terranean countries (*20*). Any occurrence of blue mold is reported to CORESTA headquarters in Paris, which informs the countries most threatened and warns correspondents in all countries.

After the 1979 epidemic, the U.S. Tobacco Disease Council established the National Blue Mold Warning System, which also covers Canada. This system has state coordinators who collect information on occurrences of blue mold and advise a central office at North Carolina State University about them. The information is analyzed at the central office and warning statements, describing the status of the disease, relevant weather forecasts, and control actions needed, are released weekly. In North Carolina, where tobacco is grown in 80 counties, the tobacco extension agent in each county serves as county coordinator.

Forecasting systems. With the advent of systems analysis and mathematical modeling, and the rapid development of computers during and after World War II, the procedures and tools needed to examine, integrate, and predict significant features of an epidemic became available. Forecasting provides a systematic way to assess the influence of environmental factors on disease progress and tells growers the probabilities of when and where a disease may appear. It thus provides a means for determining how to apply various management practices.

The development of forecasting systems is a rapidly growing aspect of plant pathology (*21*), and several blue-mold forecasting systems have been tested in Australia and Europe (*22*). Forecasting systems are also in use for other plant diseases, such as late blight of potato and apple scab.

Projection

More epidemics of blue mold are certainly possible. Plant pathogens are slippery enemies that change all the time. They constantly challenge our judgment, skill, and resources. Although the war against plant diseases may never end, we can learn to live with them.

Blue mold is a continental as well as a local problem, and its control will require the cooperation of scientists and government officials from many countries. Blue-mold epidemics have already caused enormous financial losses, upset a specialized field of agricultural production, and induced social consequences that are difficult to evaluate. Nonetheless, the very threat of recurrent epidemics may strengthen the concept of collective responsibility and the need for international collaboration that will be required to control not only blue mold but the many other diseases whose causal agents are spread principally by the wind.

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Elimination of Synapses in the Developing Nervous System

Dale Purves and Jeff W. Lichtman

The formation of neural circuitry during development is a complex and poorly understood process. In general, the nervous system must solve two problems. One problem is essentially qualitative: how are synapses established between appropriate partners? The solution presumably depends on mechanisms of differentiation, cell migration, guidance of growing axons, and ultimately the selective formation of synapses. A second problem is quantitative: how does the system regulate the number of cells in the pre- and postsynaptic populations and the number of synaptic contacts between them? In particular, how does the nervous system guarantee that every cell in the target population is promptly innervated and that, in the long run, synapses are correctly distributed among the target cells?

There is little consensus about the way the developing nervous system solves the problem of qualitative accuracy. Somewhat more is known about the strategies used to achieve quantitative accuracy. There is, for example, some agreement about the way in which the size of the innervating population is matched to the capacity of the target. Neurons in many (perhaps all) regions of the developing vertebrate nervous system are overproduced initially and appear to compete for survival in early embryonic life (*1*). Various experiments indicate that presynaptic neurons are dependent on some aspect of their target; for example, artificially increasing target size enhances the survival of innervating neurons, while decreasing target size in-

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creases the incidence of neuronal death. A good deal of circumstantial evidence suggests that a trophic factor supplied by the target is sought by the innervating population (*2–4*). Whether or not competition for trophic factors proves to be the basis of neuronal death in early development, it is clear that the number of neurons in an innervating population is not matched to the target's capacity by predestination but by feedback and consequent adjustment.

Summary. Reduction of the number of axons that contact target cells may be a general feature of neural development. This process may underlie the progressively restricted malleability of the maturing nervous system.

Another developmental adjustment that appears to ensure quantitative accuracy in neural circuits is the normal elimination of some of the synaptic connections initially formed between pre- and postsynaptic cells. Although relatively few regions of the nervous system have been examined so far, synapse elimination may also be a general feature of neural ontogeny.

Synapse Elimination in Muscle

Anatomists have long remarked on the different appearance of the neuromuscular junction in neonatal and mature muscles (*5*). Little attention was paid to this observation until about 10 years ago when Redfern (*6*) showed, by electrophysiological means, that skeletal muscle fibers in neonatal mammals are indeed innervated differently from adult cells. When motor nerves in mature animals are stimulated with progressively stronger current pulses, the postsynaptic potential recorded in most muscle fibers arises in an all-or-none fashion and does not change with greater stimulus intensity; this indicates that a single axon contacts each muscle fiber. In neonatal muscles, however, the postsynaptic response is characteristically complex; discrete steps in the synaptic potential elicited by increasing the strength of motor nerve stimulation indicate innervation by several axons with different thresholds [(*6–8*); see also (*9*)]. Studies at different postnatal ages show that the elimination of the redundant axon terminals occurs gradually, the mature one-on-one pattern being established a few weeks after birth in most muscles (Fig. 1A) (*6–8, 10, 11*). A similar sequence of events occurs in lower vertebrates (*9, 12*).

