REVIEW
Lessons from lesions: the effects of olfactory bulbectomy

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**Abstract.** Olfactory bulb removal has been used to examine a wide-ranging number of topics. The present review outlines the categories of studies employing the technique, discusses some problems with the methodology and with previous interpretations of observed results, and suggests some potential avenues of investigation.

**Introduction**

Ablation techniques have played a central role in our present conception of neural organization and function. Attempts to understand brain circuitry in the first two-thirds of this century were dominated by reports examining patterns of lesion-induced degeneration; indeed, much of classical neuroanatomy was built on the technique. Similarly, attempts to examine neural function have also relied on the lesion approach: the role of many regions has been inferred after their removal or isolation from the remainder of the brain. These studies, in turn, have been used to interpret the effects of human brain damage, or, in some cases, to suggest treatment regimens (e.g. Valenstein, 1986).

Because of their prevalence, it is important to examine lesion techniques on a periodic basis. One reason is to ensure that researchers continue to appreciate the underlying assumptions upon which the methods are based. Brain lesions result in much more than a simple destruction of a discrete area: a cascade of changes emerges after the procedure. Edema and debris initially present at the lesion site can potentially affect relatively large areas of the brain. Thereafter many secondary consequences occur, resulting from disrupted vasculature, anterograde, retrograde and transneuronal degeneration, and changes in synaptic number and function as the result of factors such as sprouting, denervation supersensitivity and other forms of synaptic rebalancing (see section IIIB). These dynamic and myriad changes are often ignored by researchers examining single functional results at a particular time, despite the fact that there have been many previous reviews of the pitfalls associated with the methodology (e.g. Isaacson, 1976; Lynch, 1976; Schoenfeld and Hamilton, 1977; Steward, 1989).

Perhaps the easiest approach to examining the consequences of lesions would be to study their effects on brain areas receiving input from primary sensory neurons. These regions are intensely studied due to the fact that information flow is easily manipulated and relatively unidirectional. As a result, their circuitry, development and chemistry are relatively well understood. A reasonable assumption is that a lesion in these zones should simply deprive animals of that sensory modality. For example, removal of a cochlear nucleus should result in unilateral deafness or the removal of the olfactory bulbs should render animals anosmic. However, there are a wealth of other consequences of these brain lesions. Studying the range of these changes should lead to understanding
of both the function of the brain regions in question and to an enhanced ability to interpret the consequences of lesion experiments in general.

A second reason to review results from lesion studies periodically is to attempt to integrate the information in order to produce a more unified view of both the function of a particular area and the consequences of the lesions. Lesions of a specific brain region are done in order to test a number of different theoretical issues or to examine function from several perspectives. Often the studies are done without regard to each other, as many investigators do not look outside their own area of interest to find alternative interpretations.

Below is a brief overview of the kinds of uses that have been found for olfactory bulbectomy, and a brief description of the changes encountered as a result. An enormous number of investigations have employed the surgical technique, and, as a result, a comprehensive list would be very difficult to produce. The present paper is designed simply to examine the numerous ways in which bulbectomy has been employed in order to demonstrate the extraordinary variety of changes which are a consequence (Section II) and to attempt to delineate both problems with interpreting the results of the technique and areas demanding further investigation (Section III).

I. Olfactory bulbectomy: the manipulation

A. Techniques

Several surgical approaches have been used to remove the olfactory bulbs. By far the most common has been to remove a portion of the overlying frontal bone and then to aspirate the bulb, sometimes after a caudal transection at the level of the rostral pole of the neocortex. Details of actual procedures are often sketchy (or even omitted) in many of the published reports, and histological verifications of the extent of the lesions, and/or correlations of lesion size with the amount of subsequent alterations in behavior, are quite rare. These details and analyses are far from trivial, as the topology of the bulb makes excision of the entire structure quite difficult, especially without damaging surrounding tissue (see below).

B. The olfactory bulb

Several excellent and extensive reviews of the anatomy, physiology and neurochemistry of the olfactory system have been published (e.g. Shepherd, 1972; Macrides et al., 1985; Switzer et al., 1985; Scott and Harrison, 1987; Halász, 1990). The olfactory bulbs, bilateral extensions of the rostral telencephalon which constitute ~4% of the volume of the rat brain (Cain, 1974a), house two separate structures: the main and accessory olfactory bulbs. The main bulb receives input from the olfactory receptor cells which reside in the caudal third of the nasal cavity in the olfactory mucosa. The accessory olfactory bulb receives its afferent supply from the vomeronasal organs, tubeshaped structures found on the ventral midline of the anterior nasal cavity (Wysoscki, 1979; Halpern, 1987; Meredith, 1991). Both regions have separate and parallel outputs. The main bulb projects via the lateral olfactory tract to the anterior olfactory nucleus, primary olfactory cortex, olfactory tubercle, entorhinal cortex, nucleus of the lateral olfactory tract, and anterior and posterolateral divisions of the cortical nucleus of the amygdala. The accessory olfactory bulb projects to separate regions of the
Lessons from lesions

amygdala: the medial nucleus and posteromedial division of the cortical nucleus (Switzer et al., 1985 and references cited therein; Price, 1987). Therefore, bulb removal results in at least partial denervation of all of these regions.

Fibers of the nervus terminalis also originate in the olfactory cavity and course along the medial surface of the bulb, entering the brain with the anterior cerebral artery and synapsing in the septal region (Schwanzel-Fukuda and Silverman, 1980; Wirsig and Leonard, 1986a,b, 1987; Meredith, 1991). Therefore, total bulbectomy would eliminate this afferent fiber system which has been demonstrated to contribute GnRH fibers to the accessory olfactory bulb and ventral forebrain. Interestingly, a superficial and incomplete bulb lesion might leave ventral portions of the main olfactory bulb intact while destroying both the vomeronasal-accessory olfactory bulb system and the nervus terminalis.

The bulb also receives a massive input from higher brain structures. Indeed, it has been estimated that there are more centripetal bulb inputs than sensory afferents. These inputs include reciprocal fibers from many of the targets innervated by the bulb, a large cholinergic and GABAergic input from the region of the horizontal limb of the diagonal

Fig. 1. Camera lucida drawings of Nissl-stained sections through the rat olfactory bulb. (A) Horizontal section. Anterior is at top, medial to right. Caudal border is in true coronal plane. Note that while border between the olfactory bulb and the anterior olfactory nucleus is quite clear, it does not lie in a coronal plane. The medial side of the bulb extends much further posteriorly than does the lateral side. (B) Coronal section (medial to right, dorsal to top) taken approximately 3/4 of a millimeter caudal to the frontal pole of the neocortex. Note that at this level a considerable amount of olfactory bulb is still present, along with a substantial portion of the anterior olfactory nucleus. Taken together, the two panels demonstrate that transection at the frontal pole will leave a significant portion of bulb intact, while damaging the rostral tip of the anterior olfactory nucleus. Key: 1 = main olfactory bulb, 2 = anterior olfactory nucleus, 3 = subependymal zone, 4 = accessory olfactory bulb, 5 = frontal pole of neocortex. Scale bar in (A) = 500 µm.
band of Broca, noradrenergic input from the region of the locus coeruleus, a serotonergic projection from the raphe and histaminergic innervation from magnocellular regions of the hypothalamus (e.g. Shipley et al., 1985; Zaborsky et al., 1986; Airaksinen and Panula, 1988; Auvinen and Panula, 1988; Inagaki et al., 1988; Halász, 1990). Bulb removal, therefore, also results in axotomy of many cells residing in these regions. If transneuronal effects also occur (e.g. changes in cells which project either to regions innervated by the bulb or regions which innervate the structure), one can easily recognize that a substantial portion of the brain might be affected.

