per cent but our diagnostic criteria may have been different from his. There were another 30 patients in our series who developed gross oedema, mainly of the lower limbs, but showed no other sign of toxaemia; these were excluded.

The cases of hydramnios were further analysed by dividing them into two groups (i) those in which there was an associated factor which could have predisposed to toxaemia by some mechanism other than simple uterine over-distension, and (ii) those in which the hydramnios was not obviously associated with any condition which in itself might have caused toxaemia.

Group (1)

In this category were 13 cases of twin pregnancy, 4 of hydrops foetalis and 4 pregnancies in diabetic women. This makes a total of 21 pregnancies of which 11 (52 per cent) were complicated by toxaemia.

Group (ii)

The remaining 148 cases are placed in this group although the cause of hydramnios was not discovered in 98. The underlying cause in the other 50 cases (details of which are given elsewhere, Scott and Wilson 1957) was a gross foetal malformation. Only 16 of the 148 pregnancies (11 per cent) were complicated by toxaemia. 43 of the patients in this group were primigravid and 105 were multigravid. The expected incidence of toxaemia in this hospital's obstetric population is 10.7 per cent in primigravidae and 7.9 per cent in multigravidae (see statistics for Hospital 'D' in the report by Gemmell et al. 1954). It can be calculated from these figures that the number

of cases of toxaemia among this group of 148 patients would be expected to be 13. The difference between the expected and actual number of cases of toxaemia is not statistically significant.

From this analysis it may be concluded that whereas review of all cases of hydramnios does show an increased incidence of toxaemia, this is only because of the inclusion of cases of multiple pregnancy, maternal diabetes and hydrops foetalis. There is no evidence that hydramnios unassociated with these states predisposes to toxaemia.

(c) If hydramnios *per se* is not associated with a significantly raised toxaemia incidence the main evidence for supposing that uterine over-distension can cause pre-eclampsia becomes invalid. The only other causes of over-distension which are quoted in support of this theory are multiple pregnancy, hydatidiform mole and hydrops foetalis; in all of these there is an alteration in placental function which, as will be shown later, is a more likely aetiological factor in the toxaemia associated with these conditions.

3. Abnormal Placental Activity.

The third possibility remains - that some abnormal activity by the placenta in hydrops foetalis leads to the toxaemia. The fact has been stressed that the placenta in association with hydrops foetalis is not merely enlarged by passive oedema but that there is regeneration with appearance of primitive double-layered trophoblast. The whole picture is one of unusual activity for the stage of pregnancy.

The view that it is the placenta itself which is responsible for the development of signs of toxaemia is supported by a more detailed study of the "placental co-efficient," previously mentioned. In the series of cases of hydrops foetalis forming the basis of this communication the average placental co-efficient in those patients who showed signs of toxaemia was 0.64 whereas it was only 0.37 in those who remained well. This finding agrees with the observations of Kloosterman (1947) whose comparable figures were 0.75 and 0.47. If the incidence of toxaemia is considered when the cases of erythroblastotic hydrops are grouped according to their placental co-efficient (Fig. C.15) the relationship of toxaemia to the relative increase in the placental bulk is even more strikingly shown. The fact that the likelihood of toxaemia is dependent on the presence of a placenta which is heavy in relation to foetal weight suggests that it is related to the placental change being one of active hyperplasia and not merely one of passive oedema proportional to the foetal dropsy (Fig. C.16). This is further borne out by evidence of increased functional activity of the chorion in these cases, as measured by chorionic gonadotrophin excretion.

Quantitative Aschheim-Zondek tests were carried out in the last 6 cases of hydrops foetalis seen. The duration of the pregnancies at the time of the test varied from 26 to 35 weeks, the assay being made on the first morning specimen of urine. The results were as follows :-

Hydrops Foetalis	Aschheim Zondek Reaction According to Dilution of Urine					Toxaemia of Pregnancy
	1:0	1:25	1:50	1:100	1:200	
Case 1.	+	+	+	+	-	Severe.
Case 2.	+	+	+	-		Moderately severe.
Case 3.	+	+	+	+		Severe.
Case 4.	+	+	+	+	-	Severe.
Case 5.	+	+	+	-		Absent except for oedema.
Case 6.	+	+	+	+		Severe.

Although the tests were carried out late in pregnancy, at a time when the excretion of gonadotrophin is normally low, a positive reaction was obtained with urine diluted 1:100 in 4 cases, and with urine diluted 1:50 in the remaining 2 cases. Moreover, there was a suggestion of a correlation between the intensity of the reaction and the occurrence of toxaemia.

By way of control, similar studies were carried out simultaneously on the urine of 16 pregnant women suffering from rhesus incompatibility but whose babies proved not to be hydropic. The duration of

TOXAEMIA INCIDENCE IN

ERYTHROBLASTOTIC HYDROPS IN

RELATION TO PLACENTAL CO-EFFICIENT

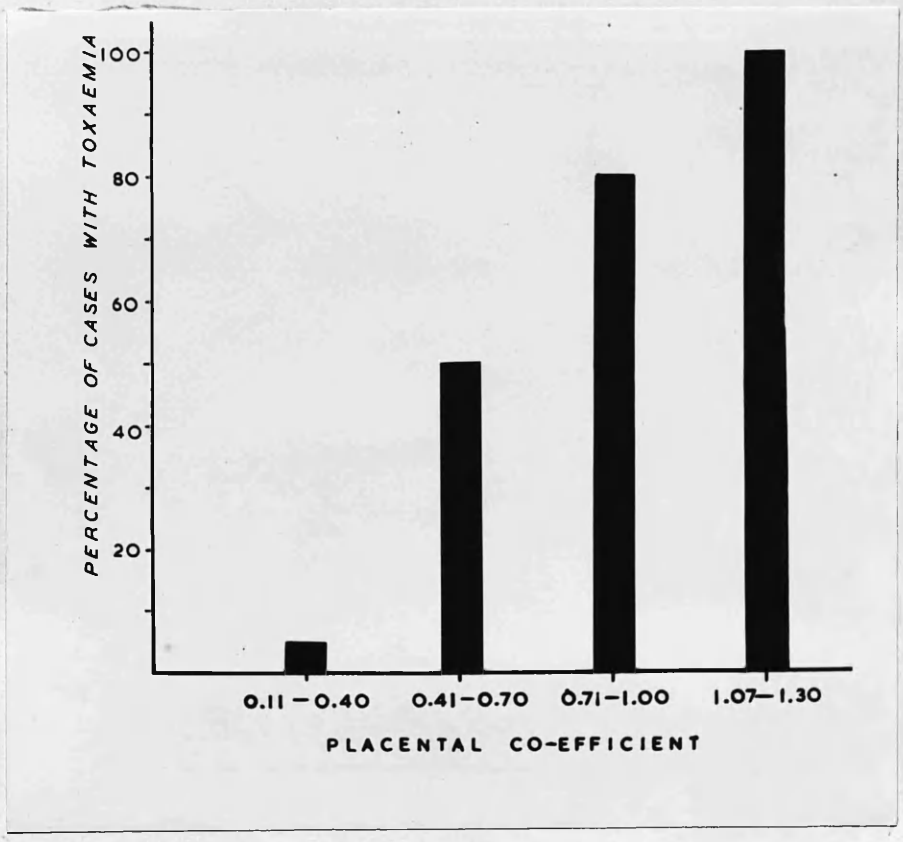

Fig. C.15. Percentage incidence of toxaemia in cases of erythroblastotic hydrops when grouped according to the placental co-efficient.

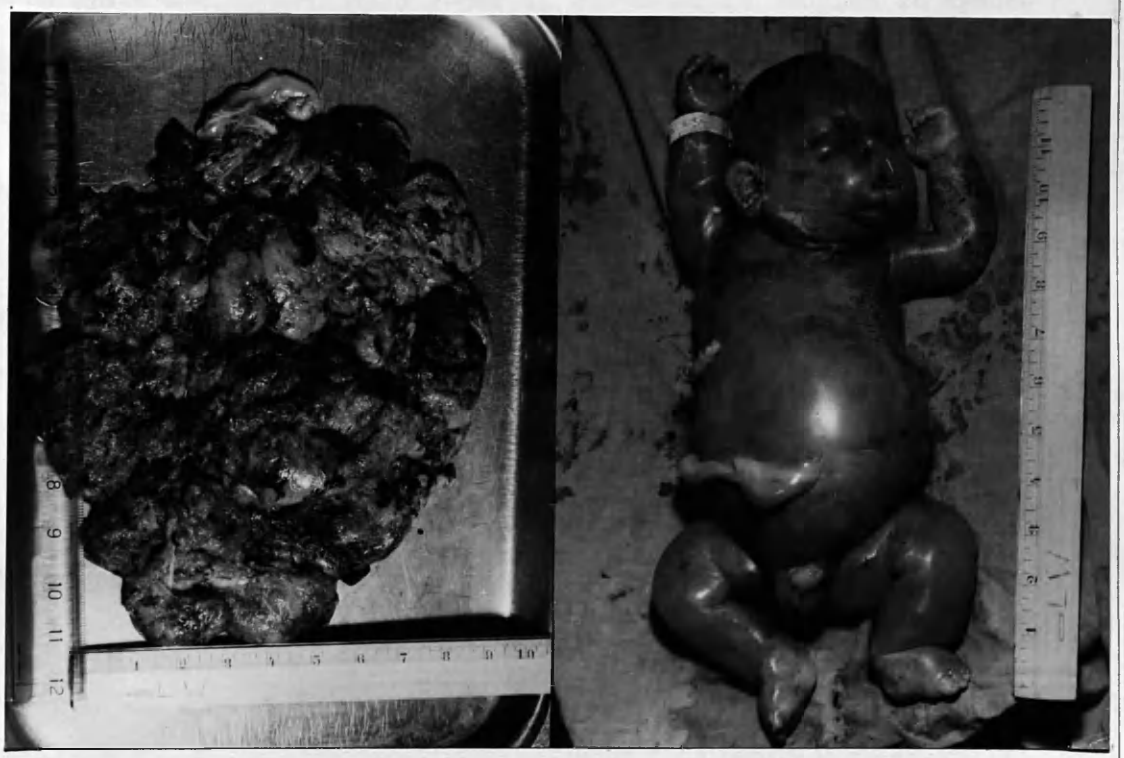

Fig. C.16. Case 49. Hydropic foetus and placenta due to rhesus sensitisation haemolytic disease. Baby 5lbs., placenta 4lbs. 4ozs. Placental coefficient 0.85. Severe toxaemia. Although foetus and placenta were photographed separately, it can be seen that the magnification is the same.

their pregnancies at the time of the test varied from 28 to 38 weeks. None of these cases gave a positive test when the urine was diluted 1:25, and none were complicated by toxaemia.

Herrnberger (1940) and Zsigmond (1941) also recorded the finding of a high gonadotrophin production in similar cases.

In view of these observations it is not surprising that theca lutein cysts are occasionally found in the maternal ovaries in association with hydrops foetalis. Burger (1947) reviewed 4 such cases. In one of Jann's (1954) series of hydrops foetalis, laparotomy was performed for a pelvic tumour discovered on examination during the puerperium; the tumour proved to be bilateral ovarian theca lutein cysts. Cases have also been reported by Schultheiss-Linder (1942) and Lermer et al. (1958).

As the evidence collects it becomes increasingly apparent that the clinical similarity between hydrops foetalis and hydatidiform mole noted earlier, is accompanied by a pathological and functional similarity. This similarity extends even to the histological features of the chorion in the two conditions for, as Hellman and Hertig (1938) pointed out, both are characterised by :- (i) hydropic swollen villi with relatively avascular cores (ii) excessive trophoblastic activity, (iii) vacuolization of the epithelial cells (Figs. C.17 and 18). In hydrops placentae, as in hydatidiform mole, the picture varies between one in which the increased cellular activity is the prominent feature and one in which the villous oedema predominates (Figs. C.17 and 19).

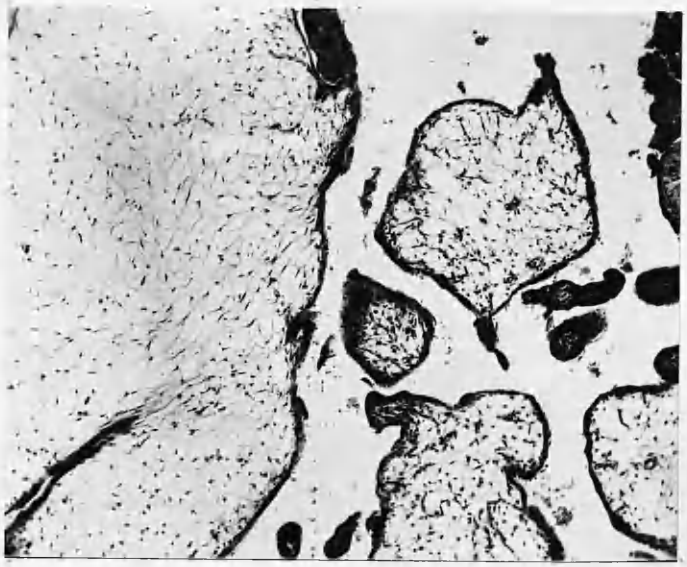

Fig. C.17. Placenta from case of hydrops foetalis due to haemolytic disease. (Case 50) showing a distinct similarity to hydatidiform mole. (Fig.C.18).

