The Canadian Medical Association Journal

JANUARY 15, 1959 • VOL. 80 NO. 2

POLYHYDRAMNIOS AND OLIGOHYDRAMNIOS*

T. N. A. JEFFCOATE,† M.D., F.R.C.S.E., F.R.C.O.G. and J. S. SCOTT,† M.B., Ch.B., M.R.C.O.G., *Liverpool, Eng.*

THEORIES CONCERNING the origin of liquor amnii were well reviewed by Shaw and Marriott[36] in 1949 and do not require repetition. Suffice it to say that most recent opinion has been coloured by observations on the transfer of radioactive isotopes to and from the amniotic cavity, and especially by the studies reported by Vosburgh *et al.*[41] These workers concluded that the water content of liquor amnii is completely exchanged every three hours. This conclusion, however, does not tally with the clinical behaviour of women who sustain a rupture of the membranes during pregnancy and who do not immediately go into labour. Such women never lose fluid at the rate of one to two pints each three hours, as might be expected if liquor is formed so quickly.

It is not always realized that Vosburgh's experiments on the rate of water exchange were limited to five women whose pregnancies varied in duration from 14 to 40 weeks. The results differed widely from case to case, without any correlation according to the period of pregnancy, and the figure of 34.5% renewal of fluid per hour was obtained by taking an average. The sodium exchange was studied in 20 pregnancies, the duration of which varied from 10 to 40 weeks; the findings were again reduced to an average to suggest a complete turnover once in 14.5 hours, a rate of renewal five times less than that of the water.

This work received a measure of confirmation by Plentl and Hutchinson,[29] but the evidence from this type of experiment is as yet so limited that the above figures should not be allowed to prejudice other observations. It would seem especially important that all future investigations in this field, whether they be by following the behaviour of tracer substances or by physico-chemical analysis, should be carried out for each phase of pregnancy separately. This is because there is much to suggest that the rates of formation and removal, as well as the origin and destination, of liquor amnii change with the progress of pregnancy. For example, the liquor is isotonic with plasma during the early months but becomes increasingly hypotonic in the later stages of pregnancy.[24] Again, its urea, uric acid and creatinine contents are similar to those of plasma up to the fifth month; thereafter they are greater.[11]

For the present, the most important contribution to knowledge made by radioactive isotope studies is the clear demonstration that the pool of liquor is not a static reservoir. Both the fluid and its chemical contents are in a state of continual flux, passing to and from their surroundings. The volume of liquor, however, remains fairly constant for each particular stage of pregnancy. The normal volume, and pathological variations constituting polyhydramnios and oligohydramnios, are likely to be determined by the *relative* efficiency of the mechanisms for production and disposal.

ORIGIN OF LIQUOR AMNII

From or Through the Membranes

Liquor appears early in the pregnancy, when the fetal tissues are underdeveloped and non-functional. Moreover, it is found within the sac of blighted ova in which the fetus is absent or rudimentary. Such observations strongly suggest that fluid enters *via* the membranes. Moreover, in early pregnancy, liquor is so similar to plasma in composition that it could well represent a dialysate. Amniotic epithelium is so constituted as to suggest that it could have a secretory function; indeed, such a function has been demonstrated histologically.[40] It is therefore possible that the amnion plays an active part in the formation of liquor. If liquor is regarded as a transudate in early pregnancy and as the product of a selective secretory action of the amnion in the later months, the progressive changes in its chemical and physical properties might be explained. It is, however, difficult to conceive of the amnion producing or transmitting fluid in *large* amounts, because most of it is not in direct contact with a rich blood supply. The exception is that portion of the membrane which covers the placenta, and it has been sug-

*An elaboration of a paper presented by T. N. A. Jeffcoate to the Section of Obstetrics and Gynæcology of the Ontario Medical Association at Toronto, May 15, 1958.

†From the Department of Obstetrics and Gynæcology, University of Liverpool.

gested that this specialized area, with its extensive vascular connections, plays some part in liquor production. The common association of polyhydramnios with hæmangiomatous tumours of the chorion is quoted in support. This finding is capable of different interpretations. Thus, McInroy and Kelsey[23] concluded that, even in these cases, it is the fetus which is responsible for the hydramnios. They argued that the placental tumour occupies so much of the intervillous space that it leads to placental insufficiency with retention of metabolites within the fetus. These in turn stimulate the fetal kidneys to excrete abnormally large quantities of fluid into the amniotic cavity (see later).

From the Fetus

The parts of the fetus which might secrete fluid into the amniotic cavity are the skin and its appendages, the respiratory tree and the kidneys. The main argument against a purely fetal origin is that liquor is present early in pregnancy before most fetal organs are formed. This objection is valid except in relation to fetal ectoderm which is present at a very early stage, which has the same origin as amnion, and which might conceivably have a similar function. Moreover, the volume of liquor in early pregnancy varies directly with the surface area of the fetus.[15]

Once fetal organs have developed, the production of liquor by the respiratory tract and kidneys, if not by the skin, becomes feasible. The lungs are generally believed to be collapsed and in receipt of a relatively poor blood supply during the antenatal period. Alveolar secretion of fluid is therefore presumably small, and a contribution from the trachea and bronchi, although possible, is unlikely to be a major one. Nevertheless, Whitehead and others,[44] Macafee[25] and Morison[26] consider that, in part at least, the liquor amnii is derived from the respiratory tract of the fetus.

The fetal kidneys have attracted attention ever since Hippocrates postulated that liquor amnii is fetal urine. That the kidneys can function before birth is made clear by the fact that a baby often voids urine immediately after birth, and by the finding of fluid in the bladders of approximately one-third of stillborn babies which come to autopsy.[20] Nevertheless, Holtermann[18] concluded that fetal urine does not contribute to the liquor amnii. He administered methylene blue to the mother and recovered colourless liquor at delivery, yet found the fetal urine stained with dye in the neonatal period. The test agent, however, was given only a short time before delivery and it now seems probable that the fetus did not have sufficient time to void dye-stained urine before its birth.