The posterior border of the bulb, its junction with the anterior olfactory nucleus, is quite sharp, but does not lie in the coronal plane (Figure 1). The medial portion of the bulb extends much further posteriorly than does the lateral. As mentioned, a commonly employed technique for removing olfactory bulbs is to transect the brain in the coronal plane at the frontal pole of the neocortex. As a result of the oblique caudal border of the bulb, the procedure allows some of the lateral portion of the anterior olfactory nucleus to be destroyed and leaves a portion of the bulb intact on the medial surface. The difficulty in removing just the main and accessory olfactory bulbs results in several problems. First, there has been quite an effort made to separate the effects of anosmia per se, the ostensive primary effect of the procedure, from the consequences of destruction of retrobulbar structures (see below). Secondly, recent research has suggested that considerable sensory function might persist if in fact some bulb tissue remains after the procedure (e.g. Hudson and Distel, 1987; Slotnick et al., 1987). Furthermore, the regenerative capacity of the olfactory mucosa might reproduce a functional olfactory system if sufficient survival times are allowed and the vacated cavity is left open for incoming receptor axons to traverse (e.g. Wright and Harding, 1982; Meredith et al., 1983; Monti-Graziadei and Graziadei, 1992).

II. Olfactory bulbectomy: the consequences

A1. Physical changes: the receptor surface

(a) The regenerative capacity of the olfactory mucosa. A considerable effort has been expended to characterize the continual proliferation and death of receptor cells in the olfactory epithelium (e.g. Farbman, 1990). One common method for inducing receptor cell production is to remove the olfactory bulb. The process axotomizes mature receptors, causing widespread cell death. An unknown signal then induces increased rounds of neurogenesis within the mucosa. Therefore, bulbectomy has been used to demonstrate the capability of receptors to regenerate, to upregulate cell production, and to examine processes of mucosal reorganization (e.g. Rochel and Margolis, 1980; Simmons and Getchell, 1981a,b; Costanzo and Graziadei, 1983; Monti-Graziadei, 1983; Costanzo, 1984; Samanen and Forbes, 1984; Hempstead and Morgan, 1985; Carr and Farbman, 1992).

(b) The instructive role played by incoming olfactory axons. The olfactory mucosa emerges quite early during development and axons from the developing receptor cells help to determine the organization of the neural tissues they contact (Brunjes and Frazier, 1986). These observations, coupled with the work described above demonstrating the regenerative capacity of the mucosa, have prompted several investigators to examine
the effects of bulbectomy on the subsequent re-innervation of the rostral forebrain. Results indicate that after bulb removal olfactory axons can make synaptic contacts with the remaining forebrain, including the olfactory tubercle, anterior olfactory nucleus, and the frontal neocortex. Furthermore, the axons do, indeed, appear to alter the cytoarchitecture of the target regions, producing cytology similar to that seen in normal olfactory glomeruli (Graziadei et al., 1978, 1979; Graziadei and Karlan, 1980; Graziadei and Samamen, 1980; Graziadei and Monti-Graziadei, 1986; Zigova et al., 1988; Monti-Graziadei and Graziadei, 1992) and inducing alterations in neurotransmitter expression (Guthrie and Leon, 1989). However, the connections do not appear to be capable of transmitting usable olfactory information (Butler et al., 1984; but see Monti-Graziadei and Graziadei, 1992).

A2. Physical changes: higher structures

(a) Connectivity. As classical tract-tracing techniques relied on degeneration argyrophilia, bulbectomy has been repeatedly used to examine olfactory system connections in a variety of species (Girgis, 1970; fish: Davis et al., 1981; reptiles: Gamble, 1956; Halpern, 1976; Ulinski and Peterson, 1981; Lohman et al., 1988; mammals: Powell et al., 1965; White, 1965; Heimer, 1968; Scalia, 1968; Lohman and Metink, 1969; Scalia and Winans, 1975; Skee and Hall, 1977; Turner et al., 1978; Turner and Mishkin, 1978; Shammah-Lagnado and Negrao, 1981; Carlsen et al., 1982; Wouterlood and Nederlof, 1983; Wouterlood et al., 1985) as well as to study the development of the olfactory system (Leonard, 1975; Singh, 1977b).

(b) The process of degeneration. The primary output pathway of the bulb, the lateral olfactory tract, forms a uniform bundle on the ventrolateral surface of the forebrain, and its terminations within the primary olfactory cortex have been well specified. As a result, olfactory bulbectomy has been used to examine the time course and morphology of lesion-induced axonal degeneration (e.g. Westrum, 1975; Caviness et al., 1977; Heimer and Kalil, 1978; Friedman and Price, 1981, 1986a,b; Leonard, 1981; Westrum and Bakay, 1986).

(c) Anatomical reorganization. Lesion-induced axonal sprouting has been demonstrated to occur within several of the projections from the olfactory bulb. For example, after partial transection of the lateral olfactory tract remaining fibers sprout around the area of injury to re-innervate caudal portions of the primary olfactory cortex. These reorganized projections have been demonstrated by performing a subsequent bulbectomy and then staining for degeneration products (e.g. Devor, 1976; Small and Leonard, 1983). Westrum and his colleagues (e.g. Westrum, 1975, 1988; Westrum and Bakay, 1986; Westenbroek et al., 1988) as well as others (e.g. Ichikawa, 1987) have performed extensive electron microscopic investigations of the sequence of denervation and re-innervation of the primary olfactory cortex after bulbectomy. Sprouting of dopaminergic fibers into the olfactory tubercle has also been demonstrated to occur after bulbectomy (e.g. Gilad and Reis, 1979). Similar sorts of reorganization have also been reported for the goldfish, which exhibits an impressive ability to compensate after central lesions (e.g. Zippel et al., 1988; Stewart, 1992).
(d) Neurochemical reorganization. Bulb lesions cause widespread changes in brain neurochemistry (reviewed by Hirsch, 1980; Van Riezen and Leonard, 1990) which have been exploited in order to examine a number of topics. Overall, the findings from the studies vary considerably, perhaps due to differences in levels of resolution of the techniques employed, and, importantly, due to differences in post-lesion survival times. As described in Section IIB10 below, bulb removal has been extensively employed as a model for studying the effects of antidepressant drugs. Many of the antidepressants affect monoamine systems and, as a result, most studies examine these transmitters. However, as outlined below, bullectomy affects many neurochemical systems.

(i) Norepinephrine: several investigators have reported that bullectomy causes generalized reductions in neocortical norepinephrine (Pohorecky et al., 1969a,b; Pohorecky and Chalmers, 1971; Eichelman et al., 1972; Oishi and Ueki, 1978; Cairncross et al., 1979a). However, Edwards et al. (1977) compared lesions of varying size and determined that the reductions were only seen after considerable damage to retrobulbar areas. Therefore, the effect seen earlier was probably due to damage to the noradrenergic fibers coursing anterior to the genu of the corpus callosum. Edwards et al.'s (1977) paper presents an important caveat to much of the work done examining changes in central transmitter content and activity (and, indeed, the bullectomy literature as a whole), by suggesting that lesions limited to the olfactory bulb may have a relatively small impact.