(x70)

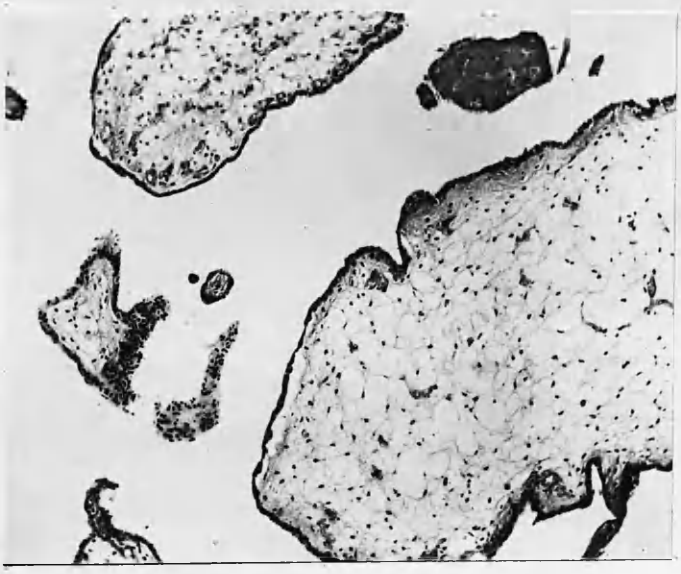

Fig. C.18. Section of hydatidiform mole; note similarity to Fig. C.17. illustrating erythroblastotic hydrops placenta of dropsical type.

(x70)

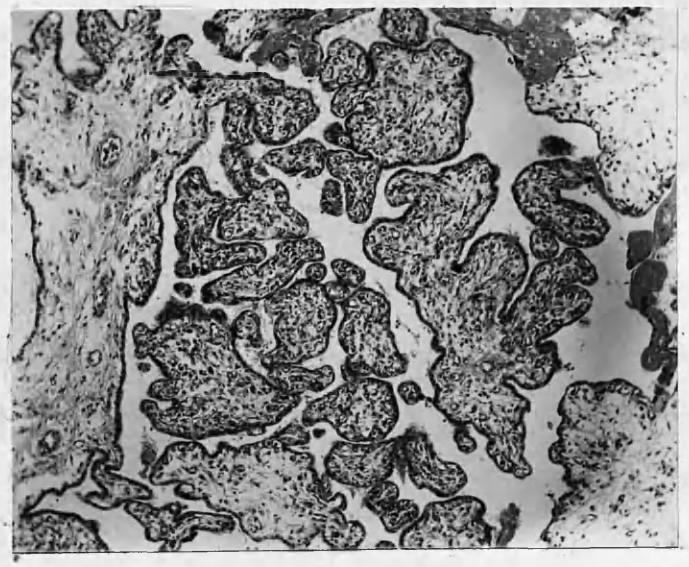

Fig. C.19. Section of placenta from case of hydrops foetalis due to erythroblastosis (Case No. 49). The cellularity is in some areas more marked than the dropsical change. (See Fig. C4. for high-power view).

(x70)

FEATURES OF THE TOXAEMIA ASSOCIATED WITH HYDROPS FOETALIS AND HYDATIDIFORM MOLE

Although an association between toxaemia and hydatidiform mole has long been assumed and described, its existence was not established statistically until the work of Page in 1939. He found that mole formation increased the incidence of toxaemia 8 times in pregnancies carried beyond the third month - a figure very similar to that obtaining in the cases of hydrops foetalis reviewed here.

The toxaemic syndrome which frequently complicates hydrops foetalis and hydatidiform mole has some special features which raise the question as to whether it represents a particular form of pre-eclampsia and whether pre-eclampsia is a single disease entity.

In the first place the syndrome appears earlier in pregnancy than is usual for pre-eclampsia as seen in the otherwise normal gravida. Moreover, the manifestations of hypertension, albuminuria and oedema are often of severe degree. Despite this, however, the patients rarely have eclamptic fits. Jann (1954) collected 124 cases of pre-eclampsia associated with hydrops foetalis from the literature and in none had the patient had fits. The same is true of 26 cases described here, even in the case of the patient who died and in whom histological changes "typical of eclampsia" were found in the liver and kidneys at autopsy.

Similar observations with regard to the infrequency of fits in cases of toxaemia associated with hydatidiform mole are made by Acosta-Sison (1956, 1957), and Theobald (1955). The latter says that eclamptic convulsions have never been seen as a complication of hydatidiform mole by any living English author, but Chesley et al. (1946) recorded a case in America and reviewed other alleged cases but not all of these had fits. Acosta-Sison records 2 fatal cases in which, despite the absence of fits in life, histological features of eclampsia were found at autopsy. These experiences tally closely with the personal one described above in relation to hydrops foetalis.

SIMILARITY OF HYDROPS FOETALIS CHANGES TO SOME EFFECTS OF DIABETES MELLITUS.

Certain aspects of the changes discovered occurring in association with hydrops foetalis bring to mind a similarity to features of pregnancies complicated by diabetes mellitus. There is first the demonstration by Smith and Smith (1940), confirmed by Loraine (1949), that the gonadotrophin output is often abnormally high in diabetic pregnancies. It has also been established for diabetes that the placenta sometimes shows unusual persistence or re-awakening of trophoblastic activity, that the placental index may be high and that this is related to the clinical presence of toxaemia (ten Berge and Van Assen, 1947).

Babies born of diabetic mothers sometimes show evidence of extra-medullary haemopoiesis (Potter, 1953) - a feature of erythroblastotic hydropic foetuses. Hydropic foetuses in turn may have islet cell hyperplasia of the pancreas such as is commonly found in the babies of diabetic mothers (Potter, 1953, Woolf and Jackson, 1957). Adrenal corticoids are not normally present in the liquor amnii but Hoet (1954) records the findings of such substances in the liquor of conceptuses of diabetic women. The level of corticoids is also raised in erythroblastotic babies and is related, apparently, to the severity of the disease (Klein et al, 1954). Hoet suggests that this is the underlying

common factor. Other similarities between hydrops foetalis and the baby of the diabetic were noted by Miller and Wilson as long ago as 1943.

Finally attention is drawn to an observation made on our cases and also noted by Hoet. (1954), namely that, at the time of the development of hydropic changes in a foetus in utero, the mother sometimes shows evidence of a disturbance of carbohydrate metabolism. Although this last matter requires further investigation, all the evidence taken together points to the occurrence, in pregnancies complicated by hydrops foetalis, of a complex and hitherto unsuspected hormonal disturbance which would seem to bear a close resemblance to that obtaining in pregnancies in diabetic mothers.

THE MECHANISM OF THE CHANGES OCCURRING WITH HYDROPS FOETALIS

It is at present assumed that in erythroblastotic hydrops foetalis, the generalised oedema is a manifestation of cardiac failure which is in turn due to the severe foetal anaemia. (Allen and Diamond, 1957) This is probably a correct assumption though other factors, such as the excess of adrenal corticoids may contribute to a lesser degree. There are, however, other features, previously referred to, which can not be explained on a simple basis of cardiac decompensation. Firstly there is the hyperplasia of the placenta with regeneration of the trophoblast and secondly the hyperplasia of the islets of Langhans in the foetal pancreas. Both of these manifestations suggest the operation of some growth-promoting hormonal factor - especially when considered in the light of the similar changes found occurring in diabetes.

In considering possible mechanisms of such a hormonal effect it is necessary to review the manner in which additional erythropoiesis develops in response to the severe haemolytic anaemia. It is frequently assumed that this is merely a simple effect of anoxia on the tissues concerned. As Whitby and Britton (1957) point out, however, there is experimental and clinical evidence to suggest that the erythropoietic

response is not merely a simple local one but is mediated through a hormonal mechanism probably initiated by an effect of the anoxia on some controlling centre. Reissmann (1950) by inducing anoxia in one of a pair of parabiotic rats observed that erythropoiesis occurred in the other animal. Erslev (1955) also supported the idea of a hormonal effect and recently it has been found that ablation of the anterior pituitary in polycythaemia reduces red cell production.

It seems probable that if a growth hormone promotes the erythropoiesis, its action is not entirely specific and it is responsible for the placental and pancreatic islet growth. Conversely, in the diabetic patients it would appear likely that the occurrence in the foetus of extra-medullary haemopoiesis, in addition to pancreatic islet, placental and general somatic growth, is a growth hormone effect. Bain (1958) has recently observed during autopsies following perinatal deaths in over-weight babies, that many of these show considerable abnormal extra-medullary haemopoiesis. In this connection it is interesting to speculate whether excessive growth of the foetal body in hydrops does not occur, in addition to passive oedema.

THE AETIOLOGY OF THE PRE-ECLAMPTIC SYNDROME

In discussing the underlying cause of the maternal toxaemia which occurs in association with hydrops foetalis and hydatidiform mole, care has so far been taken to avoid the matter of the aetiology of pre-eclampsia in general. The reason for this is a very real doubt as to whether the statistician's and clinician's arbitrary definition of "pre-eclampsia" covers more than one disease entity. However, the results of this investigation do have some bearing on views as to the aetiology of this obscure maternal reaction to pregnancy.

The evidence presented here does not in any way lend support to the utero-renal reflex theory, so persistently advocated by Sophian (1953), in which uterine over-distension is regarded as a major aetiological factor in pre-eclampsia. On the contrary, the analysis of the cases of hydramnios confirms Theobald's suspicion that the adherents to the uterine distension theory have been too ready to reach assumptions which are not supported by controlled observations. Next it may be stated that the findings and arguments presented here, which go to show that one particular group of cases of the pre-eclamptic syndrome is dependent on placental changes, are not incompatible with the placental ischaemia theory of toxaemia, associated particularly to-day with the names of Page (1953) and Bastiaanse (1949 and 1950).

Placental changes in structure, function or both, appear to be a feature of many cases of pre-eclampsia but the changes are not always the same. Indeed, they appear to fall into two distinct and apparently contradictory classes. On the one hand there is the placenta in which the normal ageing process fails to take place and in which the trophoblast (and especially Langhans' layer) is hyperplastic. This type of change is a feature of pre-eclampsia as it occurs in association with hydrops foetalis, hydatidiform mole, maternal diabetes and possibly multiple pregnancy and is frequently, if not always, associated with an excessive production of gonadotrophin. On the other hand, the placenta in many other cases of toxaemia occurring apart from the conditions mentioned above, often shows evidence of infarction and acceleration of the normal ageing process with, presumably, a decrease in functional activity. Histologically the amount of active trophoblastic tissue is reduced in these cases and this appearance tends to be associated with a diminution in the production of progesterone (Russell et al.1957 and Paine 1957).

It could be rationally postulated that whatever may be the adrenal and pituitary hormone inter-reactions bringing about its manifestation, the maternal disturbance labelled "pre-eclampsia" results primarily from an imbalance between the two different trophoblastic elements of the placenta. In one group of cases the Langhans' layer, the

gonadotrophin producing cells (Wislocki et al, 1948) is over-active while in the second group the syncytium, the steroid hormone producing zone, is under-active. The latter mechanism may operate when the placenta shows evidence of premature senility or degeneration - changes which are for the present assumed to precede and cause the pre-eclampsia. They could, however, be the result of hypertension and not its cause. This, in fact, is a conclusion reached independently by Burstein and others (1947) whose study of placentae from an unselected series of cases of toxaemias led them to postulate that all degenerative changes are, like the hepatic and renal lesions, secondary to hypertension whereas chorionic over-activity evidenced by "syncytial budding" might have an aetiological role in the disease.

The idea that the toxaemic process is associated with an imbalance of the steroid and gonadotrophic hormones secondary to an underlying alteration in the trophoblastic components is similar to that which Smith and Smith (1937, and 1940) postulated, but they arrived at it from an entirely different approach. Though the Smiths' findings have received a considerable measure of confirmation by different workers such as Loraine (1949b); Loraine and Mathew (1950) and Govan (1952) yet definite proof or disproof of their validity and relevance has been extremely elusive. There does not, however, appear to have been a systematic attempt to integrate the various hormonal changes with the trophoblastic anatomy.

THE PLACENTA AND POST-PARTUM ECLAMPSIA

The occurrence of post-partum eclampsia is the fact most quoted against a placental origin for pregnancy toxaemia and it is therefore worthy of particular consideration.

