

Development of the Dermatome Pattern in the Limb

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An erroneous view of early nerve development in human limbs is presented in many medical embryology and neuroanatomy textbooks. The early limb bud is described as having segmental dermatome stripes running across it, which later reorganize to form the adult pattern. In fact, the nerves grow first into a plexus, which they later leave to supply fields very similar to those in the adult. Since this error may have clinical consequences, in that it gives a false view of how anomalies are likely to arise, its source is identified and its propagation through the literature is traced. A brief review of the most recent findings concerning the mechanisms by which nerve patterns are established in vertebrate limbs is also given.

Key words: nerves, innervation, embryo

INTRODUCTION

The nature of the dermatome pattern in human limbs is of some clinical importance, and this is recognized in textbooks of human embryology, anatomy, and neuroanatomy, which often devote space to its development. The obvious intentions are to help the student fix the adult pattern in memory by describing its ontogeny, and to alert the future clinician to likely categories of anomaly. Among current English-language textbooks, there is a considerable degree of unanimity as to how this pattern develops (Figs. 5, 6). It is generally considered to arise from an initial segmental pattern in the early limb buds corresponding to the segmental pattern in the trunk, which subsequently is re-ordered in some way to correspond to the adult pattern. (For examples in embryology, see Williams et al., 1984; Moore, 1988; Sadler, 1985; in anatomy, see Basmajian, 1980; MacKinnon and Morris, 1986; in neuroanatomy, see Carpenter, 1976; Fitzgerald, 1985.) This widely represented view, unfortunately, is not well referenced and is difficult to

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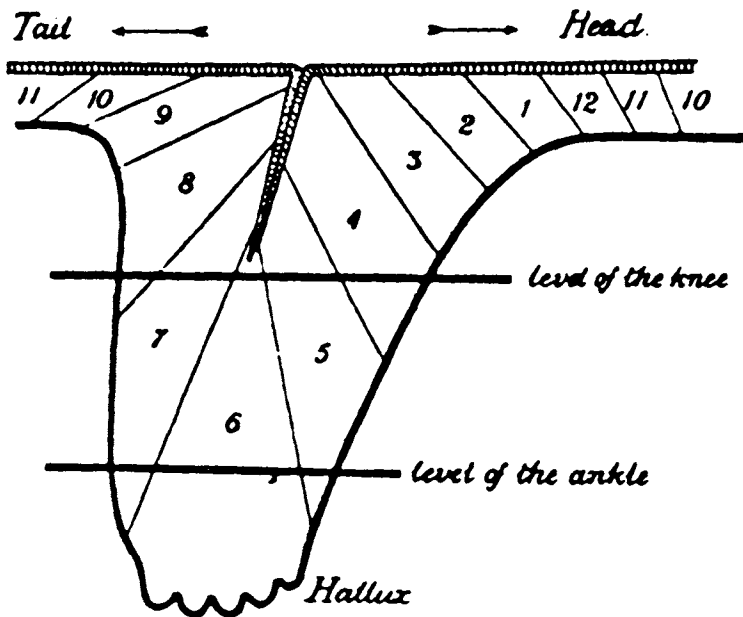


Fig. 1. From Sherrington (1893): p. 750. This is a diagrammatic version of the dermatome pattern in the adult macaque. It is unclear in the text whether the flank fold shown here has arisen in evolution or development, although the former seems more likely.

substantiate.¹ Evidence from experiments on animal models and studies of human embryonic morphology suggest that the true situation is rather different and much simpler. Nerves are not present at all in the limb at the development stages corresponding to the early limb bud profiles of Figures 5 and 6. When they first begin to grow out (substantially after this period), the nerves opposite the limb first form a plexus, and then grow more-or-less directly to their appropriate targets and establish their dermatomes at their characteristic locations. There is no major rearrangement of dermatomes as suggested in the figures.

In this review, I first consider how the current popular misapprehension appears to have arisen, and then go on to describe the current evidence for the mechanisms by which nerve patterns in the limb are established.

HISTORICAL BACKGROUND

In 1893, Sherrington published his famous paper on the limb dermatome pattern in macaque monkeys, based on experiments in which he cut particular spinal nerves, and then plotted the area of residual sensitivity. He noted that the dermatome pattern is more clearly segmental in lower vertebrates, and in a summary diagram of the adult limb (Fig. 1) seems to suggest that the pattern in the

¹ It has recently been criticized by O'Rahilly and Muller (1987), who write: "Diagrams purporting to show the dermatomes during the embryonic period are, at least in the present state of knowledge, figments of the imagination." (Ed.)

adult monkey arose from this by a bulging out from the flank, although it is not clear in the original if this is a process which occurs during development or evolution.