Noradrenergic changes have also been described in several other brain regions. Both Yoshimura and Ueki (1981) and Tonnaer et al. (1980) reported that bullectomy results in increased amounts of norepinephrine in the hypothalamus. Iwasaki et al. (1986), however, found similar changes only in those bullectomized rats exhibiting increased mouse-killing behavior (see Section IIB5). Elevated noradrenergic turnover or transmitter levels have been found in the amygdala (Tonnaer et al., 1980; Jancsar and Leonard, 1984; Iwasaki et al., 1986), although conflicting reports also exist (e.g. Broekkamp et al., 1986). The affinity of α-adrenoreceptors was increased in the amygdala and hippocampus, suggesting a supersensitivity, but affinities were not altered in the cerebral cortex (Tiong and Richardson, 1990). Higher number, but no changes in the affinity, of α2-adrenoreceptors, have also been reported in the homogenized forebrain (Hong et al., 1987). Increased norepinephrine content has been reported in the primary olfactory cortex (Harvey et al., 1975) and some authors report a small increase in brainstem norepinephrine content although the finding has been inconsistent (e.g. Hirsch, 1980).

(ii) Dopamine: several studies have examined the consequences of bullectomy on dopaminergic systems. Iwasaki et al. (1986) found decreased levels of dopamine in the lateral hypothalamus of muricidal bullectomized rats. Tyler et al. (1979) reported bullectomy-induced decreases in tyrosine hydroxylase activity in the striatum. As mentioned, bullectomy-induced sprouting of dopaminergic fibers has been demonstrated in the olfactory tubercle. After bulb removal an increase in tyrosine hydroxylase activity and immunoreactivity, high affinity uptake of dopamine, activity of dopamine-sensitive adenylate cyclase, D1 and D2 receptor density, and Na⁺,K⁺ ATPase activity occurs in the olfactory tubercle (e.g. Gilad and Reis, 1979; Lingham and Gottesfeld, 1986; Swann and Gottesfeld, 1987).

(iii) Serotonin: the fact that both raphe lesions and bullectomy induce aggressiveness in rats, along with the observation that many antidepressant drugs affect the serotonergic
Lessons from lesions

systems, has led to quite a bit of interest in bulbectomy-induced changes in brain serotonin. However, conflicting or incomplete evidence exists. For example, Neckers et al. (1975) reported decreased whole brain tryptophan hydroxylase activity six days after bulbectomy in mice. Harvey et al. (1975) and Garris et al. (1984) reported increased serotonin in the ventral forebrain. Decreased turnover of serotonin in the amygdala has also been reported (Jancsar and Leonard, 1984; Van Riezen and Leonard, 1990).

(iv) Acetylcholine: while Yoshimura (1981; see also Harvey et al., 1975) found no differences in choline acetyltransferase levels in seven brain areas between bulbectomized and control rats, Broekkamp et al. (1986) reported an increase 15 days after bulbectomy in the olfactory tubercle. Yoshimura et al. (1974) reported decreased acetylcholine content in the cerebral cortex after bulb removal.

(v) Other transmitters and neurochemicals: changes in excitatory amino acid neurotransmitters in the primary olfactory cortex have been reported after bulbectomy. Many of these studies have been done in order to determine what neurotransmitters are used by bulb relay neurons. Concentrations of amino acids in the primary olfactory cortex are compared before and after bulbectomy and any decreases attributed to the lack of bulb input (e.g. Collins and Probett, 1981; Scholfield et al., 1983; Collins, 1984; Sandberg et al., 1984; and references therein). Bulbectomy has also been reported to result in increased glycine in the olfactory cortex (Harvey et al., 1975).

Bulb removal causes a large reduction in histochemical staining for cytochrome oxidase, an enzyme involved in oxidative phosphorylation and, therefore, metabolism in the primary olfactory cortex (Onoda and Imamura, 1984). The finding is consistent with many studies of anatomical or functional deafferentation (e.g. Korol and Brunjes, 1990). Unilateral bulbectomy causes an increase in the number of opioid binding sites in the contralateral bulb (Hirsch and Margolis, 1980), and changes in DNA and RNA concentrations in the contralateral hemisphere (Shafa, 1979; Shafa et al., 1980). Alterations in amygdala GABA (Jancsar and Leonard, 1981) and glutamic acid decarboxylase activity in the ventral tegmental area (Tyler et al., 1979) have been reported, along with alterations in benzodiazepine (Hirsch, 1981) and imipramine (Al-Khatib et al., 1988) receptor binding. Changes in the physiology of the primary olfactory cortex have also been examined (Becker and Freeman, 1968).

B. Functional changes

It is apparent from the above that bulb removal induces a broad number of changes in the central nervous system, from the rewiring of synaptic assemblies to the rebalancing of neurochemical systems. The resultant changes in behavior and physiological functioning, outlined below, are certainly as diverse.

1. Anosmia. The fact that olfactory bulbectomy results in an inability to detect odors has been known for a long time (e.g. Swann, 1934; Brooks, 1937; Brown and Ghiselli, 1938; Allen, 1941), and the fact has been a primary motivation for using the technique. Bilateral bulbectomy has been demonstrated to result in deficits in olfactory detection and discrimination in rats (e.g. Long and Tapp, 1970; Slotnick and Schoonover, 1984; Amemori and Bures, 1988; Whishaw and Tomie, 1989), as well as a number of other species (e.g. salamander: Mason and Stevens, 1981; sheep: Baldwin and Meese, 1977;
Bell et al., 1979; Cohen-Tannoudji et al., 1986; rabbit: Klosovskii and Kosmarskaya, 1963; kangaroo rats: Webster and Webster, 1975; pigs: Parrot et al., 1985). However, unilateral bulbectomy apparently does not affect olfactory sensitivity (Slotnick and Schoonover, 1984). As mentioned above, the nasal cavity contains a number of chemoreceptive detectors, including the vomeronasal organ and endings of the trigeminal nerve. Bulbectomy or partial lesions are often used to distinguish which of these neural systems underlies particular behaviors (e.g. Ladewig et al., 1980; Wysocki et al., 1982; Hart and Leedy, 1985; Meredith, 1991) or to test the possibility of olfaction mediating a particular behavior (e.g. territorial marking, Thiessen et al., 1970).

2. Sexual behavior. It has been known for many years that the anosmia found after bilateral bulbectomy affects sexual behavior (e.g. Stone, 1922, 1923; Beach, 1942; Whitten, 1956; Lamond, 1958; Bruce and Parrott, 1960; Murphy, 1976). Numerous studies of rodents (e.g. Heimer and Larsson, 1967; Aron et al., 1970; Moss, 1971; Edwards and Warner, 1972; Rowe and Edwards, 1972; Thompson and Edwards, 1972; Edwards and Burge, 1973; Vandenbergh, 1973; Cain and Paxinos, 1974; Larsson, 1975; Horton and Shepherd, 1979; Edwards et al., 1990) as well as other species (e.g. hamster: Murphy and Schneider, 1969; Lisk et al., 1972; Kairys et al., 1980; gerbil: Cheal and Domesick, 1979; guinea-pig: Donovan and Kopriva, 1965; cat: Aronson and Cooper, 1974; Hart and Leedy, 1983; rabbit: Franck, 1966; sheep: Lindsay, 1965; Fletcher and Lindsay, 1968; goat: Ladwewig et al., 1980; pig: Booth and Baldwin, 1983) have been reported.