With improved standards of antenatal care, and the early recognition and treatment of pre-eclampsia, the proportion of cases (not the total number) in which eclamptic fits occur for the first time after delivery is increasing. In the Liverpool Maternity Hospital and Mill Road Maternity Hospital there were 92 cases of eclampsia during the 10 years 1948 to 1957. In 29 of these (32 per cent) the first fit occurred after delivery. The fits, however, always commenced within 14 hours of the completion of the third stage (Fig. C.20). There were other cases in which fits or coma occurring later were at first suspected as being evidence of eclampsia. In every one, however, subsequent events and investigations revealed another cause - epilepsy, phaeochromocytoma, cerebral venous thrombosis, cerebral haemorrhage and the like. This experience confirms the findings of Page (1948) and of Hofmeister and Brown (1953). Page collected the figures from 3 large maternity units in the U.S.A. and showed that the onset of eclampsia fell steeply and progressively with each 12 hours after delivery, its incidence at 48 hours or more being negligible. From Page's figures and the present analysis it may be concluded that fits beginning more

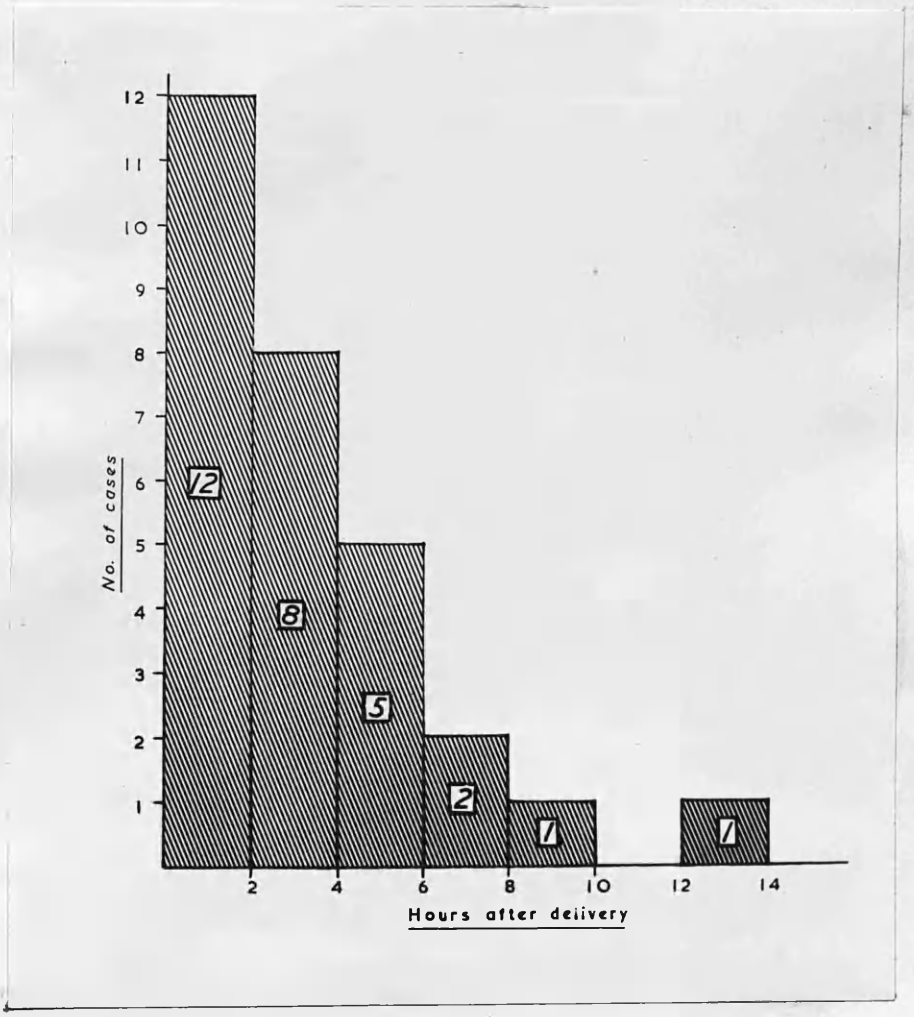

Fig. C.20. Time of occurrence of first fit in 29 cases of post-partum eclampsia.

than 24 hours after delivery are rarely if ever caused by eclampsia. It is difficult to understand Browne's (1958) recent statement that 10 per cent of all cases of eclampsia occur 2 or 3 days after delivery. Browne is so impressed by this that he advances a theory to the effect that the placenta protects the patient from eclampsia, and that it is only when its function in this respect is deficient, or when the placenta is removed, that fits occur. Pre-occupation with cases of "eclampsia" occurring a considerable time after delivery almost certainly owes its origin to observations made when diagnositic facilities were more limited than today, and when there was little or no knowledge of the other causes of puerperal fits mentioned above. Modern clinical experience makes it unnecessary to invoke a theory such as Browne's. Indeed, to do so increases the difficulty of explaining why eclampsia never occurs except in the pregnant or recently pregnant individual.

If it be accepted that post-partum eclampsia only arises within 48 hours, and usually within 12 hours of delivery, its occurrence does not run counter to any concept which postulates the placenta playing a positive aetiological role in its causation. The tumultuous activity of the uterus during the last stage of labour could well encourage a substance of placental origin to enter the maternal circulation to exert its ill effect within the succeeding few hours. This is said to happen, for example, in regard to thromboplastin and the production

of fibrinogen depletion. Again, the physical and nervous stress of parturition and of the immediate post-partum period could, by raising the blood pressure or producing a "stress" reaction in the adrenal, initiate fits in a woman already predisposed to them by a pre-existing toxaemic process.

IS "PRE-ECLAMPSIA" AN ENTITY ?

At several points in this paper doubt has been expressed as to whether or not all patients labelled as suffering from "pre-eclampsia" do in fact have the same disease. In recent years there has been an increasing demand for the application of definite arbitrary standards to the diagnosis of the condition. These were introduced mainly for statistical purposes but have tended to hinder a rational approach to the elucidation of the problem. There is no other disease in medical practice the diagnosis of which is made automatically on the presence of 2 out of 3 physical signs. Bearing in mind the "occult oedema," the lability of the blood pressure and the changes in the peripheral capillary bed in pregnancy (Landesman, 1954, 1958) which are recognised physiological reactions to pregnancy, is it surprising that oedema, hypertension and albuminuria are common in pregnancy and are they reliable signs on which to diagnose a specific disease? Govan et al. (1951) have produced suggestive evidence that in toxaemic hypertension of pregnancy different types of hypertension occur, depending upon whether or not there is a related elevation of gonadotrophin production. Similar doubts exist in regard to eclampsia. Even the evidence of the morbid anatomists is not necessarily conclusive; the renal and hepatic changes regarded as typical of eclampsia cases may be simply the result of a hypertensive process superimposed on the physiological pregnancy changes in the capillary bed.

It may well be, therefore, that the importance of the observations reported here lies not in any bearing they may have on a particular aetiological theory of pre-eclampsia but in their support for the concept that the clinical syndrome, at present automatically labelled "pre-eclampsia" by arbitrary standards, may be a manifestation of more than one disease, or it may be one disease with different sub-groups and with a variable underlying cause. On the evidence so far available it can be stated that from a hormonal, pathological and clinical standpoint the toxaemias associated with hydrops foetalis and hydatidiform mole come into one category which could be regarded as a state of "hyper-placentosis." Further investigation may confirm the suspicion that the toxaemia associated with diabetes mellitus and multiple pregnancy belong to the same category. It is even possible that certain cases of pre-eclampsia which occur without any obvious gross abnormality in the mother or her baby are also a manifestation of "hyper-placentosis."

A case encountered recently supports this idea :-

> Mrs E.L. gave a history of 3 pregnancies and 1 miscarriage, none of which had been complicated by toxaemia. She was admitted to hospital when 37 weeks pregnant with signs of severe pre-eclampsia. The highest blood pressure reading was 180/100; oedema was present and albuminuria rose to 20 grams per litre. The foetal heart sounds disappeared shortly after admission but despite this the pre-eclamptic signs continued to increase in severity. Labour was induced by rupture of the membranes and oxytocin drip infusion. A non-hydropic macerated foetus weighing 5 lbs. 8ozs. was delivered followed by a large placenta

weighing 2 lbs. 11 ozs. The placenta was in every respect identical to that found in hydrops foetalis (Figs. C.21., C.22., C.23., and C.24). The mother's blood group was A.Rhesus positive and there was no serological evidence of any form of iso-immunisation.

If the concept of "hyperplacentosis" is accepted as the underlying explanation of one form of pre-eclampsia it is not necessarily applicable to all. There are many cases in which pre-eclampsia is characterised by a small and under-active placenta but whether this is a cause or an effect remains to be established.

Strachan, in a thesis submitted for the Doctorate of Medicine of this University, as long ago as 1913 said - "Is the condition that we at present call eclampsia a single disease entity or is it not possible that various seperate conditions characterised clinically by fits are being named indiscriminately Eclampsia?"

More recently Theobald (1955) has said "there is not one eclampsia but several." The same is surely true of pre-eclampsia. Might not more progress be made in the understanding of the "disease of theories" if our present definition of pre-eclampsia were regarded as a "theory of diseases?"

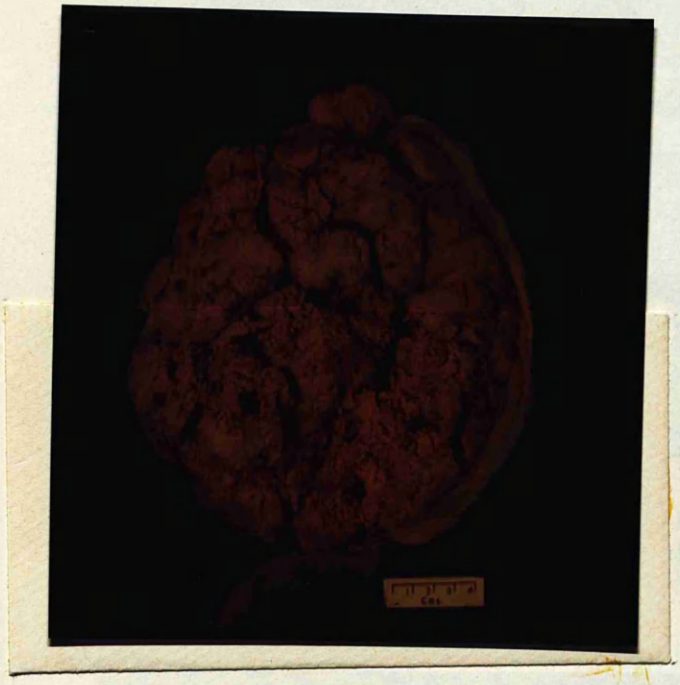

Fig. C.21.

Fig. C.22.

Figs. C.21. and 22. Placenta from Mrs E.L. Case of "hyperplacentosis" with severe toxaemia. 2lbs. llozs. placenta of hydropic type associated with a non-hydropic 5lbs. 8ozs. foetus. Note appearance of the large and prominent villi.

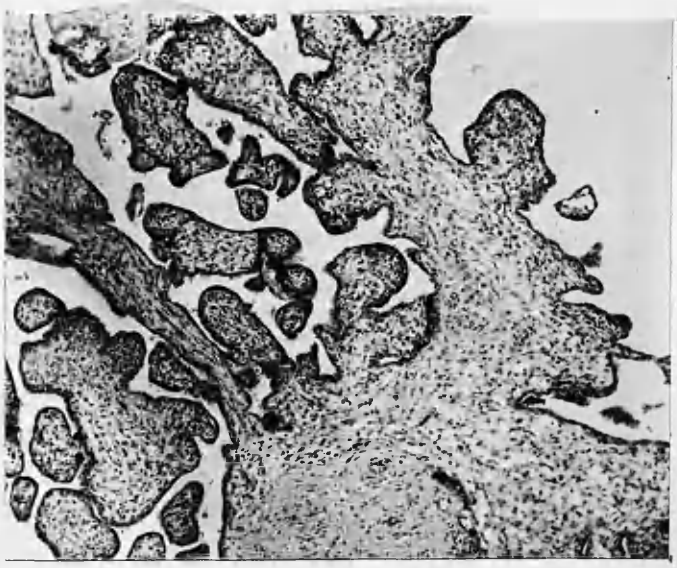

Fig. C.23. Section from placenta of Mrs E.L. - Case of "hyperplacentosis." Note cellularity of villi and immaturity of trophoblast for 37 weeks. See Fig. C.24.

(x70)

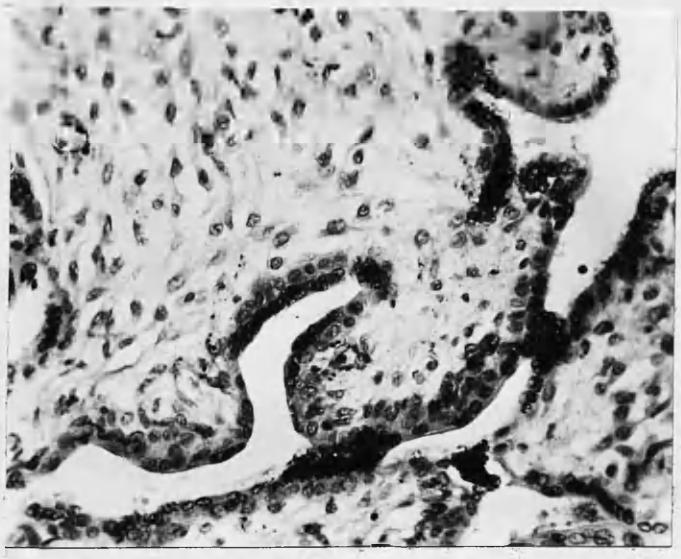

Fig. C.24. High power view from placenta of Mrs E.L. Case of "hyperplacentosis," showing presence of Langhans layer at 37 weeks. (See Fig. C.23).

(x290)

Summary :-

1. The changes which occur in the placenta in association with hydrops foetalis are described. There is an active hyperplasia with regeneration of Langhans layer of the trophoblast in late pregnancy.

2. Maternal illnesses occurring in pregnancies complicated by rhesus iso-immunisation are reviewed. There is no increase over the expected incidence of toxaemia in these cases provided the foetus is not hydropic.

3. In 26 out of 52 cases of hydrops foetalis an illness indistinguishable from toxaemia of pregnancy afflicted the mother.

4. The possible causes of the toxaemia in these cases are discussed. The mechanism is unlikely to be related to overdistension of the uterus as a review of a series of 148 cases of uncomplicated hydramnios showed no significant increase over the expected incidence of toxaemia. The abnormal placenta associated with hydrops foetalis, however, does appear to be directly related to the high toxaemia incidence. The presence of the Langhans layer of the trophoblast in late pregnancy is associated with a high production of gonadotrophin.

5. The similarity of the placental changes in hydrops foetalis to those of hydatidiform mole is striking and this extends also to many clinical features.

6. The changes occurring in association with hydrops foetalis also resemble certain features of pregnancy in diabetes mellitus. In both conditions there is placental hyperplasia, raised gonadotrophin production, a raised incidence of toxaemia, hyperplasia of the islets of Langhans, cortisol in the liquor amnii and extramedullary haemopoises.

7. The mechanism of the changes found in association with hydrops foetalis is discussed and evidence presented which suggests that it is a growth-hormone effect. This would explain the similarity to the diabetic picture.

8. The bearing of the findings presented on theories of the aetiology of pre-eclampsia is discussed. They support the idea that the underlying cause is, in some cases at least, a hormonal imbalance which can be related to the histology of the placental trophoblast.

9. The significance of the occurrence of post-partum eclampsia is discussed. From an analysis of a series of cases of eclampsia it is concluded that the time of occurrence of post-partum fits

is an argument for, rather than against, a placental aetiology.