Because of such experiments there arose, in the earlier part of this century, the concept that the kidneys do not *normally* secrete while the fetus is *in utero* and that they only do so when placental function is deficient—as it sometimes is during pregnancy and as it often is during labour. This idea, reviewed by one of us (T.N.A.J.) in 1932, is supported by little more than conjecture. The newly born baby does not have to withstand labour before voiding urine; it does so even when delivered by elective Cæsarean section. When the fetal urethra is obstructed, the whole urinary tract becomes distended with quite large volumes of fluid before labour, and that without there being any evidence of placental failure. Nevertheless, even if the fetal kidneys normally secrete before birth, it still remains possible that they pour out unusually large amounts of fluid when the function of the placenta[23] or of the maternal kidneys[45] is grossly defective.

Urine is reported to have been found in the fetal bladder as early as the 14th week of pregnancy,[24] and it is now generally accepted that the kidneys are invariably capable of some function by the 20th week. This timing may be of considerable significance in explaining the reported progressive change in the chemical composition of liquor which commences about mid-pregnancy. Summation of the evidence suggests that, up to the time the fetal organs are developed, liquor amnii is derived almost entirely from the amnion, or from fetal skin and amnion. After mid-pregnancy, an additional and perhaps even more important source of supply is the fetal kidneys, with possibly a contribution from the fetal respiratory tract. It has to be recognized, however, that the composition of the excretion of the fetal kidneys differs from that of urine excreted after birth. The renal filtration and concentration functions vary with the period of intrauterine development[11] and also change progressively during infancy. Moreover, certain components of the fetal renal excretion may be reabsorbed by the amnion. Such factors need to be considered when the results of chemical analysis of liquor amnii are interpreted.

The importance of the renal contribution to the liquor during late pregnancy is further borne out by study of cases of oligohydramnios (see later).

THE DISPOSAL OF LIQUOR AMNII

Through the Membranes

The amnion might absorb as well as secrete fluid or, depending on osmotic pressures, at least allow a transudation back into the maternal circulation. Whether production is a more important amniotic function than is disposal, and whether their relative importance varies with the stage of pregnancy, are unknown. Nevertheless, the possibility of the amnion playing some part in the return of the various components of liquor to the maternal circulation must be conceded. It is, for example, the only obvious route to account for the disappearance of fluid from the pregnancy sac after fetal death *in utero;* this at least shows that the membranous lining is not waterproof.

Absorption by the Fetus

Fetal skin, like amnion, might absorb water, but this is more likely when it is represented by primitive ectoderm than when it is a well-developed stratified epithelium covered with vernix caseosa. The fetal respiratory tract might also form a disposal route, at least after mid-pregnancy. The pathway which seems most likely to offer an exit for substantial amounts of fluid is, however, the fetal alimentary canal. The finding of epithelial debris and lanugo hairs in the fetal stomach suggested to obstetricians of the past that the fetus *in utero* does swallow. Dyes introduced into the amniotic sac were also found to stain the fetal alimentary tract. Later, at a time when amniography was considered a reasonable diagnostic procedure, radiographs often showed incidentally that the fetus had imbibed radio-opaque material which, having been introduced into the amniotic sac, could be followed through the stomach and the intestines (Fig. 1). Clinical studies of cases of polyhydramnios (see later) go to show that this disposal route is an important one, if not in terms of the total quantity of fluid absorbed, certainly in the control of the volume of liquor contained by the amnion. Of the liquor amnii swallowed, the fluid component presumably enters the fetal circulation, with or without subsequent passage across the placenta to the maternal circulation.

Rosa,[31] using inulin as a tracer substance, calculated that the fetus swallows 500 ml. of liquor amnii every 24 hours. Of this 40 ml. is excreted back into the amniotic cavity by the fetal kidneys,* and 435 ml. passes into the maternal circulation *via* the placenta. These conclusions, interesting though they be, cannot yet be accepted as final because the experimental methods employed depended on a number of assumptions. Gray, Neslen and Plentl,[13] working with an isotope tracer technique and comparing their findings in the human being with those obtained on hydrodynamic models, calculated that at least 25%, and probably more than 50%, of the water transfer from amniotic fluid to mother is accomplished through the intermedium of the fetus. Plentl and Gray[28] later gave figures for the volumes of fluid passing each way between mother, fetus and liquor, and concluded that fluid normally circulates from mother to fetus to liquor to fetus and back to mother. In hydramnios they found that this circulation, although still present and in the same direction, is reduced. In this condition they found an additional direct transfer of water from mother to liquor without passing through the fetus; this, they said, does not occur normally.

These conclusions must again be accepted with reserve because some of Plentl and Gray's arguments were based on statements about clinical

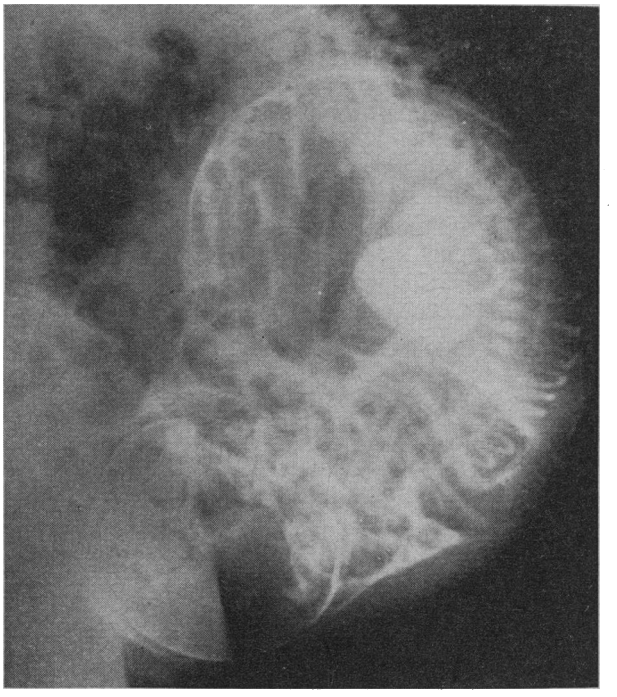

Fig. 1.—An amniograph showing that the fetus has swallowed radio-opaque material which had been introduced into the amniotic cavity. (Reproduced by permission of the Editor of *The Lancet*.)