In 1898–89, Bolk published a series of papers on the innervation of human trunks and extremities, based on dissections of adult corpses. In the course of this work (Bolk, 1898), he speculated on the likely pattern of the nerves in the embryonic limb, suggesting explicitly that these were arranged in a segmental pattern in a manner that corresponded to the arrangement of nerves in the trunk (Fig. 2), and that this pattern was subsequently rearranged by the rapid growth of internal structures such as muscle and cartilage to form the adult pattern. Comparison with Figures 5 and 6 suggests that this hypothetical proposal is the origin of the view frequently represented today.

Within a few years of Bolk’s publication, however, the golden age of the histological study of human embryonic material began. W. H. Lewis (1902), in a study of the development of the arm, showed that nerves did not invade the limb bud until after the stages implied by the limb bud shapes indicated by Bolk, and that before they invaded the later limb bud, they first formed a plexus. No evidence for an early segmental arrangement in the limb could be observed. As far as I know, no histological study of human or animal limb development has ever dissented from these views (see, for example, Streeter, 1905; 1908; Bardeen, 1906; Kollman, 1907; Gasser, 1975; Bossy, 1982).

Histological studies tend to deal with sensory and motor fibers together. However, it is also possible to study the pattern of sensory innervation directly, by electrophysiological recording from particular dorsal roots while the skin is stimulated. Application of this technique to chick embryos (Scott, 1982) shows that the

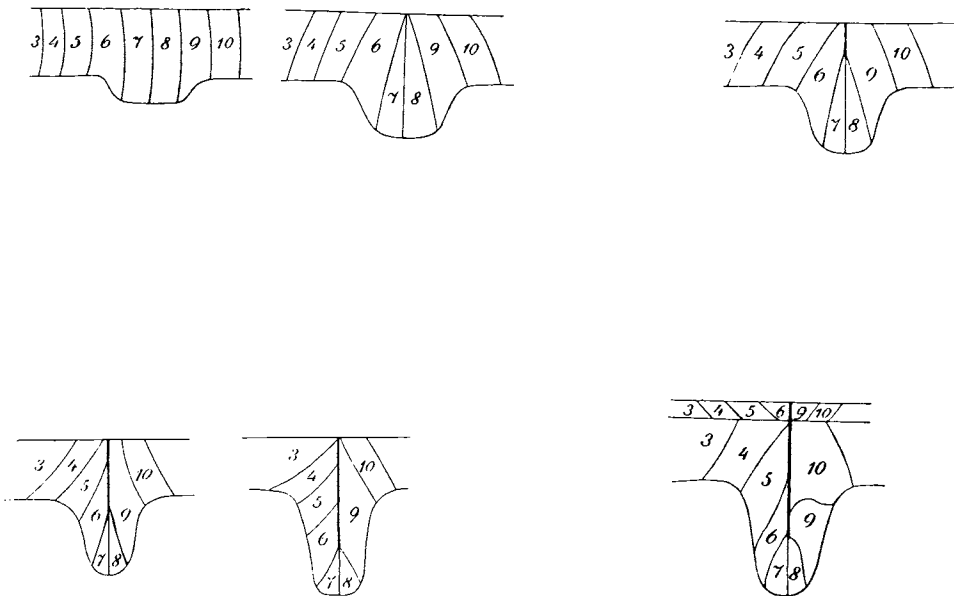


Fig. 2. From Bolk (1898): Figures 9–14, pp. 141–144. Bolk’s speculative proposals for the development of the dermatome pattern in man. The limb profiles are quite unlike the actual development of any vertebrate limb.

pattern does indeed develop from the start into that characteristic of the adult, with no primitive intermediate banded pattern. Given the similarities between embryonic limb development throughout the vertebrates, there is no reason to assume that this is not the case in mammals also.

Since all these studies essentially confirm the observations of Lewis in 1902, how has Bolk's incorrect suggestion been propagated down the years to reappear in modern textbooks?