A number of factors influence the behavioral outcomes of the lesion, including the sex, previous sexual or hormonal experience, strain and species investigated. In some species (e.g. male hamsters: Murphy and Schneider, 1970; Doty et al., 1971; Winans and Powers, 1974; male mice: Rowe and Edwards, 1972; Rowe and Smith, 1973; male guinea-pigs: Beauchamp et al., 1977; male rats: Heimer and Larsson, 1967; Bermant and Taylor, 1969; Larsson, 1975; Meisel et al., 1982; Lumia et al., 1987; female mice: Thompson and Edwards, 1972), bulbectomy generally results in a cessation of sexual behavior, although previous experience plays a role. In others recovery may occur (female guinea-pig: Donavan and Kopriva, 1965; Carter, 1973), the lesion may have no effect (e.g. rabbits: Brooks, 1937) or sexual behavior may be facilitated (female rats: Aron et al., 1970; Moss, 1971; Edwards and Warner, 1972; Larsson, 1977; Satli and Aron, 1977; McGinnis et al., 1978; Tyler and Gorski, 1980; Lumia et al., 1981; Antz-Vaxman and Aron, 1986a,b; Williams et al., 1991). Furthermore, the effects of lesions vary depending on whether surgery is performed before or after puberty (e.g. Larsson, 1975; Pollak and Sachs, 1975).

Some studies comparing anosmia produced by destruction of the mucosa (for example, via lavage with zinc sulfate, Alberts, 1974) to bulbectomy appear to suggest that sensory disturbances per se are not the cause of mating deficits, and implicate the functional disturbances of the central nervous system as a secondary consequence of bulbectomy (e.g. Orbach and Kling, 1966; Devor and Murphy, 1973; Edwards and Burge, 1973; Powers and Winans, 1973; Vandenburgh, 1973; Cain and Paxinos, 1974; Edwards, 1974). Among the kinds of evidence used to support this claim is the observation that the effects of bulbectomy may be partly counteracted by arousing stimulation (e.g. shock, noxious sensory stimulation; Meisel et al., 1980; Wang and Hull, 1980). However, three
Lessons from lesions

points must be addressed (e.g. Murphy, 1976; and Section IIIC). First, due to the convoluted nasal turbinates, lavage techniques seldom destroy all receptors. This observation may explain why some studies report that olfactory receptor damage is effective in reducing sexual behavior (e.g. Powers and Winans, 1973) while others claim it does not (see above). Secondly, bulbectomy destroys both the main and accessory olfactory systems, while nasal lavage may not affect the vomeronasal organ (but see Kelche and Aron, 1984). Thirdly, some techniques of producing peripheral anosmia can be confounded by systemic poisoning (Sieck and Baumbach, 1974).

The large number of studies examining modifications in sexual behavior after bulbectomy has prompted study of the central consequences of the procedure. For example, bulbectomy results in increased estrogen receptor binding in the amygdala of female rats (McGinnis et al., 1985) and reduced androgen binding in the amygdala and hypothalamus of male rats (Lumia et al., 1987). Changes such as these lend credence to the view that the behavioral consequences of bulbectomy may result from more complicated alterations than simple anosmia. Potential secondary changes, including widespread alterations in hormonal secretion and in photoperiodicity, are reviewed in the next section.

3. Hormones and photoperiods. Bulbectomy causes widespread and quite complicated changes in the neuroendocrine axis beyond the alterations in steroid hormone binding patterns mentioned above. For example, bulb removal sensitizes female rats to the anti-gonadal effects of melatonin administration (Reiter et al., 1980) and reverses the testicular regression induced by melatonin injections in male rats (Pieper et al., 1986b). Changes in gonadotropin and prolactin secretion also occur in bulbectomized animals (Pieper and Gala, 1979; Gala et al., 1984, 1985; Pieper et al., 1984, 1990a,b; Clancy et al., 1986) and bulbectomy prevents the negative feedback of testosterone on the secretion of both LH and FSH by the pituitary in hamsters (Pieper et al., 1987).

Interestingly, in some respects peripherally-induced anosmia appears to have similar effects as bulbectomy. Furthermore, selective lesions of the vomeronasal-AOB system are apparently without effect, suggesting that the vomeronasal-accessory bulb system is not involved in the hormonal interactions (Mediavilla et al., 1985; Sanchez-Barcelo et al., 1985; Pieper et al., 1989).

Combining bulb removal with blindness results in striking changes in the neuroendocrine axis. Reiter et al. (1970) reported that neither procedure, when performed alone, affected the reproductive organ weights of adult female rats (however, see Whitten, 1956). However, when both operations were combined, ovaries were found to be smaller than in controls (although number of eggs ovulated may not differ between groups; Peppler et al., 1973). Pinealectomy reversed the effects of the combined sensory deprivation, suggesting that changes in melatonin levels were responsible for the alterations in gonadal size. Further research (Donofrio and Reiter, 1972; Leadem and Blask, 1972a,b; Shiino et al., 1972; Blask and Reiter, 1975; Ronneklev and McCann, 1975) has indicated concomitant decreases in the size of the pars distalis of the pituitary, reductions in overall numbers of adenohypophyseal cells, smaller prolactin secreting cells and alterations in circulating growth hormone.

Seasonal breeders (e.g. hamsters) exhibit a period of low reproductive competence characterized by reductions in gonadal size and function and inhibited gonadotropin
secretion. These reductions appear to be controlled by melatonin produced by the pineal gland. As mentioned, the effects of melatonin (and thus short photoperiod) can be prevented by olfactory bulbectomy. Therefore, bulbectomized hamsters maintained on short photoperiod do not exhibit anestrus (Pieper et al., 1986) or testicular regression (Pieper et al., 1984).

Non-seasonal breeders, such as rats and mice (and pigs, Booth and Baldwin, 1983), normally are not influenced by day-length. However, olfactory bulbectomy has been demonstrated to potentiate photoperiodicity. Bulbectomized rats maintained on short daily periods of light have smaller testes and seminal vesicles and lower plasma testosterone than controls or animals on longer photoperiods, and these effects can be reduced by pinealectomy (e.g. Nelson and Zucker, 1981; Nelson et al., 1985; Nelson, 1990; Pieper et al., 1990a,b; and references therein). The hormonal underpinnings of these changes have been extensively studied (e.g. Pieper et al., 1990a,b).

Taken together, the results described above indicate that bulb lesions have robust and quite complicated effects on the pituitary-gonadal axis. Bulbectomy has also been demonstrated to interact with other hormonal systems. For example, lower basal levels and enhanced stress-induced increases in corticosterone (Loyber et al., 1976; Cairncross et al., 1977, 1979b; Broekkamp et al., 1986) heavier adrenal gland (Eichelman et al., 1972), and an enhanced insulin response to glucose overloads (Perassi et al., 1972) have been reported after bulb removal. These changes, combined with the central neurochemical alterations outlined above (Section II A2d), suggest that bulbectomy results in a complicated cascade of physiological adaptations.

4. Circadian rhythms. Bulbectomy has been reported to lengthen the active period of the circadian cycle in rats, mice and hamsters (Possidente et al., 1990; Pieper and Lobocki, 1991), to delay the onset of entrained activity by over an hour and a half (Bittman et al., 1989; Possidente et al., 1990), to increase activity levels during the dark phase of the circadian cycle (Giardina and Radek, 1991), and to result in elevated cAMP levels in the suprachiasmatic nucleus (Vagell et al., 1991). Pieper and Lobocki (1991) found circadian effects in castrated hamsters both with and without replacement hormones, and concluded, therefore, that the finding was not the result of changes in the pituitary-gonadal axis, but a direct effect on circadian oscillators in the suprachiasmatic nucleus.