associations of hydramnios for which the evidence is slender. Thus they stated that placental infarction and "especially the circumvallate placenta are significant and consistent findings" in cases of hydramnios. In a series of 578 placentæ of circumvallate type studied by one of us (J.S.S.) polyhydramnios had been an antenatal association of only 3 (0.5%). This compares with an 0.8% overall incidence of hydramnios amongst all patients delivered in the same hospital during the period of the survey. Plentl and Gray[28] also assumed that mongolism, achondroplasia and cardiac malformations are significant causes of hydramnios. We do not know of any evidence to substantiate this, and our own experience is to the contrary.

Although details remain doubtful there emerges, from the foregoing considerations, a working hypothesis. This envisages that liquor amnii is in a state of coming and going throughout pregnancy; its rate of exchange may be rapid but it almost certainly varies with different stages of pregnancy. During its continual circulation, certain constituents of the liquor are added and subtracted as in the case of the circulation of blood. The origin of liquor amnii is at least twofold: (1) from the amnion and possibly the fetal ectoderm, (2) from the fetal kidneys and possibly the fetal respiratory tract. There are at least two pathways for its disposal: (1) by the amnion, (2) by the fetal alimentary tract, and possibly by the fetal lungs or skin. The amount of liquor present at any one time is determined by a balance between flow and ebb. If the supply is relatively greater than the disposal mechanism can handle, polyhydramnios results.

*This work, if confirmed, does not mean that the total output of the fetal kidneys is only 40 ml. in day. An additional, and probably much greater, amount of urine is likely to be derived from fluid entering the fetal circulation through the placenta.

When disposal outruns supply, oligohydramnios occurs.

This concept is strongly supported by clinical observation of cases in which the amount of amniotic fluid is increased or reduced. Gross deviations from the normal volume of 500-1500 ml. of liquor in the later weeks of pregnancy are not common. In many cases where some abnormality in this respect is noted, an obvious cause is not found. Nevertheless, in a considerable proportion some factor is present which appears to be responsible for the unusual amount of liquor.

POLYHYDRAMNIOS

A review of 169 consecutive cases of hydramnios encountered in the practice of one hospital with which we are associated revealed that in 54 (32%) the excessive amount of liquor was associated with a malformation which would probably interfere with the fetus's swallowing or absorbing liquor amnii from the intestine.[33] These conditions were as follows:

Anencephaly	32 cases
Iniencephaly	2 "
Hydrops fœtalis with gross œdema of the lips and fauces	4 "
Œsophageal atresia	12 "
Duodenal atresia	3 "
Diaphragmatic hernia	1 case

1. *Anencephaly and iniencephaly.*—These malformations could interfere with swallowing, either because the deglutition centre is not developed in the brain or because of the local deformity affecting the mouth and neck. In order to establish that failure of the fetus to swallow is the mechanism whereby these lesions cause hydramnios, amniography was carried out in four cases in which anencephaly was diagnosed in pregnancy. It was expected that, unlike the normal baby, the anencephalic fetus would not show any radio-opaque material in its alimentary tract. This happened in three of the cases but the fourth fetus did swallow. This exceptional case only goes to prove the rule, because delivery showed that the antenatal radiographic diagnosis of anencephaly was incorrect. The vault of the fetal skull, together with normal cerebral tissue, was present and the actual deformity was a severe degree of occipital encephalocœle. This case, incidentally, was the only one of the four which did not show clinical evidence of hydramnios. Anencephaly is sometimes seen without polyhydramnios, but the deformity is then usually incomplete and of a degree which might still allow fetal swallowing.

2. *Hydrops fetalis.*—This interesting condition of the fetus produces hydramnios only occasionally. When it does, the fetus usually suffers from gross œdema of the lips, mouth and fauces; such swelling could prevent swallowing.

3. *Œsophageal and duodenal atresia.*—The occurrence of polyhydramnios in cases in which there is an obstruction of the upper part of the fetal alimentary tract provides the strongest evidence that swallowing and intestinal absorption play an important role in the disposal of liquor amnii. During the period under review there were in all 13 cases of œsophageal atresia but polyhydramnios was present in only 12. The one exception again goes to establish the importance of swallowing in the removal of liquor amnii. In this case the congenital defect was not of the common variety but one in which the upper and lower parts of the œsophagus had an indirect communication *via* the trachea.[33] This made it possible for liquor to reach the intestine to be absorbed.

It seems probable that, in the one case of diaphragmatic hernia, the swallowed fluid was prevented from reaching the lower absorptive regions of the intestine by obstruction due to kinking.

Polyhydramnios associated with fetal ingestion defects is rarely clinically manifest until after the 20th week. This may mean that fetal swallowing does not become the main method for disposal of liquor until relatively late in pregnancy. Alternatively, it might signify that, after mid-pregnancy, there is an additional amount of liquor to be removed and that this is more than can be cleared by routes other than the fetal alimentary tract.

It is not to be overlooked that in two-thirds of our cases of polyhydramnios there was no evidence that the fetus was unable to dispose of liquor. In these a definite causal mechanism was not found, but it can be postulated that either another outlet for liquor was not operating or, even more likely, that fluid was being produced in excessive amounts. Polyhydramnios could in theory be caused by an overactive secretory function of the amnion, a possibility which Plentl and Gray's[28] work might be construed to support. It is tempting to question whether the finding of an excessive amount of fluid in the pregnancy sac in association with maternal diabetes is related to the reported finding of cortisol in the liquor in such cases.[17]

Polyhydramnios might even be the result of fetal polyuria, a possible example of this being the excessive amount of liquor sometimes found in one sac of uniovular twins. In such case it is suggested[9, 23] that there is a placental communication between the circulations of the two fetuses and that the heart of one over-rides that of the other. The result is unequal renal circulations and functions, the dominant fetus secreting urine for both and thus surrounding itself with more liquor than normal. This largely theoretical concept *may* be supported by the following recently observed case.