Interestingly, embryology textbooks closer to Lewis in time do not make this error. Bailey and Miller (1912) describe the correct situation, as do Keith (1933) and Arey (1943); the classic work of Hamilton et al. (1945) does not discuss the early condition, but gives a diagram of a homunculus later than the limb bud stage, in which the adult dermatome pattern is already established. The Bolk diagram seems to have survived this period in works on neuroanatomy, where the writers presumably had no wider interest in embryology. The key source seems to have been the "Kompendium der Topischen Gehirn- und Ruckenmarkdiagnostik" published by Bing in 1909. This gives a diagram recognizably similar to that of Bolk, though without attribution (Fig. 3). This work went through many editions, and was translated several times into English. In particular, the 11th edition was edited and translated by Webb Haymaker, who subsequently went on to co-author an important book on nerve injuries, based on his wartime work with the American Army (Haymaker and Woodhall, 1945). In this an unattributed diagram of a segmental pattern of nerve development in early limb buds is given, and this seems to be a version of Bolk *via* Bing, redrawn to take account of information on the real external appearance of embryonic limb buds (Fig. 4).

Incomplete citations to these works are also given in later neuroanatomical literature; e.g., "after Bing" (Truex, 1959) with no further attribution, or "Haymaker and Woodhall" with no citation details (Ranson and Clark, 1959). It is presumably from such works that the Bolk diagram made its way back into the medical embryology literature.

As an alternative to the "striped limb bud" of Bolk, a completely segmented homunculus is sometimes shown—see, for example, Fitzgerald (1985), who credits Langman (1975)—but I cannot trace this diagram to an original source: perhaps it is based on a misapprehension of Hamilton et al. (1945).

The basic fault here has been the historical failure to give original references. My impression is that medical embryology textbooks are more prone to this general failing than, for instance, embryology textbooks for science students, and indeed,

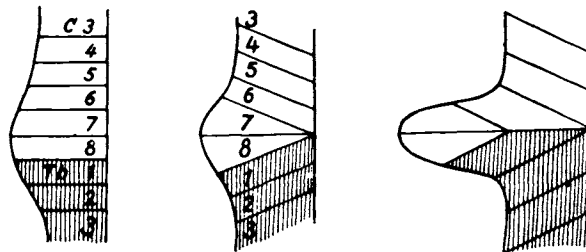


Fig. 3. From Bing (1940): Figure 13, p. 84. Bing's figure is unattributed, but plainly seems to be drawn from Bolk. This is from the edition translated by Webb Haymaker.

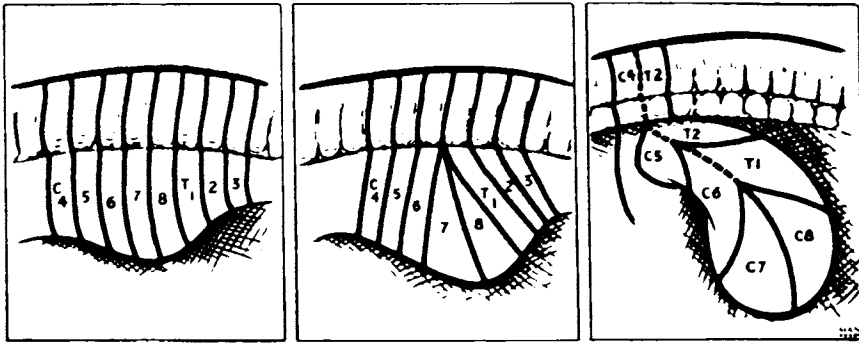


Fig. 4. From Haymaker and Woodhall (1945). (Reproduced by kind permission of Harcourt Brace Jovanovitch, Ltd.). The limb profiles shown here are much more realistic, but the dermatome pattern resembles that of Bing and Bolk. Again, the figure is unattributed.

that medical students in general are more likely to be required to accept the authority of the textbook than are students in other disciplines. If this impression is correct, negative consequences may result which outweigh the presumed intention of keeping the information presented in as simple as possible.

At best, lack of citation details deprives the student of the chance to study the original account: at worst, the transmission of serious errors can result. Certainly it makes it very difficult and time-consuming for the teacher to check the source of material, which seems puzzling in some respect, as the present author can verify.

In the case of limb innervation, this situation is doubly unfortunate, since in addition to propagating an error, it deprives the student of access to a fascinating topic which is the subject of much current experimental interest, and has implications both for the development of abnormal nerve patterns, and for regeneration of damaged nerves. As an illustration of the kind of problem that could be approached, I append a necessarily brief review of recent work on the problem of how sensory and motor nerves grow out, and how a match is formed between nerves and their targets.

