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TWIN RESEARCH 4 -- Part A: Biology and Obstetrics
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Presidential Address: The Aberdeen Contribution to Twinning

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Although Francis Galton was the first to use twins for comparative genetic studies in a scientific way, there had been considerable interest and speculation about twinning from very early times. This has been referred to in numerous publications in the past, and indeed, Professor Gedda, Founding President of our Society, has written extensively on this [9]. The earlier writings referred almost entirely to the twins themselves, and there seemed to have been little attention paid to the mothers, except that they were either considered to have had intercourse with two men, or indeed, with a deity. Galton also referred in his publication of 1876 [8] to the largeness of the families into which twins are born, but a graduate of Aberdeen University, James Matthews Duncan, had pointed out some of the characteristics of mothers having twins ten years earlier. In 1865 he published his paper "On the Comparative Frequency of Twin-Bearing in Different Pregnancies" [7] and in this he showed that mothers of twins tended to be of higher parity and older. This very accurate observation has since been confirmed, but it was not clear whether age and parity were separate factors until Anderson, again working in Aberdeen, showed in 1956 that the twinning incidence increased up to a peak at age 35 and thereafter fell [1].

We have shown more recently [4] using genetic markers to determine zygosity, thanks to the excellent collaboration of Dr. Corney and his colleagues here at the Galton Laboratories, that it is only the women in Aberdeen who are having DZ twins who tend to be older and of higher parity, and that MZ twinning is not influenced by maternal age or parity. Anderson [1] also confirmed Tchouriloff's observation made in 1877 [25] that there was an increase in twinning incidence with increasing maternal height, and later in Aberdeen it was shown that this again only applied to DZ and not to MZ twinning. Dr. Corney presented these data at the meeting of this Society in Jerusalem in 1980 [5]. We also looked at the weight for height in women with twin pregnancies in Aberdeen and found (Table 1) that it was in the heavier women that twinning was more likely to occur [3].

Although Matthews Duncan [7] pointed out some of the characteristics of the women who were likely to have pregnancies, he did not study the maternal response of the mother to her twin pregnancy. Although the weight gain in these mothers had been known to be greater than in singleton pregnancy, it was not until we studied [3] the

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weight gain throughout pregnancy that it became apparent that the maternal response to a twin pregnancy was much more marked than to a singleton pregnancy as the weight gain was greater even in the early weeks of pregnancy before the weight of the fetus and the placenta could have any influence on the overall weight gain of the mother (Table 2). It seemed then that the overall response of the mother to her twin pregnancy was greater. This was confirmed when we looked at the water retention, measured by deuterium oxide, in these mothers (Table 3) [2]. We also found a greater plasma volume in the mothers of twins compared with singletons (Table 4). Also, as has been shown by Rovinsky and Jaffin [21], the cardiac output of the mother is greater in twin pregnancies than in singleton pregnancies. Similarly, the renal function is increased, as Swapp [24] in Aberdeen showed that the glomerular filtration rate was greater than in singletons. Other changes, such as the output of placental hormones, are greatly increased in twin pregnancies compared to singletons.

It was also, however, recognised that complications of pregnancy were more likely to occur in twin pregnancies, and in our total population studies in Aberdeen, we were able to compare the incidence of complications in twin pregnancies with those in singletons. The incidence of a serious complication known as pre-eclampsia, or the hypertensive disease of pregnancy, is much greater in twin pregnancies than in singletons. From our studies, we were also able to show that it was in both MZ and DZ twin pregnancies that this increased incidence occurred (Table 5). It thus makes it unlikely that this is a condition which is influenced by genetic structure: the DZ babies, of course, have different genetic composition.

Preterm labour is also more common in twin pregnancies than in singletons and we have recently found, in our Aberdeen studies, that preterm labour is more common in MZ than in DZ twin pregnancies (Table 6) [13]. Furthermore, the preterm labour in MZ pregnancies is mainly due to early rupture of the membranes and a high boy/girl ratio in the twins (Table 7).

So much then, for our studies in Aberdeen of the types of women having twin pregnancies and the maternal response and complications. Let us turn now to consider the outcome for the babies and our story again goes back to the last century for the Aberdeen connection with twinning.