When a primigravid woman was noted to be suffering from hydramnios, radiography revealed a twin pregnancy, one fetus showing evidence of gross malformation. Because of incoordinate uterine action in labour, delivery was effected by Cæsarean section, and this allowed study of the exact state of affairs. The

amnion of the normal fetus contained more than a measured 5 pints (3 litres) of liquor; the other sac was almost dry. The fetus without liquor was an acardiac acephalic monster, with only a small amount of rudimentary renal cortex on one side and that not served by a patent ureter. The twins were uniovular and there was an obvious anastomosis between the two placental circulations. Here would at first appear to be a clear example of polyhydramnios associated with cardiac dominance. A more acceptable explanation, however, is the absence of functional renal tissue from one fetus. This could account for its own oligohydramnios and also for induced polyuria in its brother.

That cardiac dominance alone is not always an adequate explanation of polyhydramnios in one sac of uniovular twins is suggested by a second case.*

Because of the large size of the uterus at the 20th week of pregnancy, a primigravida was radiographed and found to have twins. By the 27th week so much liquor was present that the abdominal girth measured 47 inches (118 cm.). Spontaneous labour two weeks later resulted in the delivery of a stillborn hydropic fetus (weight 2350 g.) from a sac which contained a massive but unmeasured amount of liquor amnii, and of a normal fetus (weight 790 g.) from a sac containing relatively little fluid. The twins were uniovular, and the placenta was single (weight 910 g.) with a definite although not prominent vascular communication between its two halves. The exclusion of isoimmunization to any of the blood factors made it necessary to look for another cause of the hydrops fetalis. The most likely one is that the œdema was the result of relative cardiac inefficiency. A mechanical circulatory basis for hydrops fetalis is an old concept which has tended to be overlooked as a result of modern interest in rhesus incompatibility. It is supported by the fact that acardiac monsters (including the one mentioned above) nearly always show generalized œdema of the tissues. If this is the explanation of the extraordinary finding of hydrops fetalis affecting only one of uniovular twins, then polyhydramnios did not accompany cardiac dominance; it was found in the sac of the fetus with presumed cardiac inefficiency. In this case, as in the first, that is another possible explanation of the polyhydramnios, namely, hydrops fetalis alone. This condition, however, rarely operates so early in pregnancy.

OLIGOHYDRAMNIOS

Oligohydramnios is recorded far less frequently than is polyhydramnios, possibly because it tends to pass unnoticed.

In the first half of pregnancy oligohydramnios is not seen as a recognizable clinical entity. If it does occur, it is presumably the result of a fault in the amnion, or in the chemical and other mechanisms which control the exchanges to and from the maternal tissue fluids through the membranes. In fact, its occurrence in early pregnancy would almost inevitably cause abortion because the accumulation of fluid is essential to stimulate the uterus to grow to accommodate the young fetus.[15]

In late pregnancy the finding of anhydramnios or a severe degree of oligohydramnios often indicates that the fetus *in utero* is suffering from a gross renal abnormality or from an obstructive lesion in the lower urinary tract. In other words, the fetus is unable to void urine into the amniotic sac. Bardram[5] reported concomitant oligohydramnios in 10 out of 13 cases of gross defects in the fetal urinary system, and Bates[7] noted a deficiency of liquor in 13 out of 14 cases of renal agenesis and dysplasia. Shaw and Marriott,[36] as well as others, also reported isolated examples. Potter[30] reviewed 30 cases in which the fetus suffered some condition rendering it unable to void urine, and said that in none had the obstetrician seen liquor escape during labour. Selby and Parmelee[35] recorded a case in which a baby without kidneys was born with the amnion intact. There was definitely no liquor in the sac. An equally convincing account of anhydramnios discovered at elective Cæsarean section was given by Bates.[7]

One of us (J.S.S.), together with A. D. Bain,[3] recently collected 50 consecutive cases of renal agenesis and dysplasia occurring in the maternity departments of certain hospitals in Liverpool and Edinburgh. In going into the clinical histories of the mothers of these babies retrospectively, it was found that liquor amnii had been definitely seen in only one case. In 14 the records contained no comment about the presence or absence of liquor; in 28 there were various entries which strongly suggested that the liquor had been deficient; in the remaining seven there was a specific note stating that liquor amnii was negligible in amount or absent. We now have four further cases to add to this reported series; in none was a significant amount of liquor amnii present. Davidson and Ross,[10] writing in 1954, collected 232 cases of renal agenesis and severe dysplasia from the literature. The addition of cases recorded by Baron,[6] Osmond,[27] Bound and others,[8] Selby and Parmelee,[35] Welch,[43] and our own 54 cases, gives a total of 295 recorded cases. Among these there was firm or presumptive evidence of oligohydramnios or anhydramnios in 100, while in the vast majority of the others there was no statement as to the amount of liquor amnii. Amongst the very few cases in which liquor was present in normal or excessive amounts are those reported by Wagner,[42] Balard,[4] Schiller and Toll,[32] Gowar,[12] Allen and Orchard[1] and Silvester and Hughes.[37] There is, in addition, the single case in our series of renal agenesis in which liquor was definitely present: indeed this patient suffered from polyhydramnios.

Consideration of this last exception offers a clue to the explanation of the other isolated cases in which renal non-function in the fetus was not associated with oligohydramnios. In our case the fetus not only had renal agenesis but also had

*The details of this case are described by Hibbard.[16]

iniencephaly. This anomaly, as previously noted shares with anencephaly a predisposition to cause hydramnios, apparently because it interferes with fetal swallowing. It is therefore presumed that, in this case, the amount of amniotic fluid of non-renal origin exceeded that which could be taken away by routes other than the fetal alimentary tract.