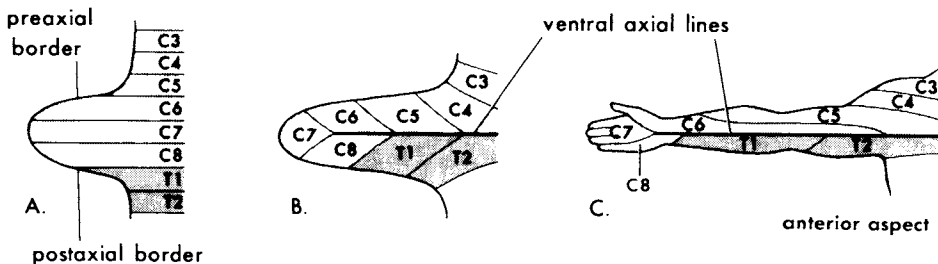


Fig. 5. From Moore, K.L. *The Developing Human: Clinically Oriented Embryology*, 4th ed. Philadelphia: W.B. Saunders Co., 1988, figure 17.4, p. 357. (Reproduced by kind permission of Professor Moore and Harcourt Brace Jovanovitch, Ltd.). A, B and C represent purported developmental stages. The segmented early dermatome pattern shown here draws its inspiration from Bolk. Note that the adult pattern has altered slightly to conform to the more modern view.

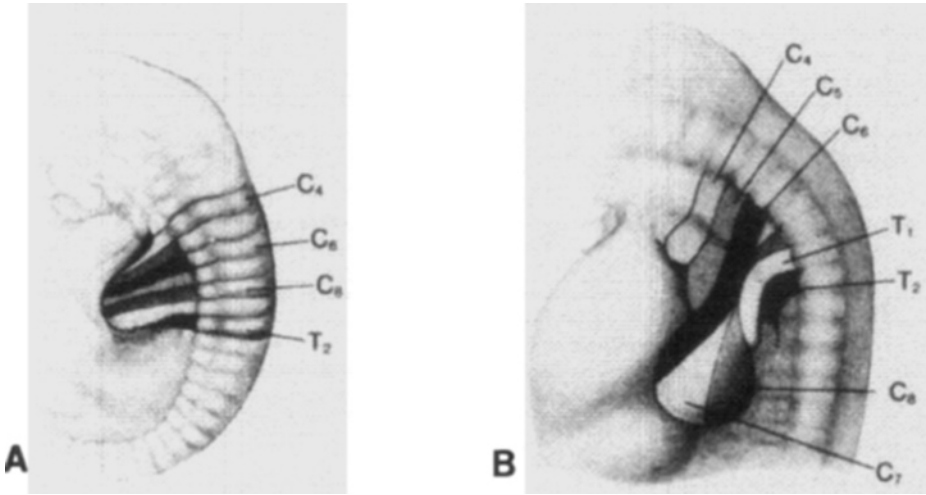


Fig. 6. From Sadler (1985): Figure 10.4, p. 152. (Reproduced by kind permission of Professor Sadler and Williams and Wilkins.) **A** and **B** represent purported developmental stages. These figures appear to be derived from Haymaker and Woodhall. Again, the later pattern is slightly altered to bring C7 to the distal tip of the limb.

DEVELOPMENT OF LIMB INNERVATION

Since the peripheral sensory innervation generally grows out in close association and slightly later than the motor fibers (Landmesser and Honig, 1986), the possibility exists that the motor nerve fibers are the major pattern-forming “pathfinders” and that sensory nerves follow them to near their final destination. As we will see, recently the two systems have been treated separately, but initial work dealt with the development of mixed nerve trunks. Experimental work is largely carried out using the developing chick embryo, though there is no reason to believe that the general principles revealed do not hold good for mammals also.

If a chick limb bud is removed prior to invasion by the nerves, and grafted to the mandibular prominence, it will be invaded by a nearby cranial nerve. The innervation pattern formed by this nerve is, however, characteristic of the normal limb, showing that the pattern is not intrinsic to the nerve (Swanson and Lewis, 1986).

Similarly, if a young limb bud is removed and replaced by an older limb bud or *vice versa*, the pattern formed is characteristic of the age of the grafted bud and not the host embryo (Swanson and Lewis, 1982).

If a limb bud is removed from a donor embryo, and regrafted to a corresponding limb stump in a different host embryo in such a way that the dorsoventral axis alone is reversed, nerves grow into the reversed limb in the normal way, and it is found that motor pools which normally innervate dorsal muscles now innervate ventral muscles and *vice versa*, even though the normal targets are close by (Summerbell and Stirling, 1981).