The relative simplicity of the neuromuscular junction has allowed exploration of several other aspects of synapse elimination. Since a large number of motor neurons normally die at about the embryonic stage when motor axons reach their target muscles [(*4*); see also (*1*)], an important question is whether synapse elimination in neonatal muscle is due to the death of motor neurons. In fact, the number of motor axons that innervate a muscle does not appear to change during the period of synapse elimination (*8*). This finding is in accord with the observation that normally occurring cell death in the motor column of the chick (where cell death has been studied most extensively) is characteristic of early embryonic rather than postnatal life (*13*). Thus there is probably little overlap between the period of motor neuron death and the phenomenon of postnatal synapse elimination; an important corollary is that each motor axon contacts more muscle fibers at birth than in maturity.

Since most skeletal muscle fibers are innervated at a single end plate in mature mammals, one can also ask whether the several endings contacting a muscle fiber at birth are confined to the same site. Morphological (*9, 10*), electrophysiological (*6, 8, 9*), and pharmacological studies (*8*), all indicate that the synaptic contacts on each neonatal fiber are located at approximately the same place (see Fig. 1A). This conclusion is important in considering possible mechanisms of the elimination process.

Synapse Elimination in Autonomic Ganglia

The postnatal elimination of some initial contacts is not limited to muscle, but also occurs when the target cells are neurons. Because the innervation of most neurons is much more complicated than that of skeletal muscle fibers, synapse elimination has been demonstrated most clearly in parts of the nervous system that are relatively simple.

The simplest neuronal system in which synapse elimination has been studied is the submandibular ganglion of the rat (Fig. 1B) (*14, 15*). The cells in this parasympathetic ganglion are similar to skeletal muscle fibers in that about 80 percent of them are innervated by a single preganglionic axon in maturity (the other 20 percent are innervated by two, or occasionally three, axons). Intracellular recordings from these neurons at birth show a pattern of innervation quite different from that of the adult: each neonatal cell is innervated by an average of five different axons. As in muscle, the initial convergence of several axons on each target cell is reduced to the adult one-on-one pattern over the first few weeks of life. Synapse elimination has also been observed in the superior cervical ganglion of the hamster (*16*) and the ciliary ganglion of the rabbit (*17*).

The findings at the neuromuscular junction and in the developing submandibular ganglion raise the possibility that synapse elimination is peculiar to those regions of the nervous system which, in maturity, have a one-on-one pattern of innervation. A study of developing sympathetic ganglia, however, shows that this is not the case. In contrast to the rat submandibular ganglion, adult neurons in the hamster superior cervical ganglion are innervated by an average of six to seven different axons (*16*). Yet at birth each of these neurons receives synaptic contacts from about a dozen different axons (Fig. 1C). As in skeletal muscle and parasympathetic ganglia, some initial connections are eliminated during the first few weeks of postnatal life. Thus synapse elimination also occurs in neuronal targets where individual cells remain innervated by a number of different axons.

Synapse Elimination in the Central Nervous System

Synapse elimination is probably characteristic of the central nervous system as well, although the evidence for this is necessarily less direct than in the periphery. The most striking indication of a process in the brain analogous to peripheral synapse elimination comes from studies of the developing visual cortex (Fig. 1D) [(*18, 19*); see also (*20–23*)]. In adult cats and some species of monkey, cortical neurons in layer IV of the primary visual cortex are segregated into columns dominated alternately by the right or the left eye. At birth, however, or in late embryonic life, there is considerable overlap of adjacent ocular dominance columns, which gradually diminishes as the animal matures (*18, 19*). Although there is no direct evidence that this adjustment of terminal branching patterns

involves the elimination of some synaptic connections, the relatively poor electrophysiological definition of ocular dominance columns in neonatal animals suggests that this is the case (*18*).

Another instance of synapse elimination occurs in the cerebellum, where each mature Purkinje cell is contacted by a single climbing fiber. Electrophysiological experiments in newborn rats suggest that Purkinje cells are initially innervated by several different climbing fibers, all but one of which are lost over the first few weeks of life (*24*). Anatomic evidence of synapse elimination in the central nervous system is the postnatal disappearance of contacts initially present on the axon hillock of spinal motor neurons (*25*).