5. Aggression. It has long been known that bilateral bulbectomy increases the irritability and aggressiveness of rats (e.g. Watson, 1907; Vergnes and Karli, 1963; Didiergeorges and Karli, 1966; Didiergeorges et al., 1966; Douglas et al., 1969; Bernstein and Moyer, 1970; Sieck and Gordon, 1972). However, understanding the effects of bulb removal on aggressive behavior is complicated by species and sex differences (e.g. Hilger and Rowe, 1975), as well as the fact that many forms of aggression exist and they are not all equally affected by the surgery. For example, removal of the bulbs inhibits intemal aggressive behavior in mice (Ropartz, 1968; Rowe and Edwards, 1971; Bandler and Chi, 1972; Denenberg et al., 1973; Svare and Gandelman, 1974; DaVanzo et al., 1983; Whalen and Johnson, 1988), guinea-pigs (Beauchamp et al., 1977), hamsters (Hilger and Rowe, 1975; Murphy, 1976) and gerbils (Christenson et al., 1973; Rieder and Lumia, 1973; Hull et al., 1974), presumably since the resulting anosmia makes the recognition of strangers difficult. Such an effect was not noted in sheep (Parrot and
Lessons from lesions

Baldwin, 1984). Similarly, bulbectomy reduces pain-induced aggression: gentle electric shocks applied to mice housed with a novel partner elicited aggressive behavior more reliably in control animals than in bulbectomized mice (Fortuna and Gandelman, 1972).

However, bulbectomy potentiates interspecies aggression in rats. Normally, only a small number (10–30%) of male rats will kill mice when the animals are confined together. However, after bulbectomy 50–100% of the subjects exhibit muricide (Vergnes and Karli, 1963; Didiergeorges and Karli, 1966; Didiergeorges et al., 1966; Bandler and Chi, 1972; Ueki et al., 1972a,b; Thorne et al., 1973, 1974; Mast et al., 1974; Yoshimura et al., 1974; Hull and Homan, 1975; Oishi and Ueki, 1978; Yamamoto and Ueki, 1978; Yoshimura and Ueki, 1981; Moutzoukis et al., 1985; Thorne and Rowles, 1988). A considerable effort has been made to examine the neurochemical changes which might underlie this behavior, with most studies concentrating on the major centripetal inputs into the olfactory bulb and, therefore, on potential retrograde changes in higher brain structures resulting from bulbectomy. Examinations of changes in the noradrenergic (Oishi and Ueki, 1978; Yamamoto et al., 1982; Hong et al., 1987), cholinergic (Yoshimura and Ueki, 1974; Yoshimura et al., 1974; Yoshimura, 1981) and serotonergic (Neckers et al., 1975; Yamamoto and Ueki, 1977, 1978; Vergnes, 1978; Yamamoto et al., 1982, 1985; Garris et al., 1984; Hong et al., 1987; Al-Khatib et al., 1988) systems have been reported (see section IIA2D).

Lesions of the amygdala reduced muricide, suggesting that disrupted relationships between it and the bulb might be responsible for the observed effects (Eclancher et al., 1975; Shibata et al., 1982). It has also been reported that androgen injections can ameliorate the effects of bulb removal (e.g. Lumia et al., 1975, 1976, 1977).

Enhanced aggression after bulbectomy has been demonstrated in several other situations. Bulb removal has been reported to result in hyper-reactivity to heat and shock stimulation (Brown and Remley, 1971), enhanced emotionality (Richman et al., 1972; Ueki et al., 1972a,b; Sieck, 1973; Nurimoto et al., 1974), and increased aggression induced by food deprivation (Fortuna, 1977). However, bulb lesions also result in a decrease in fear and timidity and, therefore, in enhanced exploration of novel environments (e.g. Mollenauer et al., 1974).

As in many of the other topics reviewed here, a considerable effort has been made to dissociate the effects of anosmia from the consequences of central nervous system damage. Several studies have compared the effects of peripherally-induced anosmia to bulbectomy and reported that only after the latter are rats more aggressive (e.g. Alberts and Friedman, 1972; Edwards et al., 1972; Spector and Hull, 1972; Sieck, 1973; Cain, 1974b; Cain and Paxinos, 1974; Tiffany et al., 1979). These studies have been used to strengthen the position that there are 'non-sensory' effects of the surgery. However, two other lines of inquiry must also be considered. First, some investigators (e.g. Murphy, 1976, territorial aggression in hamsters) have found little difference between the two techniques. Secondly, studies designed to separate the consequences of bulb removal from damage to retrobulbar regions suggest that damage to areas caudal to the bulb is more more effective in inducing enhanced aggressiveness than lesions restricted to the bulb (e.g. Sieck, 1973; Cain, 1974a; Albert et al., 1981).

6. Activity. Many investigators report that bulb removal increased exploratory activity in an enclosed arena ('open field', Klein and Brown, 1969; Sieck, 1972; Sieck and
Gordon, 1972; Sieck and Baumbach, 1973; Sieck et al., 1973, 1974; Hilger and Rowe, 1975; Burge and Edwards, 1976; Hull et al., 1979; Misslin and Ropartz, 1981; Gomita et al., 1984; Broekkamp et al., 1986; Thorne and Rowles, 1988) and decreases activity in running wheels (Marks et al., 1971; Borer et al., 1974). Once again, peripherally-induced anosmia does not seem to affect activity (Sieck and Baumbach, 1974), and considerable effort has been spent trying to determine the underlying changes in neurochemistry responsible (e.g. Leonard and O’Connor, 1987). Increased activity has been interpreted as: (i) resulting from anosmia, so that animals are forced to seek more stimulation in order to gauge the nature of the novel environment; (ii) a result of a decrease in the rate of habituation in general (e.g. Cheal and Domesick, 1979); or (iii) as a consequence of alterations in the function of the ‘limbic system’ areas innervated by the bulb (see Section IIIID).

7. Learning. It should come as no surprise that anosmic animals do poorly on tasks in which olfactory cues are salient (Herrick, 1933). However, there are many studies suggesting that more complicated changes result from bullectomy. Examinations of alterations in learning abilities in lesioned animals are complicated once again by the many tasks employed and species examined. For example, bullectomized pigeons are slower to learn to peck a key for food reward than controls, but once the habit is acquired, they are no slower at learning a visual discrimination task. Bullectomized birds were reported to be ‘hesitant and inactive during early stages of training’ (Wenzel and Salzman, 1968; see also Wenzel et al., 1969). Bullectomized rats trained in a visual discrimination task exhibit deficits in acquisition as well as in the final level of performance (Phillips, 1970). Bullectomized rats do not differ from chance in a spontaneous alternation situation, suggesting that they do not remember which arms they have previously frequented, or cannot discriminate them (Douglas et al., 1969; Klein and Brown, 1969). They also exhibit inferior performance on passive avoidance tasks (Marks et al., 1971; Sieck, 1972; Archer et al., 1984a,b; Moutzoukis et al., 1985; Thome and Rowles, 1988). The deficits in passive avoidance behavior can be ameliorated with serotonergic agonists or antidepressants (e.g. Broekkamp et al., 1980). Performance deficits have also been reported in tasks employing conditioned fear (King and Cairnecross, 1974) and in response suppression (Thome et al., 1976).

The performance of bullectomized rats on active avoidance tasks has been reported to be both better (Sieck, 1972; Sieck and Gordon, 1972) or worse (Marks et al., 1971) than controls. Animals tested on discriminated avoidance in a shuttle box apparatus exhibit slower acquisition than controls, but equal asymptotic performance, a result which was interpreted to be due to the heightened reactivity reported in irritable, bullectomized rats (Gomita et al., 1984). Bullectomy has also been reported to interfere with taste aversion learning (e.g. Hankins et al., 1976; Elkins et al., 1977; Elkins, 1980; Jancsar and Leonard, 1982).