10. The question as to whether pre-eclampsia is in fact an entity is finally discussed. It is suggested that cases occurring in relation to hydrops foetalis and hydatidiform mole constitute one group - to which cases of diabetes mellitus and multiple gestation may also belong.

Further Lines of Investigation :-

This study has posed a number of questions which invite further investigation :-

a. Is there more chance of chorion epithelioma developing after the birth of a hydropic foetus than after a normal foetus?

b. Does a study of the placental changes in hydrops foetalis offer a clue to the aetiology of hydatidiform mole?

c. Is the placental change in severe erythroblastosis sometimes more important in causing intra-uterine death of the foetus than haemolysis?

d. Does the rise in gonadotrophin excretion precede irreversible hydropic change in the foetus? If so, might it be used as a guide to the optimum time for delivery in cases of severe haemolytic disease?

e. If the trophoblastic anatomy of the placenta were studied in relation to the hormone levels in a large series of cases of toxaemia, might not the basic nature of the disorder become evident?

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SECTION D.

AMNION NODOSUM.

A description of this lesion is followed by an analysis of its clinical associations and a discussion of its aetiology. The information derived from the clinical study of these cases is then discussed in regard to its bearing on our knowledge of the production of liquor amnii. This information is supplemented by a study of the clinical presentation of fifty cases of renal aplasia, this being the condition most commonly associated with amnion nodosum. From observations presented it is suggested that oligohydramnios is a cause of poor foetal development.

AMNION NODOSUM

DESCRIPTION OF THE LESIONS

The third particular finding to which attention became directed as the result of this placental study was an abnormality of the amnion. The lesion particularly affected that portion of the amniotic membrane which covered the foetal surface of the placenta, though close examination showed that the extra-placental amnion was also affected to a less degree.

The amniotic lesion took the form of small nodules on the foetal aspect of the membranes. The colour of these nodules was commonly a dull grey-yellow (See Figs. D1, D2 and D3) and on cursory examination they resembled miliary tubercles. In one case, however, they were of brick red colour (See Fig. D4). In size the nodules averaged 1-2 millimetres in diameter but in areas these coalesced to produce plaques of considerably larger dimensions. One of the most striking features of the lesions was that they could be picked off the foetal surface of the amnion without disrupting the continuity of the underlying membrane.

Histologically (Figs. D5, D6 and D7) the nodules were shown to consist of masses of keratinized squames embedded in an acidophil matrix. The cuboidal cells of the amniotic epithelium were absent in the region of the nodules. There was no evidence in the epithelium in the vicinity of the nodules of any squamous metaplastic change.

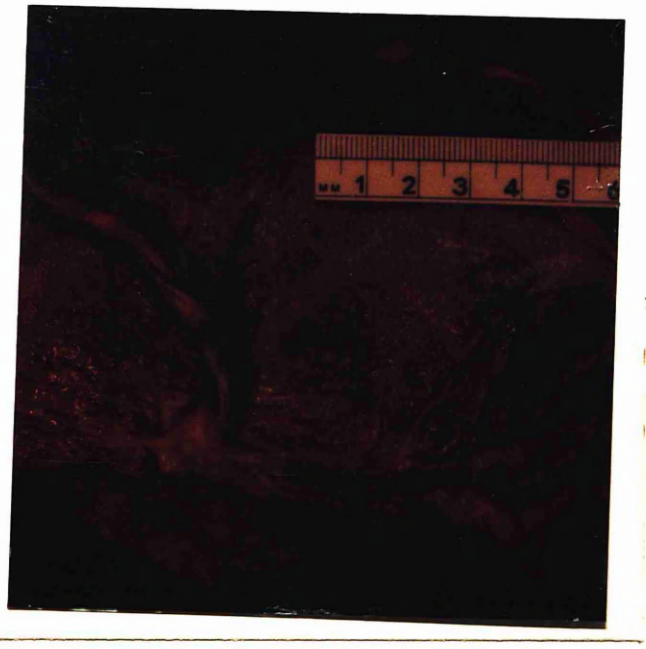

Fig. D1. Colour photograph of foetal surface of the placenta showing the characteristic nodular lesions of amnion nodosum.

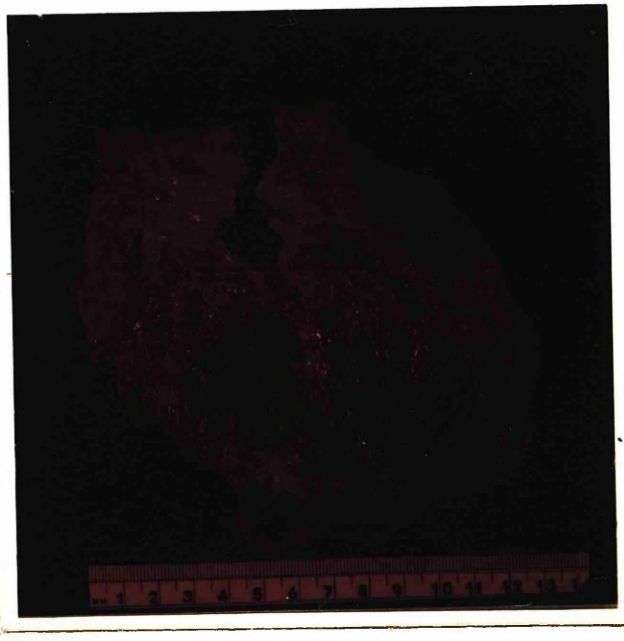

Fig. D2. Colour photograph of the placental amnion of the same case after stripping from the placenta, showing that the nodules are actually on the amniotic membrane.

Fig. D3. Colour photograph of amnion nodosum lesions in another case. In this photograph the lesions shown are on the extra-placental amnion close to the placental edge. The membranes are covering the maternal surface of the placenta in this view.

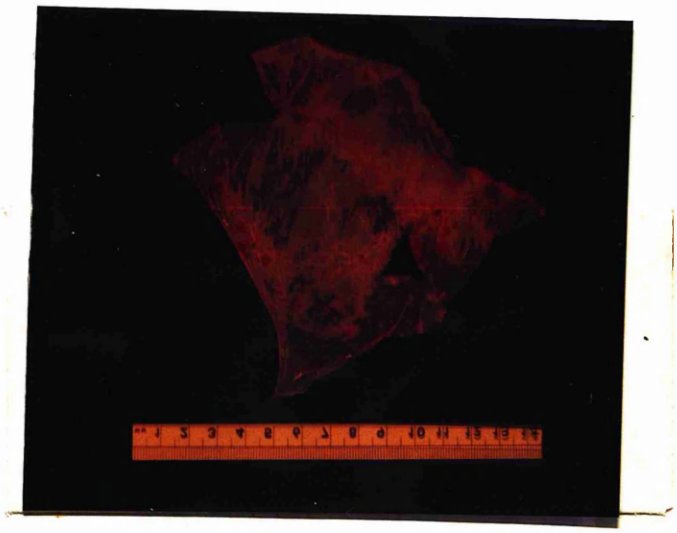

Fig. D4. Placental amnion from another case of amnion nodosum in which the lesions were brick red in colour.

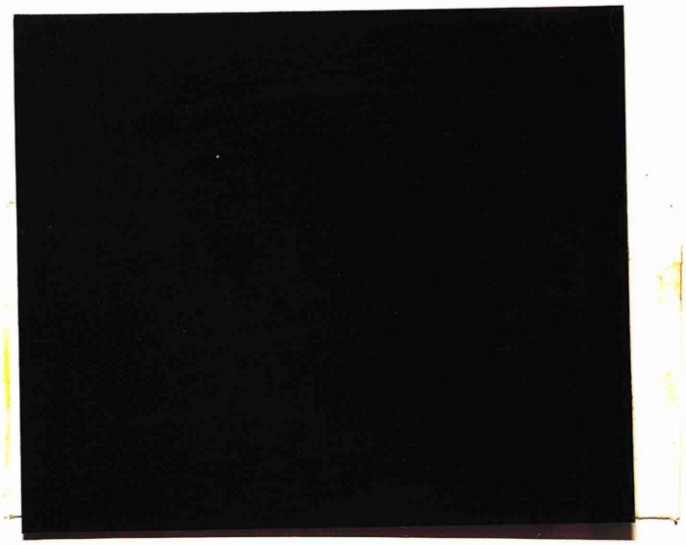

Fig. D5. Photomicrograph of a typical lesion of amnion nodosum showing keratinised squames embedded in an acidophil matrix. Note the break in continuity of the amniotic epithelium and absence of squamous metaplasia. (Stain :- Haemotoxylin and Eosin; magnification x 110).

Fig. D6. Another typical lesion. The squames show purple against the blue connective tissue. (Stain :- Massons Trichrome; magnification x 40).

Fig. D7. Another example of amnion nodosum, this time showing a polypoidal tendency.
(Stain :- Massons Trichrome; magnification x 140).

CLINICAL ASSOCIATIONS OF THE LESIONS

On going immediately from sluice to delivery room following the observation of these lesions for the first time, it was found that the baby in this case had been delivered as a breech but had survived only a few minutes. Though of 37 weeks maturity, it weighed only 4 lbs. 7 ozs. and showed peculiar facial characteristics - low set ears, beaked nose and receding chin (Fig. D8) - the combination of which occurs typically in association with renal agenesis or dysplasia. (Potter, 1946). Autopsy confirmed that there was absence of functioning renal tissue, the kidneys being represented by 2 tiny, hypoplastic nodules.

On referring to the ante-natal records of the case (No. 645) it was found that in late pregnancy the uterus had been considerably smaller than expected, though the size had corresponded with the duration of amenorrhoea when examined early in pregnancy. Rupture of the membranes had not been noted during labour and the lack of liquor had been specifically recorded.

Shortly after this, on routine examination of another placenta and its membranes, (No. 1057) a similar nodular appearance of the amnion was noted, again affecting particularly the placental amnion. These lesions differed from those seen in the previous case only in the colour intensity. (Fig. D4)

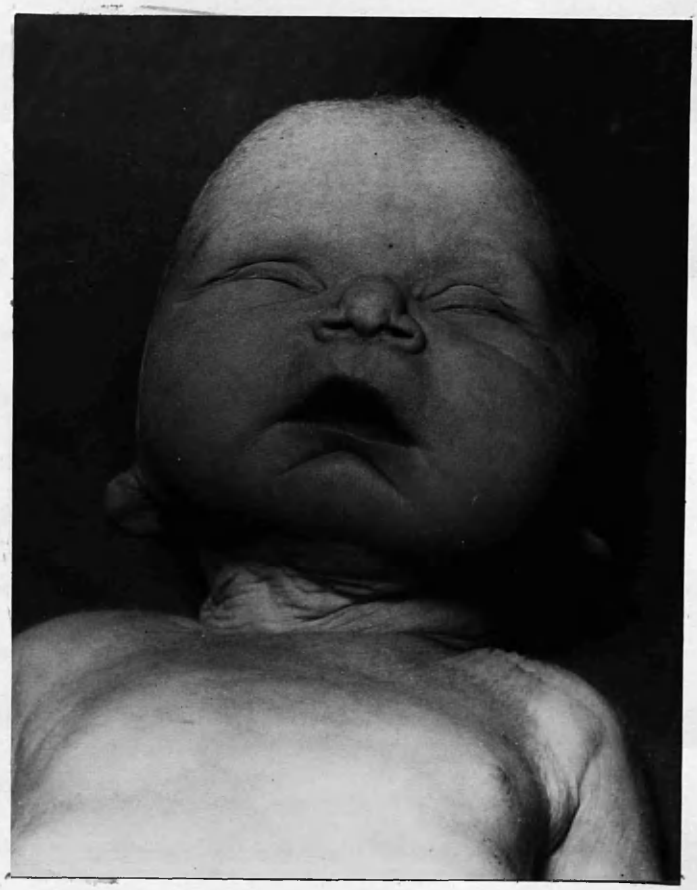

Fig. D8. Baby in Case 645, showing the low set ears, flattened nose and receding chin, typical of renal aplasia.

On examining the ante-natal records in this case it was discovered that the patient had been seen when 35 weeks pregnant. It was then found that uterine enlargement was equivalent to that of a 24 weeks pregnancy, yet when she had been examined at 12 weeks the extent of uterine enlargement had then been compatible with the duration of amenorrhoea.

At the 35 weeks examination the foetus seemed extremely small for the duration of pregnancy but the most striking feature was the apparent lack of liquor amnii. This was recorded clinically and also, quite independantly, by the radiologist, who noted hyperflexion of the foetus (Fig. D.13). In view of the experience in the case previously recorded, a note had been made in the case sheet "probably renal agenesis." Three weeks later (at the 38th week) an assisted breech delivery resulted in a 4 pounds 2 ounce baby which survived with gasping respirations for only 2 hours. No liquor escaped at any time during labour; in view of the earlier clinical note, a particular watch had been kept for this.