Some Features Common to Synapse Elimination in Different Regions

In considering how and why synapse elimination occurs, it is important to point out that the phrase synapse elimination does not fully describe the underlying phenomenon; the basic process is not a reduction of the number of synapses, but a reduction of the number of different axons innervating each cell. Because each neuron in autonomic ganglia or visual cortex receives many synaptic contacts, a reduction of polyneuronal innervation need not be accompanied by a reduction in the overall number of synaptic contacts. In fact, in both the submandibular and superior cervical ganglion, the number of synapses present at birth is only a fraction of the number evident a few weeks later (*14, 26*). A net increase in the number of synapses during early postnatal life is also characteristic of the visual cortex and some other regions of the central nervous system that have been examined (*27*). Thus if a constant number of cells in the pre- and postsynaptic populations is assumed, the number of synapses made by each axon is increasing while the number of cells it innervates is decreasing. In short, each axon progressively confines an increasing number of synaptic contacts to a smaller number of target cells.

In muscle, however, since each mature fiber is left with what is grossly a single synaptic contact, the elimination of some axon terminals appears to result in a net reduction in the number of synapses. The substructure of the mammalian neuromuscular junction is actually a plexus of endings (*10*), each of which is not unlike a terminal bouton on a ganglion cell. Since the size and complexity of neuromuscular synapses increase after birth [(*28*); see also (*10*)], the apparent net loss of synaptic contacts in postnatal muscle is misleading. The rule in muscle, as elsewhere, may be that each axon elaborates additional endings on fewer and fewer target cells.

What ultimately requires explanation then is not just the loss of some synapses, but how and why the synaptic contacts made by a particular axon are progressively confined to a smaller final number of target cells.

Possible Mechanisms

Intrinsic withdrawal and competition. Brown *et al.* (*8*) have suggested that in muscle the motive force for synapse elimination stems in part from an intrinsic tendency of developing motor neurons to reduce the size of their peripheral arborization. When the number of motor axons supplying the neonatal soleus muscle is sharply reduced by partial denervation, the number of muscle fibers innervated by each axon still decreases, albeit with a slower time course [(*8*); see (*29*), however]. Thus removing many or even most of the competing axons does not abolish synapse elimination. A possible explanation of this result is that each motor neuron can support only a limited amount of synaptic machinery. Accordingly, a developing motor neuron would have to sacrifice a fraction of its terminals to sustain an appropriate number of enlarging synapses. Nonetheless, the fact that each adult muscle fiber is normally innervated by a single axon demands that competition play a role [see (*8*)]; if the withdrawal of some axon terminals were simply random, then one would expect some muscle fibers to be left with no innervation and others to be innervated by two or more different axons.

Because competition requires an object, an obvious question is what the developing motor axons compete for. One possibility is that skeletal muscle fibers elaborate a neurotrophic agent analogous in function to the protein nerve

