serological evidence of disease activity towards normal (Pussell *et al.* 1978).

While plasma exchange has been performed in other forms of nephritis, the patients studied were too diverse to enable firm conclusions to be drawn. It seems that the more indolent forms of nephritis are not, in general, responsive to plasma exchange.

In patients with rapidly progressive nephritis, whether or not due to anti-GBM antibodies, we have noted a striking frequency of relapses associated with infection (Rees *et al.* 1977, and unpublished observations). It is becoming clear that the enhancement of tissue injury in immunologically-mediated disease following infection is a widespread phenomenon and may indeed underlie the natural history of some forms of nephritis. The increase in inflammatory mediators occurring in such infections may be responsible for the amplification of target organ damage where organs have already been 'marked out' by the initiators of injury. It is clearly important that exacerbating factors, especially infection, must be carefully documented in any evaluation of these diseases and their treatment. Furthermore, the increased risk of infection associated with steroid and immunosuppressive agents is a significant hazard of their use.

While patients with rapidly progressive nephritis or lupus nephritis form a minority of patients with glomerulonephritis, it is clear that regimes including plasma exchange can make a major contribution to reversing or preventing severe renal failure in these cases. It is less certain whether these techniques will be directly applicable to patients with the more chronic forms of nephritis. However, there is no doubt that many of the lessons learnt about the natural history of less common, more aggressive forms of nephritis can illuminate the pathogenetic mechanisms in other forms of renal disease as well as in other immunologically-mediated diseases.

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Intelligence and prenatal progesterone: a reappraisal[1]

General practitioners, especially those living on their practice premises, are natural audiences for the proud parent's orations about the achievements of their offspring. So it was that late in the 1950s, a proud mother, talking about her child's prowess at the local school, casually mentioned the names of four other children, also in the same practice, who regularly vied with her child for the exalted position at the top of the form. Later that day, the antenatal records of the children's mothers were studied and one common feature was observed – they had all received progesterone during the first trimester of that pregnancy for the relief of pregnancy symptoms, such as headaches, vomiting, depression and tiredness. One question had to be answered: 'Could the progesterone be responsible for the intelligence of these children?'

To test this possibility, 32 children aged 6–13 years, whose mothers had received progesterone, were selected from the practice records. These children will be called 'progesterone children'. An equal number of controls were matched for age, social class and parity, and with the permission of the local education officer, the head teachers were given an unmarked list of names and asked to grade them into average, above average and below average. The assessment showed 55% of the progesterone children above average compared with 41% of controls (Dalton 1968).

After that pilot study a more ambitious survey was started. Between 1955 and 1958 the author had worked at the City of London Maternity Hospital as a research assistant, selecting antenatal patients with pregnancy symptoms and treating them with progesterone to successfully reduce the incidence of pre-eclamptic toxaemia from 10% to 3% (Dalton 1957). Thus, ten years later, the hospital

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records were searched for the names of all mothers who had received progesterone during pregnancy together with the next-born normal child in the labour ward register, and the names of all those who had developed toxaemia. Permission to incorporate them in a survey was obtained from the mothers in respect of 45% of the progesterone children and 47% of control children who were then 9–10 years old. Their schools were contacted and head teachers were asked to assess the child's ability in verbal reasoning, English, arithmetic, craftwork and physical education. These results confirmed the superiority of the progesterone children in academic subjects but not in craftwork or physical education. Toxaemia was associated with lowered intelligence as was expected from earlier studies (Barker & Edwards 1967). Furthermore, the effect was dose dependent, with those receiving progesterone before the 16th week and in the higher dose showing the greatest advantage.

At this time, controlled trials into the use of progesterone in the prophylaxis of toxaemia were in progress at Chase Farm Hospital, Enfield, in which antenatal mothers were screened between the 16th and 28th weeks. Those with pregnancy symptoms were allocated randomly to a progesterone-treated or controlled group. These trials showed the advantage of progesterone injections in pregnancy in lowering the incidence of toxaemia, severe toxaemia, albuminuria and stillbirths (Dalton 1962). These children were examined on their first birthday by the local medical officers of health and district nurses. More progesterone children were standing and walking at one year but no difference was noted in teething and talking. These results were dose dependent; the children who received over 8 g progesterone *in utero* fared better than those on the lower dose (Dalton 1968).