This example serves to illustrate well that liquor amnii has multiple sources of origin and multiple routes of disposal. In the other recorded cases of renal agenesis in which liquor volume was normal or excessive it is almost certain that additional unrecognized factors either interfered with some route of disposal or caused an over-production of fluid from a non-renal source.

Babies without functional kidneys are born dead or die within a few hours of birth. Their blood urea is not raised, and they do not succumb from renal failure. Their death is usually an asphyxial one and is the result of pulmonary hypoplasia which invariably accompanies renal agenesis. It is, therefore, necessary to consider the possibility that the oligohydramnios found in these cases is the result of a failure of the lungs to contribute fluid to liquor amnii. This is unlikely because when the fetal kidneys and lungs are normal, but the urethra is obstructed, oligohydramnios still occurs. Indeed, pulmonary hypoplasia coincident with renal agenesis may well be the result rather than the cause of oligohydramnios.[3] Be this as it may, the evidence strongly suggests that the urinary tract is more important than the respiratory system in the normal production of liquor.

Although Schiller and Toll[32] noted a gross abnormality in the fetal renal tract in only 15 out of 57 reported cases of oligohydramnios, Potter[30] considered that a deficiency of liquor is rare except in association with bilateral renal agenesis or obstruction of the urethra. Excluding cases of postmaturity and of retention of a dead fetus *in utero,* in which the amount of liquor does become reduced, we did, until recently, subscribe to Potter's view. During the past 18 months, however, among approximately 5000 deliveries in one of the hospitals in which we work, there were six proved cases of oligohydramnios. In three of these the fetus suffered from renal agenesis but in the remaining three the fetal urinary tract was normal. In each of the latter group there was a history of threatened abortion in the early months of pregnancy. Moreover, at delivery, large areas of the membranes were found to be covered on their maternal aspect with partially organized blood clot. These lesions were such that they could have hindered the transfer of fluid through the membranes, so it seems likely that, in these particular cases, the cause of the oligohydramnios was a failure of the amnion to contribute its quota to the total volume of liquor.

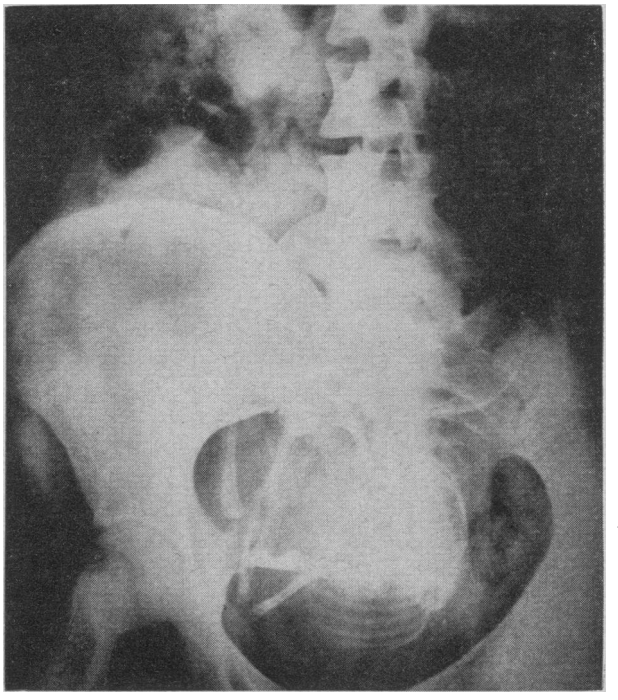

Fig. 2.—Radiograph in the case of oligohydramnios showing compaction of the fetus, extreme flexion of the spine and crowding of the skeleton towards the pelvis. The duration of the pregnancy was 34 weeks. The breech presentation is also a feature of oligohydramnios.

The low incidence of oligohydramnios in this last series again emphasizes the apparent rarity of the condition. Additional cases may, however, have passed unrecognized because the diagnosis is so difficult. It generally rests on noting during abdominal palpation a deficiency of fluid around the baby, and on observing that liquor does not escape vaginally before or during labour. Radiographs of the uterus and its contents are said to show typical signs of oligohydramnios.[21] These result from compaction of the fetus and consist of extreme flexion of the spine and crowding of the skeleton towards the pelvic cavity (Fig. 2). The appearance is similar to that described by Tager (1954) for fetal death *in utero,* except that Spalding's sign is absent. Radiographs were obtained in seven recent cases of oligohydramnios. Extreme flexion of the spine was a feature in four; in the remaining three this sign was absent but the limbs appeared cramped and the soft tissue outline of the uterus was closely applied to the fetus. The radiological signs of oligohydramnios are of interest but do not contribute much to the practical recognition of the condition, since some abnormality has to be noted clinically before radiographic examination is justified. They are therefore rarely more than confirmatory.

As a more certain means of diagnosing oligohydramnios, we draw attention to changes in the amnion which are almost specific and which, if searched for diligently during routine examination of the secundines after every delivery, should ensure that paucity of liquor is rarely overlooked. The diagnostic lesion is "amnion nodosum".[22, 34]

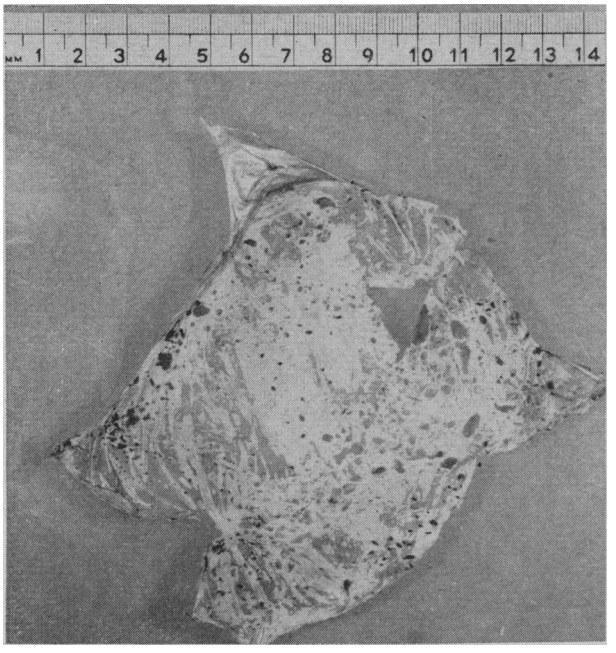

Fig. 3.—Amnion nodosum. A piece of amnion has been detached from the chorion and shows plaques and nodules on its fetal aspect. These appear quite dark because, in this particular case, they had a reddish colour; usually they are paler.