While the above results certainly suggest bullectomy affects non-olfactory learning, perhaps the most convincing line of evidence indicating that bullectomy causes a series of changes throughout the brain comes from studies employing the radial arm maze. Performance on the maze, a task theoretically designed to test the function of the septohippocampal system, is seriously impaired by bullectomy. The fact that normal rats do not need olfactory cues to navigate through the apparatus effectively suggests
that the deficit results from central imbalances consequent to bulb removal (Hall and Macrides, 1983; Amemori et al., 1989).

8. Development. The most common reason bulbectomy has been performed in developing animals is to examine the role of olfaction in particular behavior patterns. For example, bulbectomized rat and rabbit pups have difficulties in locating and attaching to nipples, and thus securing sustenance, suggesting that suckling is under olfactory control (e.g. McClelland and Cowley, 1972; Singh and Tobach, 1975; Singh et al., 1976; DeSantis and DeHerrera, 1977; Rouger and Schneirla, 1977; Singh, 1977a; Tobach, 1977; Teicher et al., 1978; Hill and Almli, 1981; Distel and Hudson, 1985; Risser and Slotnick, 1987). The fact that bulbectomy has less of an effect when performed on postnatal Day 1 than on Day 10 in rats has been used to infer that there is a changing dependence on olfactory stimulation as pups mature (e.g. Hill and Almli, 1981). It should be noted that as a result of its effects on nursing, early bulbectomy typically results in slow growth and lower adult body weights.

Bulbectomy has also been used to examine a number of other behaviors, including the role of olfaction in the hyper-reactivity normally seen in 15-day-old rats placed in a large arena (Raskin, 1982). The results of these experiments suggest that olfaction is important in allowing rats to recognize familiar situations. Play fighting in juvenile rats does not appear to be affected by bulb removal (Beatty and Costello, 1983). Bulbectomized young hamsters exhibit enhanced heat seeking on a thermal gradient and, as a result, higher body temperatures than controls (Leonard, 1978). Finally, mice bulbectomized 24 h after birth exhibit deficits in a two-choice visual discrimination task in later life (Cooper and Cowley, 1979).

Early bulb removal also affects later sexual behavior. The change may be due to disruption of crucial early olfactory experiences, to alterations in normal patterns of general brain neurogenesis and/or to alterations in hormonal status (Lumia et al., 1977). For example, bulbectomy alters the endocrine development of female rats, resulting in delayed puberty and vaginal opening (Kling, 1964). Male rats bulbectomized early (e.g. Day 2) exhibit copulatory deficits, while lesions at Day 10 have less of an effect (Meisel et al., 1982). Deficits have also been reported in female hamsters, where even unilateral bulbectomy affects later reproductive behavior (Leonard, 1972).

9. Maternal behavior. Olfactory bulb removal causes serious deficits in maternal behavior in rats, mice and hamsters. For example, bulbectomy prior to parturition in primiparous mice, rats and hamsters results in an increased tendency to cannibalize pups, and decreases in nest building, pup retrieval and nursing (e.g. Gandelman et al., 1970; Zarrow et al., 1971; Goodman and Firestone, 1973; Benuck and Rowe, 1975; Marques, 1979). However, several factors, including the amount of previous experience with pups and the physiological state of the female (cycling versus lactating) affect the results of bulbectomy (e.g. Gandelman et al., 1971; Fleming and Rosenblatt, 1974a; Pollack and Sachs, 1975; Schwartz and Rowe, 1976; Fleischer et al., 1981). Once again, more robust effects are seen with bulbectomy than with peripherally-produced anosmia, suggesting that the effects may not be simply due to anosmia (e.g. Fleming and Rosenblatt, 1974b; Seegal and Denenberg, 1974; Benuck and Rowe, 1975).
10. Model for antidepressant drugs. Several reviews have been written championing
the use of olfactory bulbectomy as a model for testing the efficacy of antidepressant
drugs (e.g. Cairncross et al., 1978, 1979a; Leonard and Tuite, 1981; Pinder, 1981;
Leonard, 1984; Jesberger and Richardson, 1986b; Van Riezen and Leonard, 1990).
The rationale for this line of research is derived from observations that a series of
antidepressants (e.g. amitriptyline, mianserin, chlorpromazine, chlordiazepoxide,
diazepam, desipramine, fengabine; see Van Riezen and Leonard, 1990) are capable
of alleviating many of the behavioral changes seen after bulbectomy. The most commonly
examined behaviors include hyperactivity in an enclosed arena, irritability, mouse-
killing, and passive avoidance deficits (e.g. Kumadaki et al., 1967; Ueki et al., 1972a,b;
Van Riezen et al., 1977; Broekkamp et al., 1980; Jancsar and Leonard, 1981; Noreika
et al., 1981; Yoshimura and Ueki, 1981; Archer et al., 1984a,b; Iwasaki et al., 1986,
1989; O'Connor and Leonard, 1986, 1988; Lloyd et al., 1987; O'Neill et al., 1987;
Stockert et al., 1988; Yamamoto et al., 1989) although examinations of other con-
sequences of bulbectomy, such as thermoregulatory deficits (Forster et al., 1980),
changes in taste aversion learning (Jancsar and Leonard, 1982), alterations in learned
immobility (Gorka et al., 1985) and circadian disturbances (Giardina and Radek, 1991)
have also been employed.

Most drugs used to alleviate depression are given chronically as their effects emerge
only after extended treatment. Interestingly, a similar consequence is seen after
bulbectomy: only chronic administration of drugs is effective in reducing the 'olfactory
bulbectomy syndrome'. Furthermore, both depressed humans and bulbectomized rats
have increased plasma levels of alpha-1 acid glycoprotein, a substance involved in
stress-mediated immune system regulation (Arnold and Meyerson, 1990). Similarities
such as these have been used to justify using bulb removal as a screening procedure
for new antidepressants (e.g. Leonard and Tuite, 1981; Van Riezen and Leonard, 1990).

Many, although not all, of the antidepressants which affect bulbectomized animals
are also monoamine agonists. As a result, considerable effort has been expended to
examine changes in the serotonergic, noradrenergic and dopaminergic systems after
bulb removal (see reviews cited above, section IIA2d, as well as Jancsar and Leonard,
1984; Jesberger and Richardson, 1986a,b; Tani et al., 1987; Butler and Leonard, 1990).
Observations of alterations in central monoamine levels have led to considerable
speculation as to the mechanisms underlying many of the behaviors affected by
bulbectomy, and to the functional relationship between the olfactory system, the 'limbic'
system and brainstem arousal mechanisms. These, in turn, have been used to describe
potential underlying mechanisms producing depression in humans (e.g. Leonard, 1984;
Jesberger and Richardson, 1986b; Van Riezen and Leonard, 1990). Several other
neurochemical systems have also been investigated (e.g. Neuropeptide Y; Widerlov
et al., 1988; GABA: Jancsar and Leonard, 1981, 1984; Lloyd et al., 1983, 1987).

11. Thermoregulation. Bulb removal results in an inability to maintain core temperatures
when rats are placed in a cold (4°C) environment (Forster et al., 1980), elevated body
temperatures at normal temperatures and reduced water consumption in warm
environments (Soderberg and Larrson, 1976). Normal rats and mice spend a large
proportion of their time contacting each other ('huddling') both for social and
thermoregulatory reasons. Edwards and Roberts (1972; Edwards, 1974) reported that
Lessons from lesions

bulbectomy eliminates huddling in response to cold temperatures. However, as they reported that other forms of behavioral thermoregulation, such as heat seeking and overeating, are not affected, the deficit may be the result of problems in social behavior.

Bulbectomized hamsters do not build nests as well as controls, a finding which has been used to suggest both deficits in behavioral thermoregulation and in maternal behavior (Kairys et al., 1980; Miro et al., 1980). As mentioned above, bulb removal also affects thermotaxic behavior in young hamsters (Leonard, 1978).