Together, these findings seem to suggest that nerve deployment is entirely passive: nerves do not seem to know where they are going at all, and nerve pattern is somehow controlled by factors in the developing limb. However, the situation is more complicated than that. If a limb bud is placed on a host stump with the *craniocaudal* axis reversed (Stirling and Summerbell, 1985), or with both dorso-

ventral and craniocaudal axes reversed by 180° rotation of a limb bud on its own stump (Laing, 1984), then motor axons prove capable of innervating their *normal* targets, even though they now have to adopt a novel path to do so. Similarly, if a short segment of spinal cord is reversed in the craniocaudal axis, then motor and sensory axons can find their normal targets (Lance-Jones and Landmesser, 1981) though this phenomenon is limited in range: if the length of rotated segment is too large, nerves deploy passively to any nearby target. Here then is evidence for active selection of targets by axons. Perhaps we can say that there are non-specific common pathways which nerves will follow *unless* they recognize a specific short-range signal which cues them they are near their normal target. In accordance with this idea, if limb muscles are prevented from forming altogether by prior irradiation of the somites, then the main nerve trunks still form as normal, but branches to the sites of the muscles are absent (Lewis et al., 1981). The molecular nature of both pathways and specific signals remains to be established, although there are a number of promising lines of work in progress (reviewed in Davies, 1987).

Information is also available on the control of outgrowth of sensory innervation, as opposed to mixed and motor axons (see Scott, 1987, for general review). If the precursors of the motor neurons are destroyed by removal of ventral neural tube (Landmesser and Honig, 1986) or by irradiating sections of the neural tube with UV light (Swanson and Lewis, 1986), then sensory branches to muscles are lacking. This indicates that proprioceptive fibers follow motor neurons to muscles. However, skin sensory axons still grow along the main nerve pathways as normal, and innervate their usual cutaneous targets (Swanson and Lewis, 1986), showing that these axons can find their way unassisted in the absence of motor neurons. This does not mean, of course, that they are unaffected by motor neurons when they are present. It is possible to rotate short regions of neural crest in the craniocaudal axis without affecting the motor neuron precursors in the ventral neural tube (Scott, 1986). This creates a mismatch between sensory and motor nerves. The outcome of this experiment is that sensory dorsal root ganglia project to skin regions characteristic of their new position rather than their former one. In other words, the distribution they adopt corresponds to that of the motor neurons, and so presumably in normal development they are heavily influenced by them.

As cutaneous axons approach their final sites, they are also influenced by the limb ectoderm. If a small region of ectoderm is destroyed by UV irradiation, then the appropriate cutaneous branches fail to leave the main trunk as normal (Martin et al., 1989). Neighbouring cutaneous nerve branches proliferate to supply unirradiated areas thus left vacant. This compensatory growth is also seen if dorsal root ganglia are removed altogether; on reaching the skin, axons from remaining dorsal root ganglia expand to fill the space provided, suggesting there is normally a degree of competition at dermatome boundaries (Scott, 1984; see also Diamond, 1982). At later stages, there is also the possibility of selective cell death refining the earlier, imprecise pattern (Pettigrew et al., 1979).

CONCLUSIONS

Several separate mechanisms seem to act in directing nerve outgrowth. There is a degree of short-range signaling, which leads to the formation of specific associations between nerves and their muscle and cutaneous targets. Passive deployment

also occurs, in which nerves supply any target they meet, perhaps in the absence of specific signals to the contrary. And there is also some competition between nerves for territories, probably associated with death of unsuccessful neurons. In a normal embryo, all of these mechanisms will tend to contribute to the same general pattern, although considerable variability is to be expected (Foerster, 1933; Dykes and Terzis, 1981). If one contributor is absent altogether in an abnormal embryo, the remaining mechanisms will successfully direct outgrowth. However, there may be a hierarchy among the mechanisms, so that if a high level component (such as motor neurons) forms in an abnormal way, then the overall pattern may suffer a degree of disturbance. In discussion of this problem, as in all aspects of development, it is valuable to give details of the sources from which information is obtained, even at the level of the student textbook.

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² To show historical development, separate references are given to Truex (1959) and Carpenter (1976), although both of these have a historical connection as Elwyn and Strong's *Human Neuroanatomy*; likewise to Sadler (1985) and Langman (1975). Otherwise, when an edition number is given, it does not imply that other editions are significantly different.

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