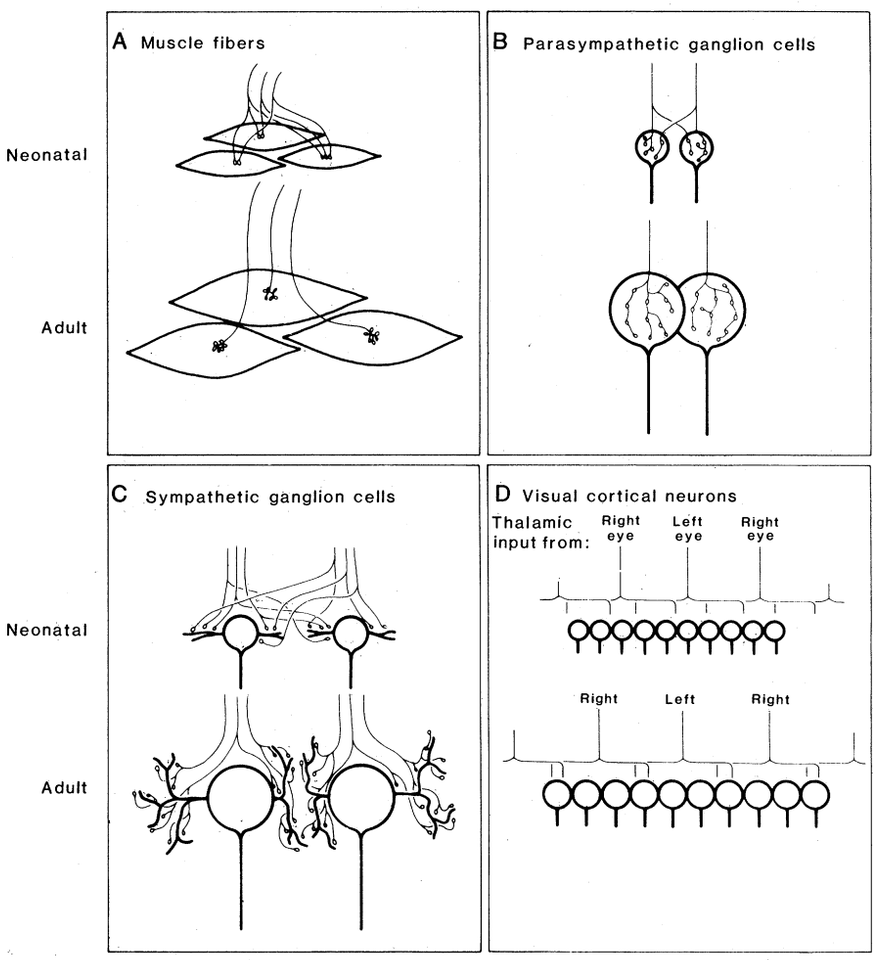

Fig. 1. Diagram of the process of synapse elimination in (A) developing mammalian skeletal muscle, (B) parasympathetic ganglia, (C) sympathetic ganglia, and (D) primary visual cortex.

growth factor for which sympathetic ganglion cells appear to compete (*2*). Indeed, one can suppose that postsynaptic cells in general secrete trophic agents that contribute to the formation and maintenance of presynaptic endings (*3*). Although alternative schemes have been suggested [see, for example (*30*)], considerable evidence supports the analogy between the autonomic and somatic motor systems (*3, 31*); of particular interest is the recent finding that a neurotrophic factor is produced by some skeletal muscles (*32*). Thus, when several different axons make contact with a developing skeletal muscle fiber, the ultimate resolution in favor of a single axonal victor may be due to positive feedback induced by uptake of trophic material; as one of the terminals begins to gain a larger share of the trophic agent than its competitors, its enhanced growth further augments its uptake of the trophic agent, with consequent reduction of the amount available to other contacts at (or near) the same site. Stability is attained only when each end plate is left innervated by a single axon. It seems likely that this sort of competition is important in neuronal systems as well.

Neural activity and synapse elimination. The idea of synapse elimination driven by a competitive principle, acting within a limit set by the amount of synaptic machinery that a neuron can maintain, does not, however, explain the single innervation of some autonomic neurons. An individual submandibular ganglion cell often receives all of its innervation [40 to 80 synaptic contacts scattered over its surface (*14*)] from an axon that makes no contacts with any of the immediately adjacent cells (*15*). This finding implies that all of the synaptic sites on a submandibular ganglion cell are somehow recognized as members of the same class. Because the mammalian neuromuscular junction consists of a plexus of discrete endings confined to a limited region of the muscle cell surface (see above and Fig. 1A), the final pattern of muscle innervation may also involve recognition of multiple postsynaptic sites as members of the same class.

A possible mechanism of such recognition is suggested by experiments on the development of visual cortical connections during a "critical period" in early postnatal life (*18, 20–23*). Wiesel and Hubel (*20*) showed that the normal pattern of ocular dominance in the primary visual cortex of kittens (but not adult cats) can be dramatically shifted by depriving one eye of normal stimulation (by suturing the eyelids, for example). This result, which has been confirmed and extended by a number of additional experiments (*23, 33, 34*), indicates that neural activity is important in establishing (or maintaining) neural circuits [see also (*35, 36*)].

