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DR T. J. DAVID: What is the structure of the blood vessels in the experimental model which can rupture? Do they have muscle in them which might respond to any stimuli?

PROFESSOR D. E. POSWILLO: These are very primitive blood vessels at that particular time of development. It is difficult to identify in them any particular feature, but it looks as though the sort of stimulus to which they respond is pressure, and that their rupture is a pressure phenomenon. It is possible that there has been embryonic hypertension or reflux vasodilatation which can burst these vessels particularly at anastomoses where they are relative fragile. The haematoma is probably not the primary event, but follows something like hypoxic hypertension which may produce pressure changes.

PROFESSOR P. BEIGHTON: Particular teratogenic agents will cause these very specific defects. Is the reverse inference true? Can one say for example that in Treacher Collins syndrome some single gene determines anomalies of vitamin A metabolism that acts only for a short time?

PROFESSOR POSWILLO: No, that we cannot state with certainty. We can only say that there is a genetically-determined biochemical problem which may kill neural crest cells in the same way as does vitamin A. Maybe there is some natural compound which acts in a similar fashion. Lots of agents will produce neural crest damage; vitamin A is just one of them, perhaps the easiest to use. We don’t really know what the biochemical event is that is triggered off by the gene.

DR J. JANCAR: In your case of mandibulofacial dysplasia did you find genitourinary defects on the ipsilateral or on the contralateral side?

PROFESSOR POSWILLO: Yes, there are some defects, there, but this investigation is still in progress. There is sufficient material to make this a very big histological study.

DR DAVID: Can you tie in these haemorrhages in the neural crest with the hypothesis of McCredie (1974)?

PROFESSOR POSWILLO: No, we can’t fit in McCredie’s hypothesis at all. We have much more against it than just these animal models. We have looked at both Old and New World Monkeys; we looked at the thalidomide-developing embryos from day 25 right through to day 100 and the simian time-scale of morphogenesis is almost identical with that of man. Professor Ian McDonald (Poswillo and McDonald, 1976) and I have looked at the dorsal root ganglia of all these animals, and there is absolutely no difference in a blind examination between the thalidomide-treated animals and the controls. Nor could we find any good evidence of thalidomide damage. Wolpert (1976) at the Middlesex Hospital does not believe that the limb development is triggered off by neural development in any case, and therefore he does not accept the hypothesis. So at present we do not support this hypothesis, despite the fact that originally it seemed a very attractive proposition, especially in view of the neural crest development in man.

DR D. C. SIGGERS: There is a recessive condition in which the face is very damaged and the hands are involved: do any of the limbs in your animal models have paw defects?

PROFESSOR POSWILLO: No. All the rest of the post-cephalic skeleton in the rats which had vitamin A was perfectly normal. Gorlin and Pindborg (1964) have described some of the hand defects in the Treacher Collins syndrome and I have corresponded and talked with them about it. They insist that this is an incidental finding. I feel that we do not know, but that it is related probably somewhere to the teratogenic mechanism. This of course only opens a small window on all these facial malformation syndromes. What some would want to do is to discover a unitary mechanism which covers all these malformation syndromes, but I am not hopeful that we shall find this.

PROFESSOR J. J. PRITCHARD: The neural crest gives rise to a lot of different cells. First of all it is only those that migrate to the branchial arches that become mesenchyme—were those the only ones tested? Secondly, what proportion of neural crest cells are destroyed? Obviously your patient did develop reasonably well: she wasn’t a bad looking girl at the end of the day. Something must have been there to make her grow!

PROFESSOR POSWILLO: It seems very likely from the work of Johnston and Listgarten (1972) and the work of Noden (1973) that we are only hitting a proportion of neural crest cells migrating from a specific region that contributes to the face. We’re not killing all of them: probably they are being killed during migration and some of them were missed and have arrived either before or afterwards. We really don’t know much about the destiny of neural crest cells, whether they are determined or not, and whether something which interferes with their migration also affects their destination. The girl you mention was a mild example and there is a good deal of clinical variation even within families. Many are more severe, but the tissues still continue to grow symmetrically. We believe that only a proportion of neural crest cells are damaged. Johnston (1965) has shown that even if a high proportion of the neural crest which will go to the branchial arches is destroyed, mesoderm from other sources can contribute to the formation of the face. So it is likely that not all of the face is built from ectomesenchymal cells from the neural crest, but the neural crest cells do seem to put in the finishing touches.

PROFESSOR PRITCHARD: Are the cells killed, or do they lose their way and not migrate properly?

PROFESSOR POSWILLO: Some of our pictures suggest that the cells accumulate at the neural crest where they
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are heaped up. If you use cadmium the cells fail to leave the neural crest and lead to much the same defect. Alternatively, when you use vitamin A it is more likely that the cells are affected during migration. As yet, this is undecided.

Professor Pritchard: This of course makes one enquire how do they migrate? What is the motive machinery of the migration? There is some suggestion that they hold hands as it were when they move around. Perhaps vitamin A loosens the contact between cells?

Professor Poswillo: Yes, that may be so. It appears from some of the present electron microscopic work on neural crest cells, that they move like tractor treads and roll from the front, and keep rolling on. But these are lipid rich cells, and it may be that the teratogen affects the cell membrane in some particular way. There is still much to be learned and we anticipate that we shall learn more from the mammalian than the avian model.

Chairman: I imagine that the teeth are unaffected? But the neuro-ectoderm is alleged to play a quite considerable part in the development of the teeth in these arches. Is this correct?

Professor Poswillo: Yes. The odontoblasts presumably come from the neural crest ectomesenchyme. In fact, in certain Treacher Collins patients there is some reduction in the number of teeth, with abnormality of their form. This has not yet been fully investigated.

References

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doi: 10.1136/pgmj.53.622.523

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