There is a plaque on the wall of a church in Aberdeen with the inscription which says that Mary Slessor was born in Aberdeen in 1856 and at the age of 9 went to Sunday School there. The Mary Slessor story is a fascinating one which I can only very briefly refer to here. At the age of 11, she was taken from Aberdeen to Dundee where she became a mill girl, working in the jute mills. She was a very religious young lady and at the age of 25, after much argument and opposition, she was allowed to go as a missionary to West Africa. At the time, as you can imagine, this was a very unhealthy hostile place, but Mary, seemingly quite undaunted, went to Calabar and helped in the missionary work there. In particular, she was concerned with orphans, but it is not so widely known that most of these orphans were in fact twins. The whole story of the taboos against twins in Africa is a fascinating one and has been well documented. It is, for example, very interesting that in some parts of Nigeria twins were welcomed, while in others they were abhorred. The fate of some of these twins was grim, ranging from being treated as outcasts with their mothers, to being brutally killed. Mary collected these twins and must have saved many lives. The fact that so many of the children were twins is, of course, accounted for not just by the taboos, but by the fact that twinning is so much more common in Nigeria than in other parts of the world (Table 8). This has been shown by Percy

TABLE 1 - Zygosity of Twins Related to Weight for Height in Aberdeen Mothers

| Kemsley scale [12] | | MZ | | DZ | |
|--------------------|---------------------|----|-------|-----|-------|
| | | N | % | N | % |
| Thin | (<25th centile) | 9 | 18.4 | 8 | 7.3 |
| Normal | (25th-75th centile) | 24 | 49.0 | 44 | 40.4 |
| Fat | (>75th centile) | 16 | 32.6 | 57 | 52.3 |
| Total | | 49 | 100.0 | 109 | 100.0 |

TABLE 2 - Mean Weekly Weight Gain (kg) in Twin Pregnancies in Primigravidas Compared to Singleton Pregnancies

| Weeks | Twins | Singletons |
|-------|-------|------------|
| 13-20 | 0.60 | 0.42 |
| 20-30 | 0.54 | 0.47 |
| 30-36 | 0.64 | 0.40 |

TABLE 3 - Total Body Water (liters) in Normal Twin Pregnancies

| Gestation (weeks) | Primigravidas | | | Multiparas | | |
|-------------------|---------------|------|-------|------------|------|------|
| | N | Mean | SD | N | Mean | SD |
| 22-24 | 6 | 35.0 | 7.55 | 5 | 30.0 | 5.92 |
| 26-28 | 6 | 35.8 | 8.29 | 7 | 39.6 | 5.34 |
| 30-32 | 11 | 39.2 | 10.01 | 25 | 38.6 | 6.26 |
| 34-36 | 11 | 43.5 | 8.23 | 29 | 41.0 | 5.95 |
| 37-38 | 4 | 50.5 | 5.76 | 17 | 43.0 | 6.34 |
| 39-40 | 2 | 52.6 | 11.81 | 9 | 41.6 | 6.93 |

TABLE 4 - Mean Plasma Volume (ml) in Normal Singleton and Twin Pregnancies at 34 Weeks Gestation

| | Singletons | Twins |
|---------------|------------|-----------|
| Primigravidas | 3830 (49) | 4275 (17) |
| Multigravidas | 4100 (19) | 4657 (34) |

Number of cases in brackets

TABLE 5 - Incidence of Pre-eclampsia by Zygosity in 355 Primigravid and 851 Multigravid Twin Pregnancies in North East Scotland, 1951-1980

| | Proteinuric pre-eclampsia | | Late pregnancy hypertension | | Normotensive | |
|--------------------|---------------------------|-----------------|-----------------------------|-----|--------------|-----|
| | % | N | % | N | % | N |
| Primigravidas | | | | | | |
| MZ pairs (N = 119) | 17.65 | 21 ^a | 26.89 | 32 | 55.46 | 66 |
| DZ pairs (N = 236) | 18.64 | 44 ^a | 24.15 | 57 | 57.21 | 135 |
| Multigravidas | | | | | | |
| MZ pairs (N = 223) | 7.18 | 16 | 13.45 | 30 | 79.37 | 177 |
| DZ pairs (N = 628) | 8.28 | 52 | 17.20 | 108 | 74.52 | 468 |

^a Including 3 eclamptics.