AMNION NODOSUM

This condition takes the form of small nodules or plaques on the fetal aspect of the amnion (Fig. 3). They are usually a dull grey-yellow in colour, but in two of our cases they were brick-red. The nodules can be found anywhere on the fetal surface of the amnion but are generally most numerous and obvious on the part of the membrane covering the placenta. They move with the amnion when it slides on the chorion but can be picked off the underlying membrane without disrupting its continuity.

Histologically, the nodules consist of masses of keratinized squames embedded in an acidophil matrix (Fig. 4). The cuboidal cells of the amniotic epithelium are generally absent in the region of the nodules but there is no sign of squamous metaplasia. In the latter condition there is a clear transition from cuboidal cells in the deep layer to flattened and keratinized cells on the surface of a stratified epithelium. In amnion nodosum there is merely a disorderly mass of keratinized squames loosely embedded on the amnion. Their attachment is so unstable that it is almost certain that they are of fetal origin, and that they represent deposits of squames shed from the fetal skin.

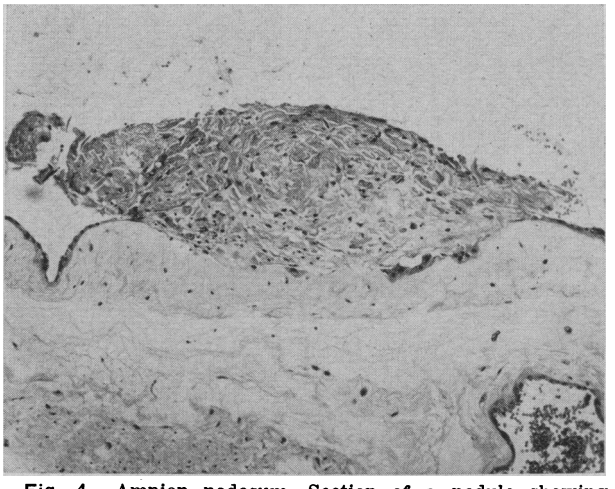

Fig. 4.—Amnion nodosum. Section of a nodule showing that it consists of degenerated squames clustered on the surface of the amnion. (Photomicrograph × 45.)

We have so far seen 14 cases of amnion nodosum, all collected within two years; nine of these were reported by Scott and Bain.[34] The accompanying conditions were as follows:

Oligohydramnios and renal agenesis	10 cases
Oligohydramnios with a normal fetal urinary tract	3 "
Intrauterine death of the fetus followed by its retention *in utero* for three weeks	1 case

The early cases of amnion nodosum were all found in association with renal agenesis and it was at first considered possible that the lesion was an associated developmental error, possibly of genetic origin. However, among 11 cases of renal agenesis in which the membranes were studied, there was one in which the lesion was not present. This was the one, mentioned earlier, in which concomitant iniencephaly caused polyhydramnios. In other words, only those cases showing oligohydramnios had nodules on the amnion. The conclusion that the lesion is associated with a shortage of liquor, and not with the renal defect directly, was confirmed by the later finding of three cases of amnion nodosum when the fetal urinary tract was normal. In these, as mentioned earlier, there was an extensive deposit of fibrin between the chorionic membrane and the decidua vera. Finally, there was one case in which a shortage of liquor resulted from prolonged retention of a dead fetus *in utero*.

In all pregnancies it is normal for superficial squames to be cast from the fetal skin into the liquor amnii. These remain floating freely. When, however, the amount of liquor is deficient, it would appear that the amniotic epithelium comes into continuous close apposition with the prominences of the fetal ovoid. This results in unusual friction which leads to excessive desquamation from the fetal skin. The squames, having little if any fluid in which to circulate, become deposited on the amnion. The amniotic cuboidal cells at the site of contact become destroyed, either by direct friction with the fetus or by the influence of the deposit of squames.

LIQUOR VOLUME AND FETAL WEIGHT

Study of the weights of babies born with renal agenesis or severe dysplasia raises another matter of some importance. Among the 50 cases recorded by Scott and Bain[34] it is known with reasonable certainty that oligohydramnios was present in 35 and it can be assumed that it was a feature of the majority of the others. Fig. 5 shows the weights

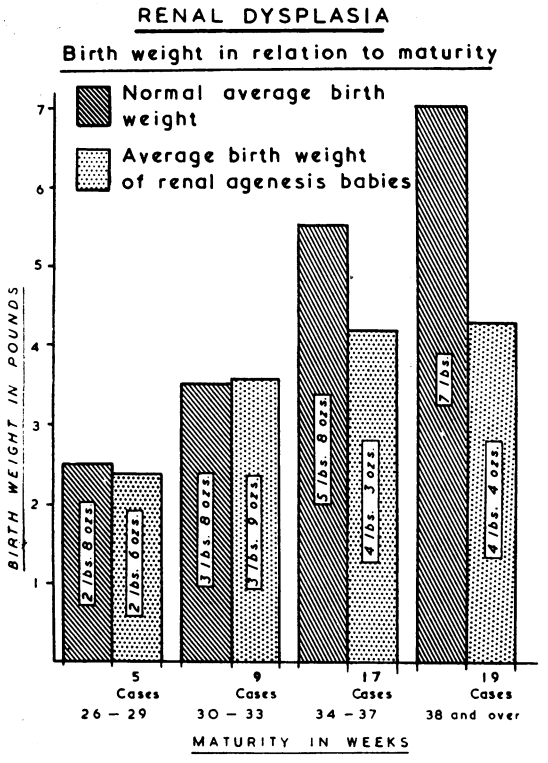

Fig. 5.—Average birth weights of 50 babies born with renal dysplasia, grouped according to maturity, compared with the average birth weights of normal babies of the same maturity.