The appearance of the baby (Fig. D9) made the diagnosis of renal agenesis suspect. The amniotic lesion was then observed and the knowledge of the previous association of this lesion with renal aplasia in the earlier case gave support to the diagnosis

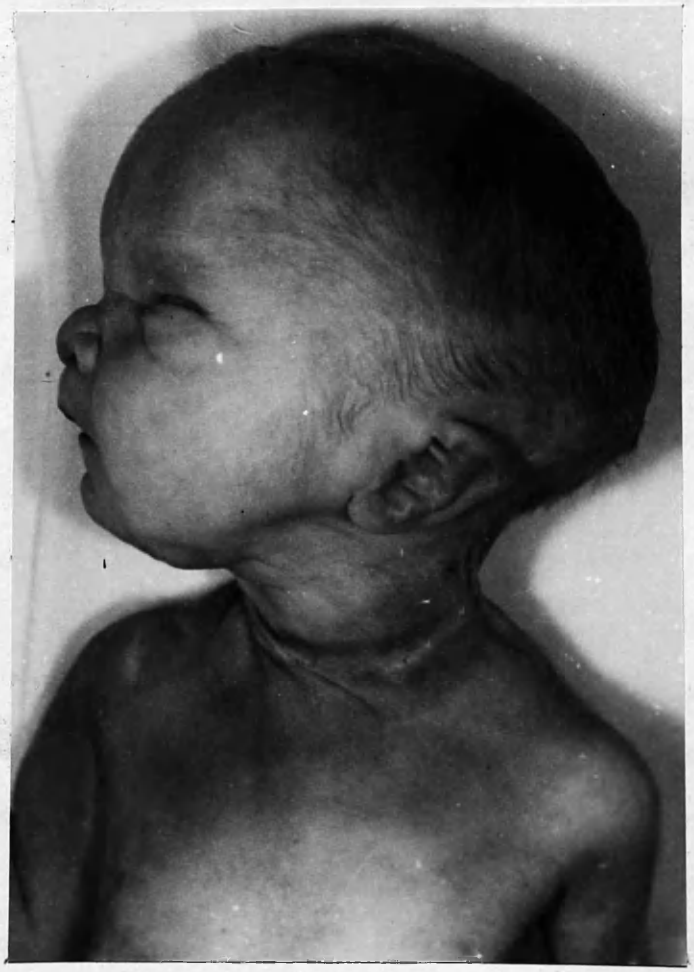

Fig. D9. Baby from Case 1057, showing features suggestive of renal aplasia.

which was later confirmed at autopsy (Fig. D.10). (In the illustration the adrenals occupying a large area of the posterior abdominal wall and the hypoplastic lungs can be clearly seen. Both these features appear to be a constant accompaniment of renal agenesis.)

The finding of this rare amniotic abnormality in association with 2 consecutive cases of renal non-development, posed the question as to whether it might be a constant association and, if so, what its significance might be.

Renal agenesis being a relatively rare condition one had to look to other sources to obtain sufficient material. I was fortunate in obtaining the co-operation of my former colleague, Dr. A.D. Bain of the Department of Pathology, The University of Edinburgh. Dr. Bain had an interest in cases of renal agenesis of some years standing and had reviewed these in 1956. He had, however, never seen this amniotic lesion but had made no particular study of the placenta and membranes. He was fortunate in having access to the perinatal autopsy material from Edinburgh and South-East Scotland. Within a few months he was able to supply, from the material at his disposal, the placenta and membranes from a further 8 cases of renal agenesis or severe cystic dysplasia. In all but one case, evidence of the same amniotic abnormality was present - though in several cases it was much less obvious, amounting only to a fine granularity of the placental amnion. This form would almost certainly have escaped attention had one not

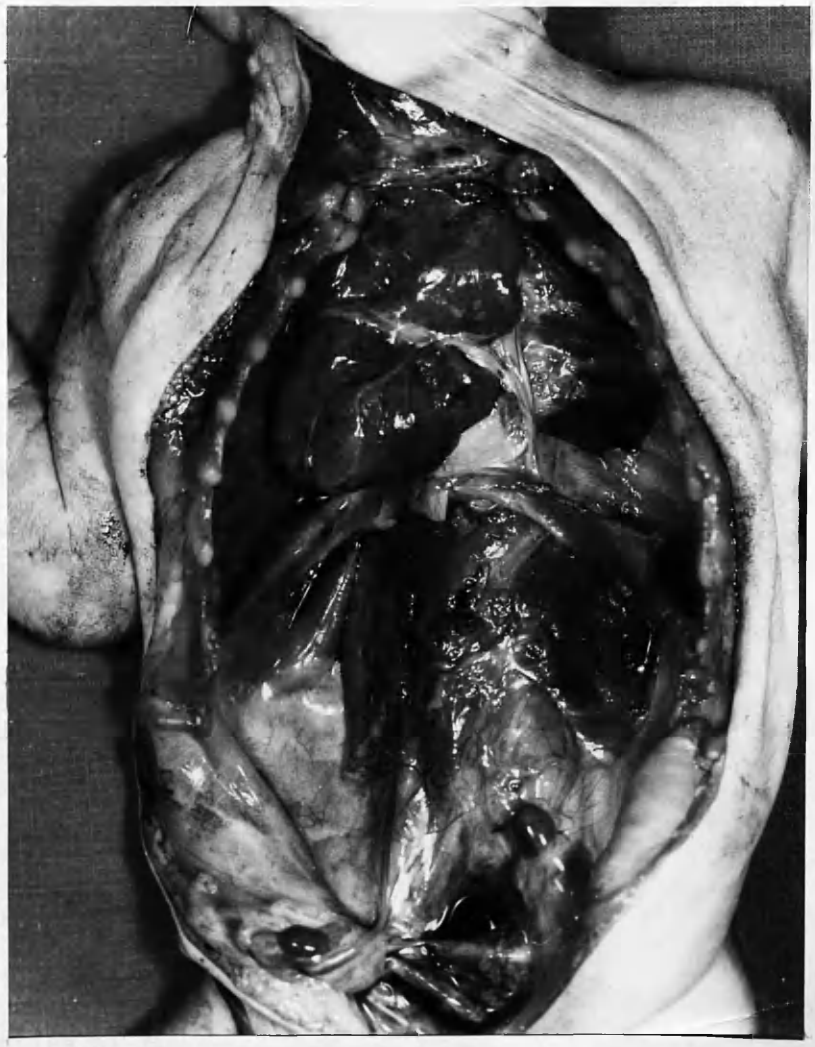

Fig. D.10. Autopsy on baby from Case 1057. The absence of the kidneys is evident, their site being in part occupied by the adrenals. The small lungs can also be seen.

been familiar with the more obvious form of the condition. It was a notable feature that in each of the 7 cases showing the lesion, (as in the 2 originally seen) clinical observations suggestive of lack of liquor had been specifically entered in the case records. The exception was the case of renal agenesis in which there was no amnion nodosum; in this case there was in fact an excess of liquor suspected clinically, which was supported by the removal of over 2 pints of liquor at amniotomy. In this particular case the renal agenesis was associated with iniencephaly. The significance of the combination of these 2 anomalies will be discussed later.

This then gives a total of 10 instances of renal aplasia in 9 of which amnion nodosum was observed.

Amnion Nodosum not associated with renal agenesis

No instance of amnion nodosum was observed in the personal study of 3,161 consecutive placentae and their membranes, except for the 2 cases in which there was renal aplasia. Since then, however, in addition to the 7 Edinburgh cases associated with renal aplasia I have seen 2 examples of the condition not associated with renal aplasia. In both instances oligohydramnios had been suspected on ante-natal examination and it had been requested that the membranes be preserved at delivery for study. The ante-natal suspicion of oligohydramnios was confirmed by the absence of liquor at delivery in each case. The liquor deficiency in both seemed to be due to extensive involvement

of the chorionic membrane by organising blood clot. (See section on "Oligohydramnios not associated with renal aplasia.")

I have also observed a third example - in this case associated with the delivery of a grossly macerated stillbirth on which autopsy was not performed. There was no information on liquor volume in this case and it is possible that it was in fact a case of renal aplasia. Another explanation, however, is that as the result of the dead foetus being retained in utero for approximately 10 weeks, resorption of liquor had occurred and this had in turn lead to the development of the amniotic lesion.

The total number of cases of amnion nodosum discovered is therefore 12, distributed as shown on Table DI.

In order to extract the maximum amount of information from the small quantity of material at our disposal, Dr. Bain and I pooled our cases of renal agenesis - he studying the foetal pathology and myself the clinical features and the changes in the placenta and membranes. Part of this study has been briefly recorded previously (Scott and Bain, 1958). In the present discourse only that part of the study particularly concerned with the amniotic lesions and their significance, which I have personally carried out, is presented. The work done by Dr. Bain is referred to where it throws light on my own studies.

T A B L E 'DI'

AMNION NODOSUM CASES

Number of cases	Sample from which obtained	Oligohydramnios				Renal agenesis
		Definitely	Probably	No information	Definitely not	
2	From 3,161 consecutive placentae personally examined.	2	-	-	-	2
7	From 8 cases of renal agenesis.	3	4	-	-	7
2	From 2 cases with clinical oligohydramnios out of approximately 4,500 patients.	2	-	-	-	-
1	From 65 stillbirth placentae examined since the consecutive series.	-	-	1	-	-
TOTAL 12		7	4	1	-	9

THE NATURE AND CAUSE OF THE AMNIOTIC LESIONS

The question then arises as to the nature of the amniotic lesions. Histologically, as stated, the amniotic nodules or plaques consist of masses of keratinised squamous cells embedded in an amorphous, acidophilic matrix. This is quite distinct from the condition of squamous metaplasia of the amnion. In squamous metaplasia the change can be clearly seen (Fig. D.11) of the amniotic epithelium from its normal simple cuboidal form, to the squamous type with the clear transition of the various squamous layers, from cuboidal cells in the deep layer to flattened and keratinised cells on the surface.

If the squames have not arisen as the result of metaplasia of the amnion what other possible source is there? As these lesions are on the foetal surface of the amnion and as they can be picked from that surface without disrupting the continuity of the underlying membrane, the idea occurred that the squames might be derived from the foetal skin. This possibility was supported by the fact that these lesions were only present in the 9 cases of renal aplasia where liquor was known to be deficient and were absent in the single case where there was definitely liquor present. Yet further support for this concept was the finding of identical lesions in 2 cases where oligohydramnios was present but the foetal kidneys were normal. All the evidence suggests that the lesions are a consequence of oligohydramnios and

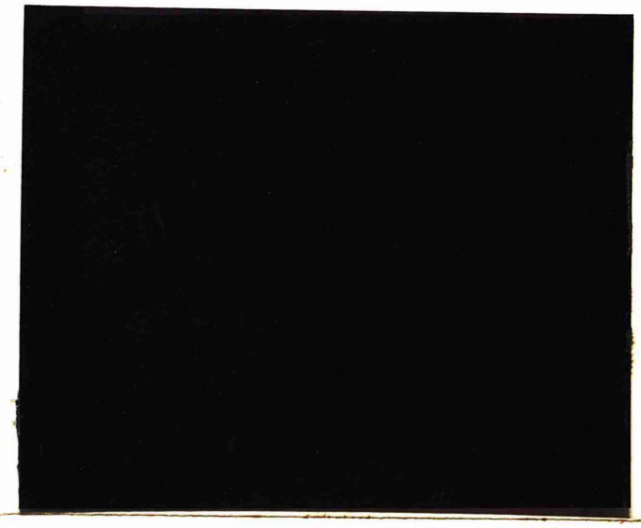

Fig. D.11. Section of squamous metaplasia of the amnion, showing the transition of the normal single layered epithelium to stratified squamous.
(Stain :- Haematoxylin and Eosin; magnification x 45).

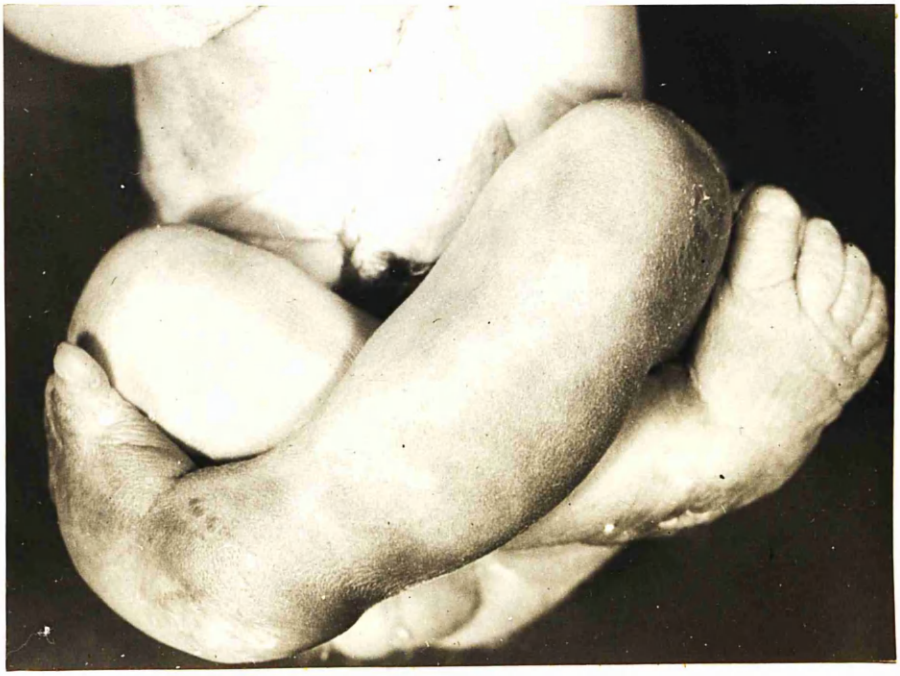

Fig. D.12. Case of renal agenesis associated with oligohydramnios and amnion nodosum. Note the position of the legs and the glazing of the skin over the external malleoli suggestive of pressure.

not a direct accompaniment of renal agenesis by a genetic linkage.

It is known that in pregnancy associated with a normal quantity of liquor the superficial squames are cast into the liquor, in which they are to be found floating free and discrete. It would appear to the writer a reasonable explanation that, as a result of the deficient liquor, the amniotic epithelium comes into continuous close apposition with the skin over the foetal prominences; the unusual friction leads to disruption of the cuboidal celled layer of the amnion and the superficial desquamating cells of the foetal skin become transferred, by a detritic mechanism, to the amorphous, acidophil material which underlies the cuboidal layer of the amnion - thus producing the typical lesions. In several of the cases scaliness of the foetal skin has been a feature and in Fig. D.12 the dry, glazed skin over the external malleoli can be seen, suggestive of external pressure.