TABLE 6 - Preterm Delivery by Zygosity in Twin Pregnancies

| | All | MZ pairs | DZ pairs |
|----------------------------------|-----|-------------|-------------|
| Term | 624 | 240 | 384 |
| Term deliveries | 448 | 160 (66.7%) | 288 (75.0%) |
| Preterm deliveries | 176 | 80 (33.3%) | 96 (25.0%) |
| Induction and cesarean section | 31 | 16 (6.6%) | 15 (3.91%) |
| Spontaneous premature labour | 72 | 25 (10.4%) | 47 (12.2%) |
| Spontaneous rupture of membranes | 73 | 39 (16.25%) | 34 (8.85%) |

TABLE 7 - Preterm Delivery and Sex of Twins

| | MM | MF | FF | Total | | MF ratio |
|---------------------------------------|--------|-------|---------|---------|---|----------|
| | | | | M | F | |
| All (624) | 223 | 198 | 203 | 644/604 | | 1.07 |
| Preterm deliveries (176) | 74 | 45 | 57 | 193/159 | | 1.21 |
| Induction and cesarean section (312) | 13 (9) | 6 (3) | 12 (10) | 32/30 | | 1.07 |
| Spontaneous premature labour (72) | 28 | 24 | 20 | 80/64 | | 1.25 |
| Spontaneous rupture of membranes (73) | 33 | 15 | 25 | 81/65 | | 1.25 |

Nylander [19], another graduate of Aberdeen University, who is now the professor of obstetrics and gynaecology in Ibadan and a well known member of this Society. The cause of this incidence is not known, but it is quite clearly, as shown by Percy Nylander, due to a much higher incidence of DZ twinning. The MZ twinning rate is about the same as in other parts of the world. The cause of this higher incidence in Nigeria, and indeed the low incidence in places like Japan and China will be speculated on later.

The fate of the twin children in Africa was, to a large extent, determined by the care which they were given after birth and, of course, this applied to the babies born anywhere. It seems, however, that there is a difference in the risks to MZ and DZ twins. In our studies in Aberdeen we have found that the perinatal death rate in MZ twinning is higher than in DZ twins. This is only partly due to the fact that the abnormality rate is higher in MZ than in DZ twins. This has been shown by the studies of the Aberdeen group in association with Dr. Corney's group at the Galton Laboratories [6]. This was also shown in the National Collaborative Perinatal Project study in America [16]. However, although deformity is a common cause of death in singletons, it accounts for only a small number of deaths in twins. Similarly, pre-eclampsia does not seem to be a major cause of death. The main cause of death in twins is due to the small size of the babies, either because of preterm delivery or growth retardation. The greater death rate in MZ compared with DZ twins is due to the smaller size and greater discrepancy in birthweight between MZ than between DZ twin pairs, and the greater tendency to preterm delivery in the MZ twins.

It seems, then, that there are marked differences in types of women who have twin pregnancies, and in the outcome of the pregnancies, depending on whether they are MZ or DZ twins, and it is thus interesting to speculate on the causes of the two types of

TABLE 8 - Comparison of the Incidence of Multiple Births in Some Populations in Nigeria, the UK and USA
 Expected Incidence, Calculated by Hellin's Formula, is Shown in Parenthesis