of these abnormal babies, grouped according to maturity, compared with the average weights of normal babies of similar maturity. From this it is clear that whereas growth continued as expected up to the 34th week of pregnancy, the affected babies thereafter failed to gain weight. Indeed the heaviest birth weight recorded was 5 lb. 1 oz. (2300 g.). The findings are too consistent for them to be dismissed as a chance happening. Nor can they be explained simply on the basis of absence of certain organs, because: (1) the weight of the kidneys is trivial compared with the overall body weight; (2) 22 babies suffered cystic renal dysplasia and their kidneys were heavier than normal; (3) it is only in *late* pregnancy that the fetal weight is less than expected.

It has previously been assumed, even by those who accept that urine is normally secreted before birth, that this function is not essential to the baby's health. Our findings, however, suggest that, without it, there is retardation of growth. For this there are three possible explanations.

1. That the fetal kidneys normally remove from the fetal blood stream some noxious metabolite and excrete it into the liquor amnii where it exerts no ill effect. This concept is contrary to the common view that the placenta exerts a comprehensive excretory function for the fetus. Moreover, the urea and electrolyte levels in the blood of babies without kidneys are normal at birth.[10, 2]

2. That the fetus derives some of the nutriment necessary for its growth by imbibing liquor amnii, and that deprival of this impairs its weight gain. It is unlikely that the fetus thrives on what it has already excreted, which is the logical implication of this idea. Even if it is postulated that the low birth weight of the fetus is merely the result of its failing to drink sufficient water, it has to be recognized that, except for some dryness of the skin, these babies do not show signs of dehydration at birth.

3. That normal growth of the fetus depends on its fluid environment. An adequate amount of liquor amnii could exert its effect by allowing the fetus freedom of movement, by stimulating growth of the uterus, and possibly by encouraging a good placental circulation. This view, which appears the most reasonable, is in accord with the findings of Harrison and Malpas.[15] They studied liquor volumes and embryo sizes during the early months of pregnancy and concluded that the function of the liquor, even at that time, was so to distend and stimulate the uterus as to allow the proper development of the fetus. They showed, too, a definite correlation between liquor volume and fetal size.

If it be accepted that the fetus which fails to urinate becomes stunted because of the associated oligohydramnios, it is relevant to emphasize that its growth is slowed only from the 34th week of pregnancy onwards. This again suggests that the renal contribution to liquor amnii is relatively

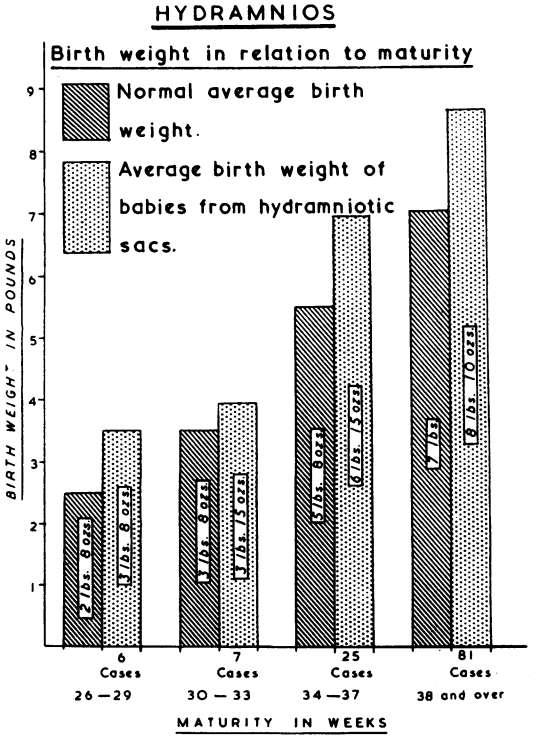

Fig. 6.—Average birth weights of babies born from polyhydramniotic sacs, grouped according to maturity, compared with the average birth weight for normal babies of the same maturity. Hydropic fetuses and those born to diabetic mothers were excluded because their excessive weight could have been caused by factors other than polyhydramnios. Anencephalic fetuses were also excluded because it was impossible to allow for their structural deficiency. The figures for both columns apply to single pregnancies only.

important only in late pregnancy. Earlier, the fluid is derived mainly from other sources.

It may be added that an association between birth weight and liquor volume has long been noted by clinicians. Thus it is commonly stated that a large fetus is a cause of polyhydramnios. Excluding those whose weights could have been either increased or decreased by another condition, we studied 119 babies born from mothers who suffered from polyhydramnios, comparing their birth weights with those of babies of similar maturity born from amniotic sacs containing a normal amount of liquor. The results, expressed as averages, are shown in Fig. 6, and confirm the general impression that a large baby and a large amount of liquor often go together. The nature of the association, however, is not necessarily the accepted one, and our observations lead to the suggestion that whereas oligohydramnios causes dwarfing, polyhydramnios encourages excessive fetal development. It follows that it may also be necessary to revise the outlook in regard to the small fetus with its small volume of liquor described as part of the ill-defined syndrome of placental insufficiency. What is the sequence of events? Is it small placenta → small baby → small volume of liquor? Or is it small volume of liquor → small placenta → small baby?

PLACENTAL SIZE AND LIQUOR VOLUME

Evidence on the growth of the placenta with the advance of pregnancy is conflicting, but it does seem that the chorionic plate continues to increase in area beyond mid-pregnancy.[14, 39] It is difficult to conceive that the placenta has a growing edge or that it shifts its connections to accommodate its increasing area. It must, therefore, be presumed that placental growth occurs *pari passu* with that of the portion of the uterine wall to which it is attached. This means that the greater the uterine distension the larger the area of the placenta, and so may be explained the rough correlation (for each phase of the pregnancy) between a large baby and polyhydramnios, and a small baby and oligohydramnios.