12. Heart rate. Normal rats exhibit heart rate deceleration in response to a novel tone. After repeated tone presentation the animals habituate (heart rate responses are no longer observed). Bulbectomized animals also exhibit initial decreases in heart rate, and subsequent habituation, but even after many presentations they still exhibit some cardiac deceleration: that is, their asymptotic rate of responding does not return to zero (Phillips and Martin, 1971). Interestingly, similar results were found when bulbectomized rats were compared with animals who had undergone olfactory nerve section, a finding which suggests that changes in heart rate are due to anosmia, and not to central alterations (Phillips and Martin, 1972). Similar changes in heart rate habituation are not observed in the goldfish (Rooney and Laming, 1984).

Kawasaki et al. (1980a,b) reported that bulbectomized rats have a lower resting heart rate, lower heart rates when placed into a novel enclosed arena, and potentiated pressor responses to posterior hypothalamic or midbrain reticular formation stimulation when compared to controls. They suggested that the bulbectomy-induced alterations in autonomic regulation are perhaps due to altered function in either the amygdala or in the noradrenergic system.

13. Other. Bulbectomy has been shown to affect many other behaviors, although these changes have received less attention. Some of these topics are outlined below.

(a) Convulsions and seizures. Araki and Ueki (1972) reported that bulb removal increases the threshold for electroconvulsive shock and reduces the duration of the subsequent postictal coma. Convulsions induced by the drugs pentetrazol and picrotoxin were not affected, but seizures induced by either strychnine and aminohexan were inhibited. Millan et al. (1986) similarly observed that bulb removal protected against the effects of seizure-inducing systemic injections of pilocarpine. Both groups of researchers suggested that their results were due to alterations in basal forebrain and limbic structures affected by the surgery. Bulbectomy decreases the threshold for the induction of kindling, an animal model of epilepsy (Watanabe et al., 1982).

(b) Water consumption. Olfactory peduncle transection results in increased water consumption (Novakova and Dlouha, 1960). Bulbectomized rats have been reported to drink more 1% NaCl solution than normal rats (Chiaraviglio, 1969) and to have disruptions in normal patterns of prandial drinking (Larue, 1975).

(c) Feeding behavior and food preferences. In both the chicken and red-winged blackbird, bulbectomy results in increased food ingestion, oxygen consumption and thyroid function (Robinson et al., 1977, 1979). Hyperphagia has also been reported for the European hamster (Miro et al., 1982). Several studies have examined the effect of bulbectomy on the feeding and body morphology abnormalities induced by ventromedial and lateral hypothalamic lesions (e.g. Larue and LeMagnen, 1970; Kemble,
1973; Edwards et al., 1979). Others have examined flavor preferences in rats and reported decreased aversions to caffeine, a bitter compound (Gesell and Fisher, 1968), and normal responses to alcohol (Kiefer et al., 1988). Bulbectomized sheep exhibit alterations in salt preferences (Bell et al., 1979) and the timing of meal bouts (Baldwin et al., 1977; but not pigs: Baldwin and Cooper, 1979).

(d) Immune function. Komori et al. (1991) recently reported that bulb removal inhibits the formation of plaque-forming cells, and causes thymic involution and immunosuppression in response to stress. As mentioned above, bulbectomy also results in elevated plasma levels of alpha-1 acid glycoprotein levels (Arnold and Meyerson, 1990).

(e) Viral infections. The olfactory mucosa incorporates many agents and transports them to the olfactory bulb (e.g. Shipley, 1985). Bulbectomy has been used to demonstrate that this route is a way in which viruses can gain access to the central nervous system (e.g. Perlman et al., 1990).

(f) Blood glucose. Bello and Rummler (1980) reported that both bulbectomy and peripheral deafferentation results in hypoglycaemia in turtles 4, 6 and 8 months after surgery. As mentioned above, alterations in insulin secretion in rats have also been noted (Perassi et al., 1972).

(g) Sleep. Decreased amounts of paradoxical sleep in the week following bulbectomy have been reported in rats, while slow wave sleep is unchanged (Araki et al., 1990). Bulbectomy-induced alterations in EEG patterns in the pyriform cortex during sleep have also been examined (Becker and Freeman, 1968).

III. Conclusions

(A) Bulbectomy has broad consequences

Olfactory bulbectomy results in a remarkably broad set of behavioral, hormonal, neurochemical and anatomical changes. Indeed, the list of consequences outlined above goes far beyond any a priori expectations of what might occur when a primary sensory nucleus is removed from the brain. The observed alterations would be quite hard to explain on the basis of anosmia alone and, therefore, suggest that bulbectomy initiates a very complex cascade of changes within the brain. The diversity of effects of bulbectomy explains why the technique has been so often employed.

(B) Many studies employing bulbectomy are incomplete

A surprisingly large proportion of the studies reviewed above are quite brief and lack important details which might help our understanding of the broader effects of bulb removal. For example, most lack a clear description of the surgical methodology, making it difficult to determine how replicable the procedure was from animal to animal or the extent to which retrobulbar structures were damaged. Similarly, few present histological data from post-mortem examinations. This oversight yields at least three problems. First, the lack of lesion verification reduces the reader’s confidence that all bulb tissue was removed. As mentioned above, complete bulb removal is quite difficult (Section IB), and olfactory function can apparently be maintained with only a very small bulb remnant (e.g. Hudson and Distel, 1987; Slotnick et al., 1987). Therefore, adequate confirmation of the surgical procedure is crucial.
Lessons from lesions

Secondly, lesion verification allows the direct determination of the extent of damage to non-bulb regions. Without this information authors viewing functional deficits might be tempted to interpret the change as mediated by bulb removal (the intended target), when the alteration is actually the result of damage to other brain regions. The point is especially important given that several studies (e.g. Sieck and Gordon, 1972; Sieck, 1973; Cain, 1974a; Edwards et al., 1977; Albert et al., 1981) have demonstrated that many of the changes attributed to ‘bulbectomy’ may actually result from damage to retrobulbar areas. This point cannot be overemphasized. As suggested by Schoenfeld and Hamilton (1977), in an ideal study one would attempt to correlate lesion extent with the severity of functional alterations.

Thirdly, histological examinations would allow investigators to ascertain whether regeneration of connections between the receptors and the central tissue had occurred. Many studies of bulb removal report quite long intervals between surgery and testing, thus such reestablishment of connections is quite possible (e.g. Wright and Harding, 1982; Meredith et al., 1983; Monti-Graziadei and Graziadei, 1992).

A further problem with many studies is that animals were examined only at a single time point. Bulbectomy doubtlessly results in an immediate cessation of bulb-driven neural activity in higher brain centers. This, of course, in many studies, is the goal of the surgery and the only factor to which many of the functional changes are usually ascribed. However, one would also expect a series of other neural changes which might vary depending on both the time post-lesion and the location within the brain (see also Isaacson, 1976; Lynch, 1976; Schoenfeld and Hamilton, 1977; Steward, 1989; Cajal, 1991).

(1) Lesion-induced local changes. One might reasonably expect to find a broad area of the forebrain affected by bulb removal. The surgical procedure employed (typically the aspiration of the bulbs) will result in the physical manipulation of the anterior forebrain, and the removal of the bulbs doubtlessly will be accompanied by edema and vascular disruption. These sorts of surgical traumas may be expected to affect a broad area for several days after the surgery.