| | Total number of maternities | Incidence (per 1000 maternities) | | | | Reference |
|-----------------------|-----------------------------|----------------------------------|-------------|-----------------|--|---|
| | | Twins | Triples | Quadruples | | |
| Nigeria | | | | | | |
| Igbo-Ora | 6,160 | 47.0 | 1.62 (2.2) | | | Present study |
| Ibadan | | | | | | |
| Adeoyo and U.C.H. | 21,940 | 66.5 | 1.78 (4.4) | 0.06 (0.29) | | Present study |
| Ilesha | | | | | | |
| Wesley Guild Hospital | 10,800 | 76.1 | 1.94 (5.8) | | | Mulligan [15] |
| UK | | | | | | |
| England and Wales | 5,956,220 | 11.4 | 0.10 (0.13) | 0.0015 (0.0015) | | Registrar General [20] |
| USA | | | | | | |
| White * | 23,751,611 | 10.0 | 0.09 (0.10) | 0.001 (0.001) | | Statistical Bulletin of Metropolitan Life Ins. Co. [23] |
| Negro * | 3,946,146 | 13.4 | 0.14 (0.18) | 0.0018 (0.0024) | | |
| Sweden | 3,188,149 | 13.6 | 0.13 (0.18) | 0.0016 (0.0025) | | Herrlin and Hauge [11] |

* Figures refer to multiple births where at least one infant survived.
 Reprinted from Nylander [17] with kind permission of the editors of Annals of Human Genetics and Cambridge University Press.

twinning.

As MZ twinning seems to be such a chance occurrence, occurring with almost equal frequency throughout the world, it is difficult to speculate on the cause. One clue seems to be that the curious animal, the nine-banded armadillo, has litters of MZ quadruplets. Why the single fertilised ovum should divide into four is not clear, but it is thought that it is due to the long term which elapses between fertilisation and implantation which leads to relative anoxia and a tendency to splitting of the ovum. There is, however, a similar delay in implantation in the roe deer and badger without MZ twinning. There is no evidence that there is delayed implantation in the human when MZ twins occur.

The cause of DZ twinning also remains obscure, but, of course, it is now well known that when gonadotrophins are given to the mother, they are liable to produce multiple pregnancies. For example, the sextuplets of Florence, which were reported at the last conference by Giovannucci-Uzielli and coworkers [10], resulted from overstimulation with gonadotrophins. Professor Nylander has shown [18] that women who have twin pregnancies tend to have a greater production of follicle-stimulating hormones than those with singletons, and it is interesting to speculate that it is the taller, heavier, more fertile women who produce more follicle-stimulating hormones from the pituitary gland. Does this suggest, then, that the mothers of DZ twins are better reproducers, and, indeed, a type of superwomen, or is it that DZ twinning is an atavistic reversion? With Galton's close connection with Charles Darwin, it could be speculated that Darwin might have suggested that in the course of evolution there was sometimes a reversion, and that this could explain DZ twinning.

Now, obviously I wish to remain on good terms with both the mothers of DZ twins and the DZ twins themselves who are indeed such stalwart supporters of this Society, and I think that I should opt for the mothers being "supermums", and not adhere to the atavistic reversion theory.

But what about the fathers of DZ twins? Being a father of MZ twins, I can opt out of this question personally and, indeed, I am a little hesitant to put forward the speculation because the evidence at the moment is very scanty. I referred earlier to the low incidence of twinning in the Japanese and I believe, although I have no figures, that there is a lower incidence in China. The only figures I have were kindly given to me when I was in Malaya earlier this year by Professor Sen of Kuala Lumpur [23]. This certainly indicates that there is a lower incidence in the Chinese (7.0%) compared with the Malays (10.4%) and Indians (11.9%), in Malaysia, in 4982 deliveries, in 1980. To return to the speculation, I had a personal communication from Professor Roger Short, who is now working in Melbourne (Australia), saying that in strains of mice in which the males have small testes, the females have low ovulation rates, whereas in the strains with large testes, the females have high ovulation rates, and he also reported that the testes of Chinese in Hong Kong were less than half the size of Caucasian testes. I have no evidence to show that the fathers of DZ twins are "superdads" in that way, but again it is interesting to speculate that possibly the number of sperms might in some way determine whether the fertilised ovum will split or not. However, we know that the DZ twinning rate is low in Japan and Nylander has speculated that FSH levels are low in Japanese women.

There is much to be learned from the study of twins and twin pregnancies and by comparisons of MZ and DZ pregnancies, and I would like to close by recording my sincere thanks to those supermums of Aberdeen who have so willingly volunteered to take part in our studies.

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