A previous interpretation of these relationships was that the unusual placental size accounts for the abnormal liquor volume;[40] this may still hold good in certain circumstances. However, in the two groups of cases with which we are mainly concerned, viz., polyhydramnios associated with failure of the fetus to imbibe fluid, and oligohydramnios associated with failure of the fetus to void urine, it is almost certain that it is the fetal abnormality which initiates a whole chain of events. The first result is an alteration in the volume of liquor; this then affects the uterine dimensions which control the placental size; the last is mainly responsible for determining the fetal bulk.

CONCLUSION

There is clearly no simple solution to the problems of the origin and fate of liquor amnii. From the evidence available it seems certain that each function is covered by more than one mechanism, and that the relative importance of different mechanisms changes with the progress of pregnancy.

Our clinical observations lead us, so far as late pregnancy is concerned, to disagree with Plentl and Gray's[28] statement that "Fetal micturition and deglutition play, at most, a very subordinate role in the physiology and physiopathology of the amniotic fluid." The exact place of these mechanisms in normal physiology remains to be decided, but failure of one or other of them is practically always associated with a disturbance of liquor volume. *Provided the other mechanisms for the production and absorption of liquor are operating normally,* pathological conditions of the fetus which are incompatible with fetal micturition cause oligohydramnios while lesions which prevent the fetus swallowing and absorbing liquor from the intestine result in polyhydramnios. Moreover, irrespective of their cause, oligohydramnios retards fetal growth and polyhydramnios encourages it.

The conclusion of Hutchinson *et al.*,[19] from their isotope experiments, that the rate of water exchange is independent of liquor volume may offer a basis of explanation for some of the apparent contradictions between the findings of clinicians and those of experimentalists. The actual volume of liquor at one time may not be determined by its *rate* of renewal and removal. Fetal swallowing and voiding could hardly be responsible for the enormous turnover of water which is suggested by those working with tracer substances, yet these two mechanisms do seem to be of vital importance to the control of the volume of liquor amnii found in late pregnancy. This raises the idea of a pool of fluid, the volume of which is largely *though not entirely* controlled by a relatively simple "tap" inflow (fetal micturition) and a "drain" outflow (fetal deglutition), with its molecules meanwhile constantly diffusing in and out of the maternal and fetal circulations. It is a concept which, although highly conjectural, might reconcile apparently valid clinical observations with the results of the radioactive isotope experiments so far reported. Failing such a reconciliation, however, well-documented clinical happenings cannot be ignored merely because they do not tally with experimental findings.

ADDENDUM

According to D. C. McKay, C. C. Roby, A. T. Hertig and Margaret V. Richardson (*Am. J. Obst. & Gynec.*, 69: 722, 1955), the liquor amnii in the early months of pregnancy is hypotonic to maternal plasma and not isotonic. This is contrary to the findings of Makepeace *et al.*,[24] which are quoted in the introduction, but it does not affect our main arguments and conclusions.

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CARDIOVASCULAR MANIFESTATIONS OF RHEUMATOID ARTHRITIS*

C. P. HANDFORTH, B.Sc., M.B., B.S. and
J. F. L. WOODBURY, B.Sc., M.D., C.M.,
Halifax, N.S.

RHEUMATOID ARTHRITIS is a chronic inflammatory disease of unknown etiology, the principal manifestations of which are polyarthritis and subcutaneous nodules. Rheumatoid disease of the cardiovascular system is known to occur but is rare by contrast with rheumatic heart disease.[1, 2] The pathological changes which may occur in the heart in rheumatoid disease are distinct from those caused by rheumatic fever. The object of this paper is to record three examples of fatal rheumatoid cardiovascular disease.

MATERIAL

CASE 1.—A 16-year-old white girl was admitted to hospital in 1957 because of fever and pain in multiple joints. These symptoms had been present for two weeks and followed a mild sore throat for which she had not sought treatment.

A maternal uncle had died at the age of 48 after having rheumatoid arthritis for 11 years. The cause of his death is unknown.

In 1951, at the age of 10, the patient had had pain and swelling of multiple joints lasting for three months. During this illness her heart was apparently normal and she had no residual joint deformities afterwards. In 1954, at the age of 13, she had a further attack of polyarticular pain and swelling associated with fever and anorexia. There had been some preceding lassitude but no apparent respiratory infection. She became bedridden and remained in bed for about nine months, during which time her weight fell to 66 lb. The wrists, cervical spine, hips and knees were the most prominently affected joints. Flexion deformities developed in her hips and knees (Fig. 1).

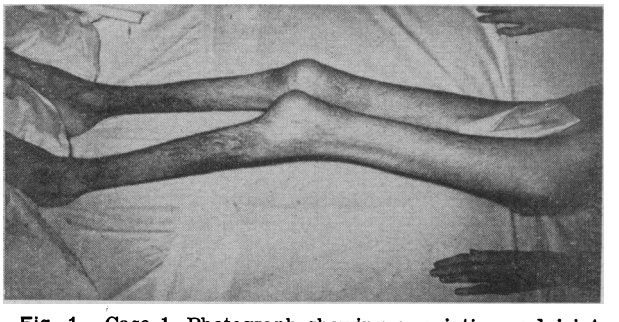

Fig. 1.—Case 1. Photograph showing emaciation and joint deformities.

There was no enlargement of the spleen or superficial lymph nodes, no psoriasis and no clinical evidence of heart disease. Radiography showed partial fusion of the sacroiliac joints, narowing of the joint spaces of the hips and skeletal rarefaction. She was treated in hospital for one year with an active physiotherapeutic regimen and some cortisone. When she returned home she weighed 80 lb. She was able to walk with the aid of canes but her wrist movements were limited to a few degrees.

*From the Departments of Pathology and Medicine, Dalhousie University and the Victoria General Hospital, Halifax, Nova Scotia.