Several recent experiments have tested directly the influence of neural activity on synapse elimination. In the neuromuscular system, synapses are eliminated more slowly under conditions of decreased activity (achieved by tenotomy or tetrodotoxin block of motor nerves) (*37*), and more rapidly by enhanced activity (*30*). These experiments seem to support the idea that neural activity is a determinant of synapse elimination. Results obtained in the developing visual cortex, however, show that synaptic rearrangement is dependent on an imbalance of activity among competing inputs, rather than on the level of activity per se. This implies that simply changing the level of activity in the peripheral nervous system (by blocking a motor nerve, for instance), may have little effect on the final outcome of the elimination process, in spite of altering its time course. Evidence for the importance of imbalance in the visual system is that binocular deprivation (bilateral lid suture) has little or no effect on ocular dominance (*20*). Moreover, a change occurs without obvious deprivation if the two eyes are simply made disconjugate (by cutting one or more of the eye muscles) or if the two eyes are occluded alternately during the critical period (*21*). In these cases both eyes receive the same amount of stimulation, and at maturity the animals appear to see normally with either eye. Yet, recordings from the visual cortex of animals raised with strabismus or alternating occlusion show a reduction in the number of binocularly driven cells. These results led Hubel and Wiesel (*21*) to suggest that asynchronous activity enhances competition between axons innervating the same cortical neuron, whereas synchronous activity of the axons innervating a cell somehow impedes their competitive interaction [see also (*34*)]. Thus, reduced competition between synchronously active terminals could also promote the innervation of all the synaptic sites on a submandibular ganglion cell (or skeletal muscle fiber) by the terminals of a single presynaptic axon during synapse elimination (*15*).

The occurrence of synapse elimination in peripheral systems suggests that the basis of the critical period in the development of visual cortex is quite general. Thus a greater number of axons initially in contact with each neuron may allow malleability of visual connections. As redundant axonal contacts are gradually eliminated through competition, the malleability of the system decreases. In this view, the critical period ends when the process of synapse elimination has progressed to the point where few, if any, synapses are still capable of competitive interaction. The sparing effect of synchronous activity appears to modulate this underlying process so as to maintain on a single neuron inputs derived from corresponding points on the two retinas.

Cellular geometry and synapse elimination. Autonomic neurons that have one or a few axonal inputs appear to have a different shape than neurons with many different inputs. Thus, multiply innervated ganglion cells have an extensive dendritic arbor, whereas singly innervated cells in the same ganglion do not [(*38*); see also (*16*)]. A similar correlation is evident when the average innervation of different autonomic ganglia is compared with what is known of ganglion cell geometry (*14, 39*). This suggests that the persistence of two or more axons innervating the same cell is also favored when the sets of synapses from each different axon are separated from one another. Thus a major function of dendrites (or dendritic branches) may be to establish relatively distinct spatial domains to minimize or preclude competition between presynaptic axons. This idea is made more plausible by evidence for the importance of distance between synaptic contacts in the normal development (*9*) and reinnervation (*40*) of skeletal muscle. For example, dual innervation of muscle fibers in either normal or experimental circumstances appears to require that the two inputs be separated by a considerable distance along the fiber length. Since it is obvious that different classes of inputs (for example, excitatory and inhibitory) can coexist in close proximity along neuronal dendrites, one would have to assume that different classes of axons ignore each other during the competition that establishes the final pattern of innervation. Regions of a particular dendrite, however, might come to be largely or exclusively occupied by boutons from a single axon during synapse elimination, as at a muscle end plate or on the surface of a parasympathetic ganglion cell.

Conclusions

The elimination of some synaptic connections during early life occurs in skeletal muscle, autonomic ganglia, and at least some regions of the central nervous system. Studies of this phenomenon suggest the following generalizations.

1) Each target cell is innervated by

more axons initially than in maturity, in spite of the fact that the overall number of synapses in target tissues increases during the intervening period. In consequence, each innervating axon progressively confines an increasing number of endings to a smaller number of target cells.

2) A major purpose of this process may be to regulate the number and distribution of synapses made within a target. Initial redundancy and subsequent elimination of some innervation is a strategy well suited to ensuring both the prompt innervation of all the cells in a target and, ultimately, a quantitatively appropriate distribution of synapses among the target cells.

3) The motive force for this synaptic rearrangement is probably competition for trophic factor. An additional influence is a limit on the amount of synaptic machinery each innervating cell can maintain.

4) Synchronous impulse activity of the different axons initially innervating a cell impedes synapse elimination, whereas asynchronous activity allows (or perhaps enhances) competition.

5) Competition between the axons innervating a cell ceases when (i) a single input remains, (ii) only synchronously active inputs remain, or (iii) multiple inputs initially capable of competitive interaction become spatially segregated on neuronal dendrites.

The progressive confinement of neural connections by means of synaptic rearrangement seems a likely basis for the gradual decrease in the malleability of the developing nervous system evident in a variety of experiments. This process may also contribute to the clinical observation that the ability to recover from nervous system injury (or the ability to learn) gradually diminishes as a child grows up.

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