It could be claimed that progesterone merely hastens development before puberty, or that the teachers were biased to a particular type of child, such as an outgoing child or a well-behaved one. Thus further assessment was made at the ages of 18–20 years of all children who had received progesterone between January 1955 and May 1958, either in hospital or in my general practice, together with controls, who were either the next born in the labour ward register or in my practice register; a 52% response was received. The progesterone and control groups did not differ in age, father's education, mother's education, family size or ordinal position. The children were asked to complete a simple questionnaire giving their age at leaving school and details of 'O' and 'A' levels and particulars of further education. The progesterone children stayed at school longer, attained more 'O' and 'A' levels and 32% of the progesterone children went on to university in contrast to 6% controls who went to university; 6% is also our national average as well as the average for ILEA and the Borough of Haringey in which most of the children lived. Again these results were dose dependent, with the best results in those whose treatment started before the 16th week, continued for longer than 8 weeks and with a high dosage. Of particular interest was the selection of 'A' level subjects, with a significant number of progesterone children choosing the sciences or 'male orientated subjects' (Dalton 1976).

When this news crossed the Atlantic, Stanford University sent over two psychologists, John and Patty Zussman, who did full psychological testing. Children who had completed the educational attainment questionnaire were invited to an interview for testing. Unfortunately their sample was biased as controls, whose educational attainments were low, did not agree to participate, so it was necessary to abandon any comparison between controls and progesterone children. Nevertheless, the Zussmans were able to show that within the progesterone group the greatest advantage was in numerical ability, with a lesser advantage in mechanical ability and spatial ability. These effects were all dose-related depending on the time of administration, duration and dose. Furthermore, they found that the girls showed no tendency towards being tomboys at the ages of 5 to 10 years and their pubertal changes had occurred normally (Zussman *et al.* 1975). Three progesterone girls have had normal children.

Professor Hutt and his colleagues, of Keele University, tested the 16-year-olds from the controlled trials at Chase Farm Hospital, whose mothers had received progesterone by injection, and also 2-year-olds from a controlled trial at the City of London Maternity Hospital, where progesterone suppositories were used. By the protocol of the controlled trial, women with pregnancy symptoms between the 16th and 28th weeks of pregnancy were allocated blind by the random envelope system to either the progesterone or control group, so Professor Hutt was unable to study the effect of progesterone administered to mothers before the 16th week. Professor Hutt got 15 progesterone children and only 11 controls in the 16-year-old group, and 20 progesterone and only 13 controls in the 2-year-old group, which was a mere 20% response. They could find no difference in their battery of psychological testing (Lynch *et al.* 1979). This is a very important finding, suggesting that any benefit to the children, deriving from progesterone, depends on the administration of progesterone before the 16th week. In this respect it may be compared with thalidomide and rubella whose effect is limited to the first 16 weeks of pregnancy.

How does the suggestion that progesterone is efficacious if administered before the 16th week of pregnancy fit in with our current ideas on development?

Both intrinsic and extrinsic factors are known to affect brain growth and behavioural development (Dobbing & Smart 1974). Money & Lewis (1966) studied patients with adrenogenital syndrome and found a mean IQ significantly above that of the normal population. Adrenogenital syndrome is a genetically recessive disorder in which, due to an enzymatic defect in the synthesis of cortisol, there is excess progesterone and adrenal androgens in the amniotic fluid. The raised intellectual performance of children with the adrenogenital syndrome was noted especially in the male superior skills such as mechanical and numerical ability. In other words, that was a very similar finding to that of the Zussmans and the selection of science subjects at 'A' level by the progesterone children. The adrenogenital syndrome females were, however, more masculine with marked tomboy traits.

Among the children of mothers who had been given synthetic progestogens during early pregnancy to prevent habitual or threatened abortion, there is always the possibility of masculinization of the female (Wilkins 1960). The synthetic progestogens used for the prevention of abortion have androgenic properties, and cannot be used in the adrenal synthesis of progesterone to the various corticosteroids. No case of masculinization of the female or other abnormality has been noted with progesterone. Ehrhardt & Money (1967) showed that when such masculinization occurs following the use of progestogens, the female has a high IQ and has a tendency to be a tomboy. Reifenstein (1958) also noted that children whose mothers had received progestogen during early pregnancy reached maturity more rapidly. It will be noted that in the instances mentioned of the adrenogenital syndrome and where progestogen is given for the prevention of habitual and threatened abortion, the excess progesterone or androgen is present before the 16th week of fetal life.

It would seem that progesterone administered in early pregnancy is beneficial not only for the relief of pregnancy symptoms and the prophylaxis of pre-eclamptic toxaemia but also to enhance intelligence. It will not produce a race of geniuses but merely ensure full brain development. This is also seen as an example of clinical observation in general practice and demonstrates how the general practitioner can open the eyes of research workers in other disciplines, who can then probe deeper into the possibilities which have been offered to them.

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