Why should the lesion affect the placental amnion to a greater degree than the extra-placental membrane? There would seem to be 3 possible explanations :-

(i) The placental amnion is probably in rather more intimate contact with the foetus as it is projected slightly into the uterine cavity by the bulk of the placenta which it covers.

(ii) The amnion over the placenta is less mobile than it is elsewhere, being anchored at the site of attachment of the umbilical cord.

(iii) There are certain histological differences; the amniotic cells tend to be more cylindrical over the placenta and contain fewer fat globules (Shaw and Marriott (1949)) and it is possible that these cellular differences in some way make the placental amnion more susceptible to the development of the lesions.

Nomenclature.

Six records of lesions of an apparently similar type have been traced. Of these, the first 5 authors between them describe 11 cases, (von Franque (1897); Holzapfel (1903); Sitzenfrey (1911); Schulz (1929); and Bergendal (1930)), and use the term "amnionknotchen" (or amniotic nodules) to describe the lesions.

Bardram (1930) recorded a case of renal aplasia with oligohydramnios in which the placental amnion was covered with a "lot of miliary round yellow-white bumps." These were presumably also such amniotic nodules though he failed to obtain histological confirmation of their nature.

The only record which I have been able to discover of such lesions having been recently described is by Landing of the United

States in 1950. He described 8 cases, 5 in association with major urinary abnormalities in the foetus. The label of "amnion nodosum" which he gave to the lesions has been adopted in this discourse.

Differential Diagnosis.

Two conditions in my experience require to be differentiated from amnion nodosum and there is a third condition which may be confused but which I have not encountered :-

(i) Squamous Metaplasia of the amnion.

Naked eye this condition may simulate the coalescent type of nodular lesions but on microscopic examination, as already mentioned, the correct diagnosis can be made readily. (See Figs. D5 and D.11)

(ii) Sub-chorionic Fibrin Deposits.

On inspection of the foetal surface of the placenta subchorion fibrin deposits if small and discrete, as they occasionally are, may simulate the amniotic lesions. Differentiation can be easily achieved, however, by placing a finger on the placental amnion and sliding the amniotic membrane gently over the placenta - if the lesions are chorionic they remain stationary - if they are amniotic they move over the placenta. Recourse to microscopy is not necessary to distinguish these two conditions.

(iii) Polypoid Hyperplasia of the Amnion.

This condition is mentioned by Landing as a source of possible confusion. Microscopically, active hyperplasia of the amnion is evident. No instance of this has been encountered in the present study.

Observations on quantity of liquor amnii in cases of renal aplasia.

The finding of these amniotic lesions in cases of oligo- or anhydramnios in association with renal agenesis or severe cystic dysplasia directed one's interest to the extent and significance of the foetal urinary contribution to the amniotic fluid.

I was able to gain access to the records of 50 cases of renal agenesis, or severe dysplasia with obvious absence of renal function.* These records were analysed firstly with regard to information concerning the presence of liquor and its quantity. The results were as follows :-

Deficiency or absence of liquor specifically recorded :-	7 cases.
Notes suggestive of liquor deficiency	28 "
Relevant information not recorded	14 "
Liquor present	1 case
Total	50 cases

The presence of the following features was regarded as "suggestive" of oligo-hydramnios.

(i) The uterus at late pregnancy examinations consistantly noted as being smaller than expected from the duration of amenorrhoea.

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* The term "renal aplasia" will be used to cover both types of failure of renal development.

(ii) Failure to record rupture of the membranes or liquor escaping at any time before, or during, labour. The space on the case sheet for the insertion of the time of rupture of the membranes was frequently left blank; in the hourly or half-hourly labour records, the membranes were often stated to be intact within 10 or 15 minutes of the time of delivery yet no record appeared of their having ruptured, or been ruptured, between this time and the delivery.

To control these observations, a series of 100 case records of patients who delivered normal babies was reviewed. Only 3 out of the 100 had the features regarded as suggestive of liquor deficiency. The finding of these features in 28 out of the 42 renal aplasia case records which lacked specific information on the liquor is therefore extremely significant.

Further evidence suggestive of the common deficiency of liquor in these cases was obtained from an analysis of the presentation of the foetus at delivery in the 50 cases of renal agenesis. The findings were as follows :-

Breech presentation	30 cases
Vertex presentation	19 cases
Presentation unknown	1 case (caesarean section)
Total	50 cases

It will be seen that 60 per cent of the babies were delivered by the breech. The high incidence of breech presentation in similar circumstances has also been recorded by Bardram (1930) and Hürzeler (1921). This extremely high incidence of breech presentation is not explained by prematurity, for 36 out of the 50 babies in this series were delivered after the 34th week of pregnancy. It is almost certainly a consequence of the lack of liquor preventing the foetus turning to adapt itself in the normal way to the uterine shape in late pregnancy.

Yet further evidence suggestive of liquor deficiency was provided by Dr. Bain's analysis of the incidence of talipes in these cases. Excluding 11 cases in which the baby was macerated or had other gross defects (such as spina-bifida with hydrocephalus, syrenomelia or monomelia), 28 out of the 39 remaining babies showed talipes - either unilateral or bilateral. This, of course, is according to the views of Dennis Browne (1955) that oligohydramnios and talipes are closely related.

The most significant findings, of course, are those in the first group - where specific record was made of the liquor deficiency. Three of these cases were personally observed during the past three years, and in two of these the condition was suspected at antenatal examination and the virtual absence of liquor confirmed by particular observation during delivery.

Interest naturally focussed on the exceptional case in which not only was liquor present but definitely present to excess. The other features in which this case differed was that the renal agenesis was associated with the condition of iniencephaly and it was the only one, out of 10 cases inspected for amnion nodosum, in which amnion nodosum was not found.

In a previous study of cases of excessive accumulation of liquor in relation to foetal swallowing defects (Scott and Wilson, 1957), it had been found that cases of iniencephaly, in common with cases of anencephaly, showed a high incidence of hydramnios and, by injection of radio-opaque medium into the liquor and subsequent X-ray, it had been shown that this was apparently a consequence of failure of the foetus to swallow - presumably due to absence of the necessary neurological centres. It seems likely that in this fact lies the explanation for the accumulation of an excess of liquor in this particular case of combined iniencephaly and renal agenesis. (See section on "Proportion of Liquor Derived from Various Sources.")

Previous observations on liquor volume in relation to renal aplasia.

The only series of comparable size to the one presented here is Potter's (1952). She stated that she had failed to find an obstetrician who had seen liquor escape from the uterus in any of the 30 cases of renal agenesis which she reported. There is not, however, complete agreement in the rest of the literature and at many points the situation is clouded by statements apparently without any authoritative basis and reports so incomplete as to be valueless.

Selby and Parmelee (1956) made a most important contribution in recording a case in which a baby without kidneys was born with the amnion intact. There was definitely no fluid in the amniotic sac. A similar record of definite absence of amniotic fluid was made by Bates (1933), - in a case delivered by elective Caesarean section. He also recorded a case delivered as a breech in which no liquor was observed. He reviews a total of 7 cases of bilateral renal agenesis in which lack of liquor was observed in 6 cases; in the 7th case there was no note in the case record concerning liquor volume. He also refers to 7 cases of extreme renal hypoplasia, in all of which deficient liquor was noted, making a total of 14 cases with absent or grossly deficient renal function, in which the absence of liquor was noted in 13.

To this may be added Bardram's (1930) careful survey of 20 years material in Copenhagen. He also recorded oligohydramnios in

10 out of 13 cases of renal agenesis or severe cystic dysplasia in which renal function was apparently absent.

Overall, out of the 242 cases of renal agenesis found recorded prior to this treatise, oligohydramnios was definitely noted in 66. In the vast majority of the others, however, there was no reliable information as to the presence or absence of liquor.

Several authors including Hinman (1940) and Plentl and Gray (1957) state that normal amounts of liquor "may be found" or "are frequently found" in association with a congenital anomaly incompatible with micturition. They do not, however, support these statements with facts and figures. In all the papers, however, in which a critical concern has been displayed with regard to the volume of liquor, the conclusion has been reached that oligohydramnios is an extremely common, though not quite universal, accompaniment of non-function of the foetal kidneys in utero. Many of these less critical authors have clearly taken the fact that there was no record concerning liquor in the case notes, to mean that the volume was normal.

Probably the strongest evidence for a foetal urinary contribution to the liquor comes from cases where the baby has a urethral obstruction - organic or functional - and this is associated with accumulation of large amounts of urine in the bladder and upper urinary tract. Jeffcoate (1932) recorded a case in which the bladder was distended to hold over 1,000 ml. while Thierstein, Coleman and

Tanner (1948) reported one with 4,200 ml. of urine in the foetus. It is of interest that in this case the foetal abdominal distension was such that examination of the mother's abdomen gave a clinical impression of hydramnios. Such a mistake might account for some of the reports of normal or excessive liquor volume in association with obstruction to the foetal urinary out-flow.

The only substantial evidence offered <u>against</u> foetal urine contributing to the liquor amnii is the experimental work of Holterman (1924) who administered methylene blue to the mother and recovered colourless liquor at delivery. After delivery the foetus passed urine stained with the dye. However, in these experiments the dye was only administered a short time (circa 8 hours) before delivery and it is extremely probable that the foetus had not had sufficient time to void dye-stained urine while still in utero.

Having reviewed the literature, it is evident that the present survey represents the most extensive study on liquor production in the absence of foetal renal function which has yet been recorded. It strongly supports the conclusion, that foetal urine <u>does</u> contribute to the volume of liquor amnii and that, particularly in late pregnancy, this contribution is probably a major one. Furthermore, this opinion is supported by the finding, (in 9 out of 10 cases of renal aplasia,) of amnion nodosum - a lesion that seems to be a direct consequence of oligohydramnios.

Oligohydramnios not associated with renal aplasia.

Potter (1952) makes the statement that oligohydramnios is rare except in association with bilateral renal agenesis or obstruction of the urethra. This is a statement with which many obstetricians would probably not agree. Yet it does correspond with my own experience, since I have been particularly interested in such cases. Two cases of extreme oligohydramnios* not associated with renal abnormality have been seen in the same period as three cases associated with renal aplasia. In both of these cases amnion nodosum was observed and they are of some interest, for in each instance the early months of pregnancy had been complicated by threatened miscarriages. At delivery the membranes were found to be covered with partially organised blood-clot over an extensive part of their surface area. This finding suggests that in these cases the amniotic contribution to the liquor was deficient and accounted for the oligohydramnios.

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* Footnote.
This refers only to cases in which oligohydramnios has been suspected early in the last trimester - circa 28-30 weeks - and this impression has continued at each examination till delivery. Cases of post-maturity where the liquor volume possibly became deficient after term are not included; they constitute an extremely debatable clinical group but are certainly entirely different from the cases described here.

Non-renal sources of liquor :-

This review makes it quite clear that foetal urine is not the only source of liquor, for in the case of renal agenesis associated with iniencephaly, liquor definitely accumulated and did so to excess.

The other possible sources of liquor are listed below :-

1. Foetal lungs.

The idea that this is a source of liquor is favoured by Whitehead, Windle and Becker (1942) on the basis of their animal experimental work. Macafee (1950) and Morrison (1952) also support the idea because the pulmonary capillary bed seems to be the only surface in continuity with the amniotic sac which is of sufficient area and vascularity to allow the rapid turnover of water which has been demonstrated by recent work with isotopes. It is worth bearing in mind that in the present study, pulmonary pypoplasia was found as a universal accompaniment of renal aplasia, so it is possible that the finding of liquor deficiency is in some measure explained by the poorly developed lungs.

2. Secretion of the amniotic epithelium.

This undoubtedly occurs and Taussig (1927) considered it the main source. Recently, however, in the light of isotope studies, it has been seriously doubted that it could account for the rapid turnover of water. It is also notable

that secretory activity in the amniotic epithelium is less evident in late pregnancy when the volume of liquor is increasing. Before the stage of organogenesis, however, liquor is present and this must presumably come from the amniotic epithelium.

3. Buccal and nasopharyngeal mucosa of the foetus.

This is put forward as a source by Reynolds (1953) on the basis of animal experimental work but it seems unlikely to be a major one.

4. Transudate from maternal circulation.

This might contribute a little but the freezing point of maternal serum is lower than that of amniotic fluid (Zangemeister and Meissl (1903)) and this is against it being a pure filtrate. This is of course, not an argument against there being some fluid derived from this source.

5. Transudate from the foetal circulation.

This is supported by the occurrence of hydramnios in association with chorioangioma and other congestive states of the placenta (McInroy and Kelsey, 1954; Plentl and Gray 1957).

6. Foetal sweat glands etc.

Small amounts may come from this source but it is hard to imagine that the contribution is of any great significance.

With the last decade has come the "Dynamic Concept" of liquor production and disposal which has resulted from work with radio-active isotopes. Much of the evidence of this work is contradictory to older experimental work and to clinical observation.

The first workers in the field were Vosburgh, G.J., Flexner, L.B., Cowie, D.B., Hellman, L.M., Proctor, N.K., and Wilde, W.S. (1948). They calculated that a volume of water equal to that present in the liquor is exchanged between the mother's extra-cellular fluid and the amniotic sac every 2.9 hours while sodium is replaced much more slowly. As this is the work probably most frequently quoted today, in connection with the discussion of liquor production, it is perhaps worth bearing in mind that the figure on water exchange is based on an average of the results from only 5 cases. The range was from 13.4 to 74.0 per cent of water in the amniotic fluid renewed hourly. (See Table D.II) Not only was there this wide range but the experiments were all carried out at different stages in pregnancy yet the results showed no chronological pattern suggestive of any gradual trend in the rate of liquor production.

Their finding does not correspond with clinical observation of the quantity of liquor which drains when the membranes have been ruptured for some time. It presumably only applies when the liquor is in intact membranes and refers to molecular diffusion - not to rate of production.

TABLE D.II.