(2) Primary degeneration. Anterograde degeneration of the axons of bulb relay cells will occur over a period of several days. Retrograde degeneration of axons of cells projecting into the bulb will also occur. Both processes will result in glial responses and debris removal throughout much of the forebrain. Axotomy might also result in cell death throughout the many regions innervating the bulb. Alternatively, axotomized cells may exhibit reduced function while healing, and/or a period of collateral growth as they reestablish their axonal arbors (see below).

(3) Secondary changes. As a result of the changes described above, a period of synaptic rebalancing is likely to ensue in remaining neurons. Many changes are possible, including the sprouting of axons into denervated regions or changes in synaptic strength, such as denervation supersensitivity (see below).

As a result one would predict that different functional changes might be observed at various times during the course of recovery. Furthermore, it is apparent that cataloging these evolving symptoms might aid in our understanding of the cascade of events induced by bulbectomy. Nevertheless, rarely have time-courses of change been examined.
Different results emerge when bulbectomy is compared with anosmia performed by damaging receptors ('peripheral anosmia')

There have been many tests of this notion; the literature is replete with examples of differential effects when bulbectomy and, for example, intranasal lavage with zinc sulfate are compared (e.g. Edwards, 1974; Cain, 1974a). However, as mentioned, several factors must be considered. First, it is difficult to destroy all receptor cells with nasal lavage due to the convoluted nature of the nasal cavity (e.g. Slotnick and Gutman, 1977). Secondly, the effects of many of the substances used to destroy the olfactory mucosa are potentially confounded by the fact that their ingestion (or inhalation) may cause undesirable side effects (e.g. Sieck and Baumbach, 1974). Thirdly, regeneration of functional connections might occur after long survival times.

Just as in investigations of bulbectomy, in many studies examining ‘peripheral anosmia’ subjects were tested only at one time point. Experimental results might be expected to differ between subjects tested just after treatment and those examined several weeks later. For example, functional states during early periods after nasal lavage might be affected by secondary consequences of the cytotoxic chemicals employed, while later results might be influenced by newly arriving axons contacting the bulb. Furthermore, histological verification of receptor damage after lavage is as rare as that for determining the extent of bulbectomy. It is possible that a correlation might exist between functional deficits and the amount of damage done to the mucosal sheet, but observations such as these are rarely reported.

Nevertheless, it appears obvious that different results are obtained when the effects of the two manipulations are compared. However, the observation should be expected given the different outcomes of the surgical procedures. De-afferentation would affect primarily the synaptic organization within the olfactory bulb, with perhaps some rebalancing of fiber systems entering the bulb from higher brain centers. It is likely that these changes would not match the scope or severity of those seen after bulbectomy.

The effects of bulbectomy have been often overinterpreted

The observation that bulbectomy has broad consequences which are not seen with peripheral deafferentation has led many authors to infer that there are ‘non-olfactory’ roles of the bulb (e.g. see Spector and Hull, 1972; Sieck, 1973; Cain, 1974a; Hull and Homan, 1975), and that these functions are unmasked by its removal. For example, as mentioned several times above, many discussions are made of the interactions of the bulb and limbic system, and the inference is drawn that it is the ‘limbic’ nature of the bulb which induces these changes. However, anatomically the bulb contains the apparatus for receiving odor information, processing it (with such processing dependent on input from higher brain centers, e.g. Taylor and Keverne, 1991; Leon, 1992) and transmitting it to other areas for further use.

A far simpler view would be to assume that the ‘non-olfactory’ effects of bulbectomy simply result from the higher-order changes occurring in the rest of the brain. Several examples may serve to elaborate this point. The removal of the bulb (and, in many cases, of retrobulbar tissue) results in physical alterations of, for example, the noradrenergic projection from the lateral tegmental/locus coeruleus region and from the serotonergic projection from the raphe to the bulb (see Section IB). These brain regions are involved in diffusely modulating overall brain activity. Projections to the
Lessons from lesions

bulb are quite dense. For example, Shipley et al. (1985) have estimated that over 40% of the 1600 norepinephrine-containing cells of the locus coeruleus of the rat send axons into the bulb. What sorts of changes might one see as a result of their axotomy? Some candidates include:

(1) **Cell death.** The noradrenergic and serotonergic cells innervate large reaches of the brain through diffuse axonal fields (e.g. Loughin and Fallon, 1985; Tork, 1985). If cell death did occur it would doubtlessly translate into a concomitant loss of innervation in many other regions, and therefore widespread alterations in neural activity. As a subsequent result other changes might occur, including: (i) secondary, retrograde alterations in the numerous regions which innervate the monoaminergic nuclei; (ii) competition for the synaptic sites vacated by the cell death; and (iii) a period of widespread changes in synaptic sensitivity.

(2) **Cellular rebalance.** Another scenario, which is not mutually exclusive to that above, is that cells surviving axotomy might undergo a period of repair. During the period one might expect the axotomized cells to exhibit a temporary decline in function as healing proceeds and, thus, a period of decreased synaptic output. Alternatively as has been described in several catecholaminergic populations, there might be cellular compensation through an activation of neurotransmitter synthesizing enzymes (e.g. tyrosine hydroxylase), enhanced gene expression in order to increase enzyme production in residual neurons, and augmented transmitter release and turnover (e.g. Zigmond et al., 1990). Alterations in postsynaptic receptor number or affinity might also bias synaptic sensitivity.

(3) **Collateral sprouting.** Distal axotomy can result in collateral sprouting by proximal portions of the axonal arbor (e.g. Lynch, 1976). Such a process could potentially result in hyperinnervation of remaining areas, once again disrupting the overall brain activity. As mentioned (Section IIA2dii), sprouting of dopaminergic fibers does occur after bulb removal in the olfactory tubercle.

Due to their widespread connections, changes in monoaminergic systems are good candidates for explaining some of the effects seen after bulbectomy. However, bulb removal alters synaptic relationships in many other systems (see Section IB). For example, there is a substantial cholinergic and GABAergic input from the nucleus of the diagonal band (e.g. Zaborsky et al., 1986; Woolf, 1991), as well as efferent connections to regions thought to be involved in movement (the ventral striatum; e.g. Heimer et al., 1991), emotions (the amygdala; e.g. Davis, 1992) and memory (the entorhinal cortex; e.g. Eichenbaum et al., 1991; Lynch and Granger, 1991). Cell death, rebalance and sprouting could potentially occur in any of these circuits. If both secondary connections (tissue synaptically related to areas directly innervated by the bulb, e.g. the mediodorsal nucleus of the thalamus, hypothalamic regions, hippocampus, neocortex, etc.; e.g. Switzer et al., 1985; Price et al., 1991) and retrobulbar zones potentially affected by the surgery are also considered, it becomes apparent that complex, time-dependent changes can occur as a result of bulb removal. Therefore, it seems much simpler to ascribe changes seen after bulbectomy to potential denervation effects occurring in higher brain centers than it does to posit a diffuse 'limbic' or 'non-sensory' role of the olfactory bulb.

747
(E) Much could be learned by studying the sequences of central changes occurring as a result of bulbectomy

What occurs after bulbectomy? The discussion above suggests we have a relatively broad understanding of the behavioral changes associated with the surgery. However, little attention has been paid to understanding post-lesion progressions of functional alterations. Furthermore, it is difficult to determine how many of the results attributed to olfactory bulb removal are really the result of damage to retrobulbar structures. We also lack an adequate understanding of the sequences of physical brain changes, either within those regions where the primary function appears to be processing odor information or within the systems involved in relaying sensory information to the rest of the brain. Rigorous examinations of the succession of lesion-induced events at levels from the molecular to the molar are certainly needed in order to be able to understand the wealth of changes induced by bulbectomy.

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