Weeks of Gestation	Percentage of H_2O of amniotic fluid renewed hourly
14	37.6
16	26.9
18	13.4
30	74.0
40	20.6
	Average 30.5

(From Vosburgh et al. 1948)

PROPORTION OF LIQUOR DERIVED FROM AND DISPOSED THROUGH VARIOUS SOURCES

The results of the present study and the review of the literature leave little room for doubt that liquor has more than one source of origin and probably more than one route of disposal. Yet many writers on the subject have assumed a single source and, of those who have come to the conclusion that there are multiple sources, very few have made any attempt to calculate the quantity derived from the different sources.

Rosa (1951), by injecting inulin into the amniotic sac, concluded that 500 ml. of liquor was swallowed by the foetus every 24 hours. Of this he calculated 40 ml.* was excreted back into the amniotic cavity by the foetal kidneys, while 435 ml. passed via the placenta into the maternal circulation. However, this can only be considered as an interesting attempt at answering the problem - for the validity of his method would appear to depend on a number of assumptions that are apparently unsupported by any reliable evidence. One must at least presume this to be so, for the paper is destitute of references.

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* FOOTNOTE
This work, if confirmed, does not mean that only 40 ml. of foetal urine is contributed to the liquor each day. There may be a much greater contribution but this volume of fluid comes from swallowed liquor - any over and above this will come through the placenta.

More recently Gray, Neslen and Plentl (1956), working with an isotope tracer technique, and comparing their findings in the human with experiments on hydro-dynamic models, calculated that at least 25 per cent, and probably more than 50 per cent, of the water transfer from amniotic fluid to mother is accomplished through the intermedium of the foetus.

Plentl and Gray (1957), both of whom have been concerned with a great deal of the isotope work on the subject, give the most recent authoritative statement from the information so derived. In their paper "The Aetiology and Management of Hydramnios" they state that liquor cannot be a simple transudate or dyalisate of the maternal plasma because the liquor electrolytes have different rates of exchange from the water. They claim to have demonstrated the volumes of the fluid passing in each direction between (1) mother and foetus (2) foetus and liquor (3) liquor and mother. They state that normally there is a net circulation from mother to foetus to liquor and back to mother. In hydramnios they state that there is still a net circulation in this direction but that this is reduced. They claim that in hydramnios there is a direct transfer of water from mother to liquor, without passing through the medium of the foetus, which does not occur in the normal case.

These workers, however, do not give sufficient information about their techniques to enable one to make any assessment of their validity. For a number of reasons this is particularly unfortunate. Plentl and Gray's figures for the rate of water transfer in hydramnios are

apparently in direct contradiction of the statement of Hutchinson, Hunter, Neslen and Plentl in 1955, that the rate of water exchange was independant of liquor volume. They make no attempt to explain, or even mention this discrepency. They quote the classical work on the subject of Makepeace et al. (1931), supporting a renal contribution but, unfortunately, they state these observations as the complete converse of what they actually were.

They then turn to the clinical field and make statements on the association of hydramnios with (1) placental infarcts - based on a remark of Taussig over 20 years ago - and with (2) circumvallate placentae - for which they give no authority. These they say are "especially significant and consistent findings." They use them to support the results of their isotope experimental work and then go on to inculpate a circulatory defect in the placenta, with placental failure, in the aetiology of hydramnios. This might indeed occasionally be the case - for it is quite evident that there is more than one cause of hydramnios. These two circumstances which they quote, however, would seem very dubious grounds on which to base any argument. Very few would regard an infarcted placenta as likely to be the cause of hydramnios and the present studies have shown no such relationship. In fact, the converse association of oligohydramnios is probably a more common experience in cases of placental infarction. With regard to circumvallate

placentae, the Section B of this treatise, which refers to this, shows quite clearly that there is no relationship between circumvallate placentae and the development of hydramnios.

Such statements tend to cast doubt on their experimental work, the method of which is incompletely described. To culminate their clinical arguments they quote a series of congenital anomalies not associated with swallowing defects - such as mongolism, achondroplasia and cardiac abnormalities - and state that some mechanism other than failure of deglutition must account for hydramnios in these cases. Yet, there seems no reliable evidence that such conditions <u>are</u> associated with a raised incidence of hydramnios; they certainly quote none nor produce any of their own.

The previous analysis of 169 cases of hydramnios (Scott and Wilson, 1957) showed that excessive accumulation of liquor occurs most consistently in states which render the foetus mechanically or neurologically incapable of swallowing. In that series 54 out of 169 cases of hydramnios (32 per cent) came into this category. The 54 cases included 32 of anencephaly and 2 of iniencephaly. That this failure to swallow is the mechanism of development of the hydramnios which accompanies so many cases of anencephaly and iniencephaly was demonstrated by means of radiological studies following

lipoidal injection. There were no cases related to the foetal anomalies quoted by Plentl and Gray.

This common association of hydramnios with foetal swallowing defects is a fact rarely stressed in text book discussions of hydramnios yet it would seem to be an observation of some importance, both practically, as it may be an important aid to early diagnosis of upper alimentary atresias, and theoretically for the light it throws on the disposal of liquor. It should not of course, be assumed from this that it is the only, or major, route of disposal but it is one which seems to control the liquor volume to a large extent.

These findings are in disagreement with Plentl and Gray's statement that "Foetal micturition and deglutition play, at best, a very subordinate role in the physiology and physiopathology of the amniotic fluid." The extent of the physiological part of these mechanisms is still open to question but failure of one or other of them is practically always associated with pathological disturbance of the amniotic fluid volume.

From the case of combined iniencephaly and renal agenesis reported here in which hydramnios developed, can be made the rather oblique statement that in that case :- "The volume of liquor supplied by sources other than the foetal kidneys, exceeded the volume disposed of by routes other than the gastro-intestinal tract."

It is very evident that there is much need for further knowledge on the proportionate supply and disposal of liquor by various routes.

The author is at present co-operating in a study which it is hoped will show the extent of the contribution of the foetal urine. The substance being used is chloral hydrate and the basis for the technique is that chloral which has passed through the kidney is converted to urochloralic acid, while chloral which has not passed through the kidney exists in the body as trichlorethanol and trichloracetic acid. By estimating the proportion of urochloralic acid in the liquor after administration of chloral to the mother, it is hoped to ascertain the extent of the foetal urinary contribution. It is intended to combine the chemical method with chloral isotope tracer studies as a cross check on the results.

CORRELATION OF CLINICAL AND EXPERIMENTAL INFORMATION ON LIQUOR FORMATION AND DISPOSAL

Consideration of the clinical information available - the cases of renal aplasis with oligohydramnios and those with swallowing failure and hydrammios - suggests that the rate of liquor renewal, as demonstrated by the isotope workers, is independant of the control of volume of liquor. The foetal swallowing mechanism and urinary system would hardly be responsible for the enormous turnover of water recorded by the isotope experiments - yet, clinically, these two foetal systems do seem to control the liquor volume to a very large extent. Such an idea is in fact supported to some extent by the findings of Hutchinson, et al. (1955) working with radio-active isotopes. They showed that the rate of exchange of the water in the amniotic fluid was independant of the volume of liquor i.e. the same rate of exchange of labelled water molecules occurred in oligohydramnios, polyhydramnios and with a normal volume of liquor.

This gives the idea of a collection of water, the volume of which is largely, though not entirely, controlled by a relatively simple "tap" inflow - (foetal micturition) - and a "drain" outflow (foetal deglutition) - yet its molecules are constantly diffusing in and out of the maternal circulation. It is a concept which, in the present state of our knowledge, is hard to accept, yet it seems the only one which will achieve an integration of the apparently valid clinical observations with the

results of the experiments using isotope techniques. It may be that further knowledge will show that such an arrangement is possible and does exist.

Until such time the issue must remain open - but meanwhile clinical observations should not be ignored because they do not happen to coincide with the results of the isotope experiments. The maxim that in research the simplest technique of observation carries the smallest number of fallicies, is as true today as ever.

CLINICAL PRESENTATION OF RENAL APLASIA

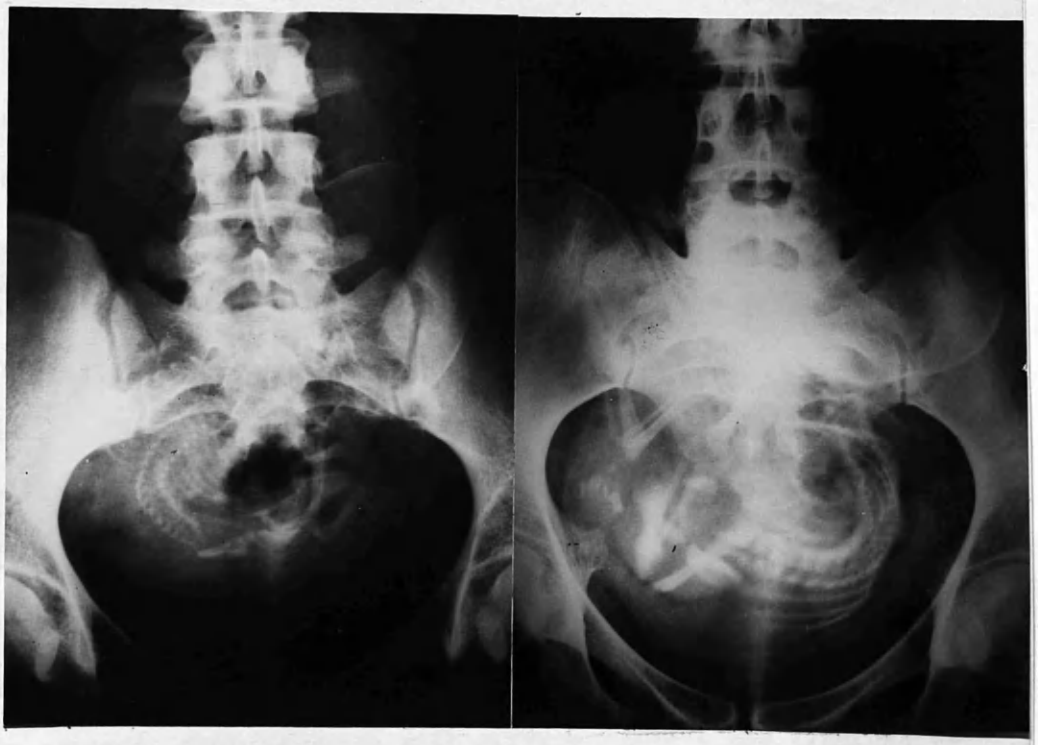
From the study of these 50 cases of renal aplasia information of some value concerning their clinical presentation has been obtained. The incidence of the condition calculated from this series is approximately 1 in 2,500 deliveries, though this figure does not allow for the possibility that the abnormality exists in some macerated foetuses which do not come to autopsy. It compares with the recent estimates of 1:3000 (Green, 1955) and 1:2,500 (Silvester and Hughes, 1954), and 1:1,300 (Welsh, 1958).

From the first report of the observation of bilateral renal agenesis by Wesalius in 1543 till Davidson and Ross's paper in 1954 a total of 232 cases had been recorded. Since then a further 10 cases have been reported and the additional 28 cases of complete agenesis in this series, bring the total to 270. The condition is relatively uncommon and it might be doubted if its recognition was of any great importance. It is, however, of greater concern than the incidence would suggest for the clinical presentation is such that there is a considerable likelihood of Caesarean section being performed. This is confirmed in the literature - a large proportion of the cases recently recorded having been delivered by Caesarean section. This, of course, is a minor tragedy - the mother being subjected to a major operation for the salvage of a child which is quite incapable of survival.

Ante-natal Presentation :-

At early ante-natal examinations the findings are usually entirely normal and the uterus is found to correspond in size to that expected from the duration of pregnancy. When seen in late pregnancy, however, certain deviations from normal are usually evident.

1. The uterus is almost invariably smaller than expected, this being of particular significance when associated with a reliable recording that the uterus was enlarged to the size expected in the early weeks of pregnancy.
2. The foetus itself may appear to be smaller than expected.
3. The presentation will frequently be by the breech and be resistant to attempts at version.
4. Palpation may result in a suspicion that the quantity of liquor is deficient.
5. Radiological examination will usually show marked hyperflexion of the foetus. The foetal spine appears to be collapsed and on antero-posterior picture it is confined to the projected outline of the pelvic brim (Figs. D.13 and 13a). This gives an appearance identical with that which Tager (1954) claimed was diagnostic of foetal death in utero. Kent, Rubin and Dann (1957) recently pointed out that oligohydramnios can simulate this sign of foetal death. Antenatal radiological



Figs. D.13 and 13A. Ante-natal X-rays of two different mothers who subsequently delivered babies with renal aplasia. Note the hyperflexion of the foetal spine in each case simulating the collapse which occurs with intra-uterine foetal death.

hypertension, pre-eclampsia, chronic nephritis etc. - then the presence of renal aplasia should be suspected.

This is, to say the least, extremely unsatisfactory and it might well be argued that one would lose more by hazarding foetal lives through wrongly suspecting renal agenesis in such circumstances, than one would gain from avoiding the occasional unnecessary Caesarean section. Nevertheless, attempting to make the diagnosis ante-partum is clearly worthy of consideration - and in connection with the work at present being carried out on chloral hydrate transfer to the liquor, we have hopes that a simple test may be devised which could give a definite answer where the condition is suspected in late pregnancy. No suitable opportunities have yet presented to give this method trial.

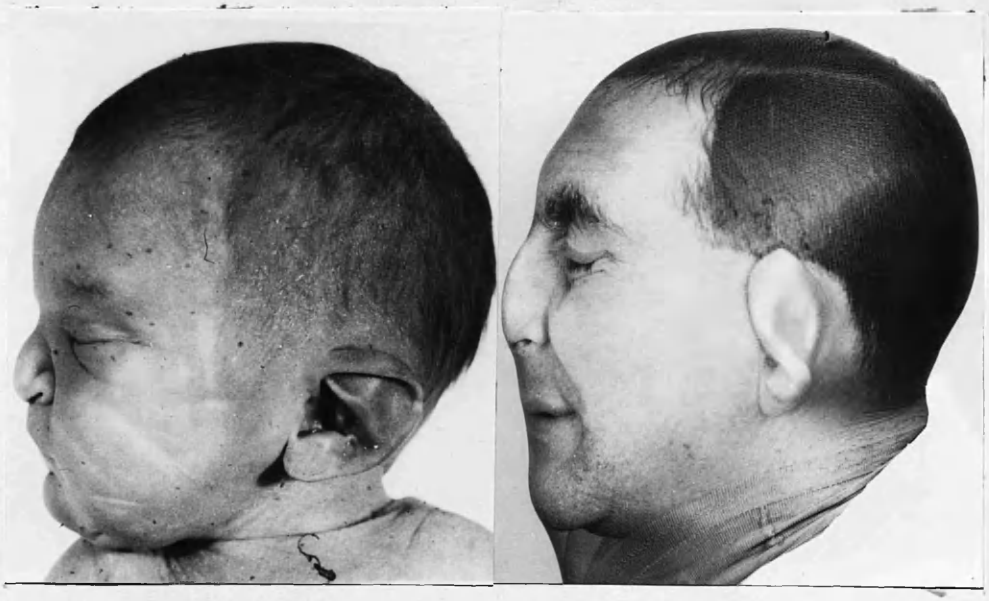
Neonatal Presentation :-

Potter (1946 and 1952) first drew attention to the association of certain peculiar facial characteristics with renal agenesis. These usually enable the condition to be recognised merely from inspection of the baby (Figs. D.8 and 9). It is not intended to dwell on these here; the 50 cases in this series have been analysed in this respect by my colleague Dr. Bain. He has come to the conclusion that many, though not all, of the concomitant features of renal agenesis are secondary to a deficiency of liquor, being produced by compression of the foetus (Bain, 1958). This agrees well with the clinical observations on liquor deficiency in the series. Support for this concept is perhaps

offered by a comparison of Fig. D.14 and Fig. D.15. The former shows a typical face of a baby with renal agenesis, while Fig. D.15 shows what would appear to be a case of renal agenesis which has, for some remarkable reason, survived to adult years! As it happens, it is a photograph of the writer - and the characteristic facial appearances are produced in this case, not by the pressure of the amniotic membrane but by a nylon stocking!

Three points evolve from the clinical study of the cases of renal aplasia presenting in the neonatal period :-

1. The babies born alive (33 out of the 50 in this series) die early in the neonatal period, not from the effect of anuria but from the concomitant pulmonary hypoplasia. The clinical presentation is of respiratory distress with asphyxia. The average age at death in this series was 3 hours 9 minutes; the longest period of survival was 36 hours.
2. The recognition of renal agenesis from the external characteristics is not quite such a worthless procedure as Ellison Nash suggested in his 1951, Arris and Gale lecture. Having quoted American references on the subject he went on to "doubt very much whether there is anything to be gained by the ante-mortem diagnosis of bilateral renal agenesis in this country."



Figs. D.14 and D.15. The left hand picture is of the face of a baby with renal agenesis, showing the typical facial features. The right hand picture is of an adult with similar facial appearances. These were produced in this instance by the writer covering his head with a nylon stocking. The similarity to the baby's facies suggests that these features are a result of the tight application of the amniotic membrane to the baby's head in utero - a consequence of the oligohydramnios.

On 4 occasions it has been my lot to deliver by the breech babies with renal agenesis - after apparently smooth and satisfactory deliveries these babies have failed to establish satisfactory extra-uterine existence. In the last 3 cases recognition of the typical external appearances has brought personal relief in the realisation that the babies' condition was not the result of the breech delivery.

3. In cases where the external characteristics of the baby are not entirely typical, inspection of the membranes for evidence of amnion nodosum may clinch the diagnosis.

Intra-uterine Foetal Growth in Renal Aplasia

Babies born with absent or non-functioning kidneys tend not only to have dry skins but the skin is also often loose and wrinkled - giving in some cases an appearance of "premature senility." (Fig.D.16) In general the babies seem small for their maturity and look as if they had failed to gain weight or even to have lost weight.

That this was not merely a clinical impression was confirmed by making a detailed survey of the birth weights of the 50 babies with renal aplasia. The weights were grouped according to the maturity at the time of delivery. In Fig. D.17 is shown the average weight of the renal aplasia babies compared with the average weight of normal babies of similar maturity. It will be seen that up to 34 weeks the abnormal babies are of approximately the expected birth weight yet beyond 34 weeks there is apparently an almost complete failure of the babies with renal aplasia to increase in weight.

This is unlikely to be a chance finding for 32 of the babies came into this group. The heaviest birth weight was only 5lbs.1oz. Nor is it likely to be simply a measure of the absent organs, because (1) the weight of the kidneys is quite trivial compared with the overall body weight, (2) twenty-two of the cases were of cystic dysplasia in which these would tend to be an <u>increased</u> weight of nephric tissue and (3) it is merely in <u>late</u> pregnancy that the foetal

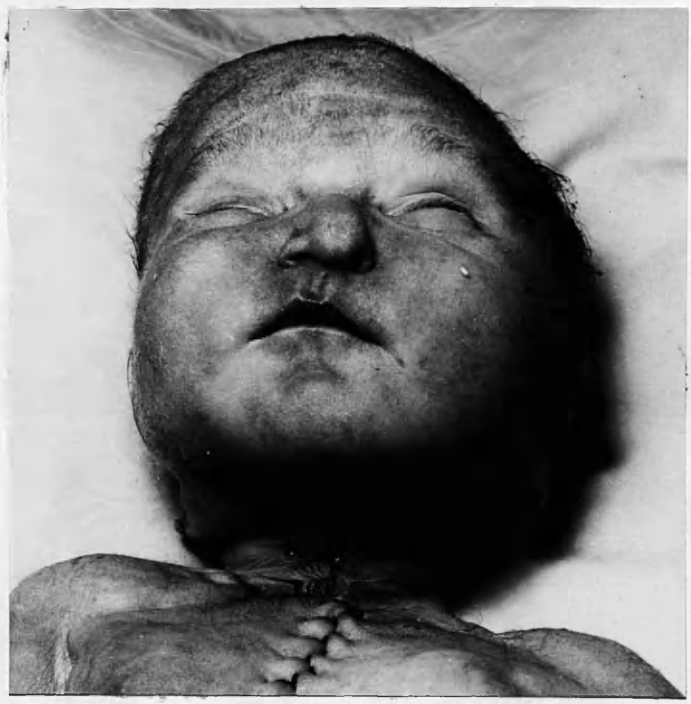


Fig. D.16. A baby with renal agenesis showing the facial appearances suggestive of "premature senility." The mis-shapen nose and asymmetrical head are presumably the result of pressure secondary to the oligohydrammios.

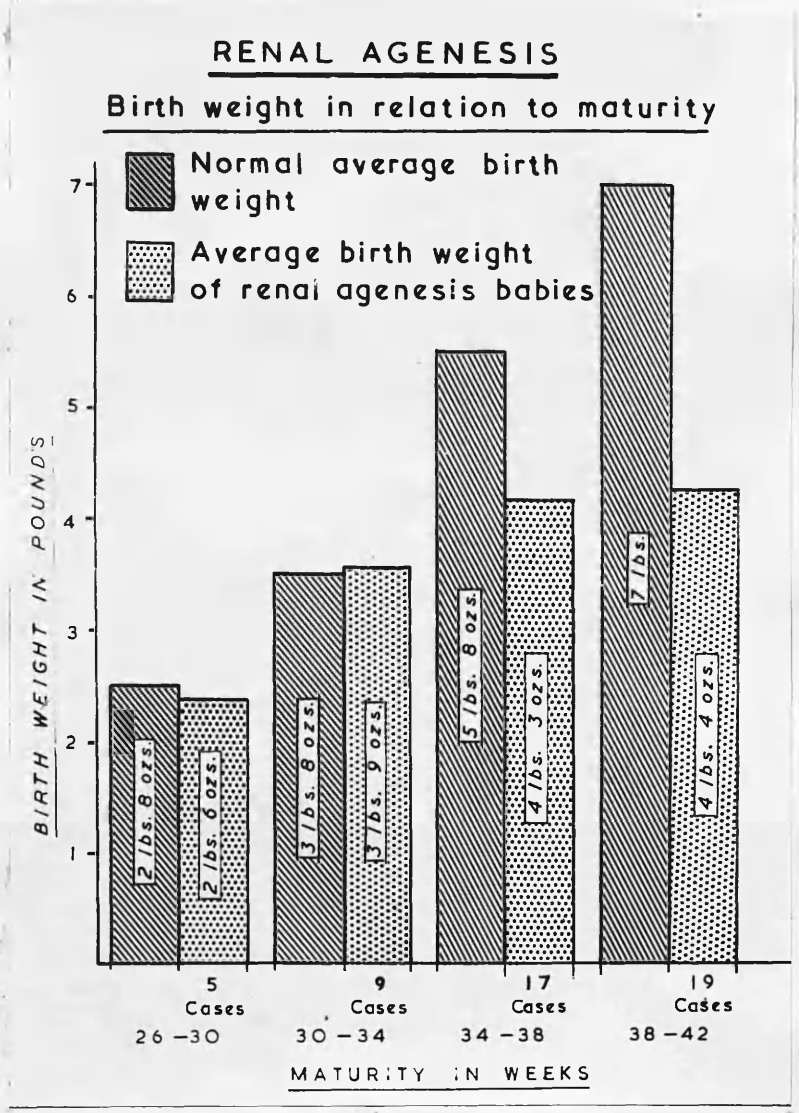


Fig. D.17. The average birth weights of babies with renal aplasia, grouped according to maturity, (stippled columns) compared with the normal average birth weight of babies of comparable maturity (obliquely hatched columns). It will be seen that the babies without kidneys fail to gain weight as expected beyond 34 weeks gestation.

weight is less than expected.

This is a most interesting observation and immediately raises a host of questions in one's mind. It has previously been assumed, even by those who accepted that ante-natal secretion of urine occurred, that this was not essential for the babies health. This would appear to be a mistaken assumption.

By what mechanism could the renal non-function produce this effect on the foetus? Three possibilities present themselves :-

a. It may be that the foetal kidneys normally remove from the foetal blood stream some noxious metabolite or other harmful substance and excrete it into the liquor amnii where it exerts no ill effect. In the absence of this action the noxious substance might accumulate in the foetal blood stream and thus retard growth. If this were the correct explanation it would invalidate the common view that the placenta exerts a comprehensive excretory function for the foetus.

Strong evidence against this mechanism has been produced by Bain (1958). He conducted investigations of the blood urea and electrolyte levels in several of these babies at birth without finding any significant deviation from normal.

b. It may be that the foetus derives some of the nutrient necessary for its growth by imbibing liquor amnii and that a deficient oral intake of this leads to failure to gain weight.

It would be strange indeed if this were the explanation, for it seems quite clear that the oligohydramnios in these cases is due to lack of foetal urination. It is hard to believe that the foetus would be dependant for normal weight gain on imbibing something which it has already secreted.

c. The third possibility presents that the liquor amnii in normal pregnancy is beneficial to foetal growth by its bulk and resultant distensile effect on the uterus. This might act by improving the placental blood supply.

This last explanation seems the most reasonable though the matter is clearly a long way from being proven. It is in agreement with the conclusions of Harrison and Malpas (1953) who, working with early pregnancy material, came to the conclusion that the function of liquor at that stage of pregnancy is to provide a distension growth stimulus to the uterus. They showed a definite correlation between liquor volume and foetal size.

This observation opens up other most interesting problems. Textbooks have for long recorded the association of hydramnios with large babies and oligohydramnios with small babies but it has always been

assumed that the volume of liquor is secondary to the foetal size. Could it be that a large volume of liquor is conducive to growth whereas a small volume leads to retardation of growth? Could it be that in the "placental insufficiency" syndrome in which oligohydramnios is described as a feature, it is in fact sometimes the primary cause?

Summary and Conclusions :-

From the studies which have evolved following the original observation of these amniotic lesions in cases of renal aplasia the following deductions can be made :-

1. In cases of oligo-hydramnios or anhydramnios, the amnion tends to develop nodules which are composed of masses of keratinized squames, apparently transferred from the foetal skin by direct contact.
2. Oligo-hydramnios appears to be a constant accompaniment of renal agenesis, provided that the foetal swallowing mechanism is operating normally.
3. Liquor amnii has more than one source of production in late pregnancy of which foetal urination is definitely one. The exact proportion contributed by the foetal urine still awaits determination but from these observations, together with other studies, it seems probable that it is a major one. Studies to determine this point are proceeding.
4. Whatever the main sources of supply and disposal of liquor and whatever the rate of production it would appear that foetal swallowing and urination to a large extent control the volume of liquor.

5. Cases of renal agenesis present in late pregnancy a typical clinical and radiological picture which is like that found in association with "placental insufficiency." There is, however, no factor present likely to be causing such insufficiency.

6. The diagnosis of renal agenesis in the foetus from the external appearances may be aided by inspection of the membranes for the presence of amnion nodosum.

7. Many of the external features found in association with renal agenesis appear to be secondary effects of deficiency of liquor amnii.

8. Reasons are given to show that both the ante-partum suspicion of renal agenesis and, after birth, what might be termed the "ante-post-mortem" diagnosis of the condition are matters of greater importance than might be thought.

9. The most surprising discovery from the whole study was the observation that babies with renal agenesis though of normal size in early pregnancy, failed to gain weight in the last 6 weeks of pregnancy. This opens up several entirely new lines of thought on the factors controlling foetal development :-

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