SOME ASPECTS OF THE FUNCTION OF THE OLFACTORY SYSTEM

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TABLE OF CONTENTS

I. INTRODUCTION

The ability to react to chemical stimuli is a common functional feature of living tissue. The effect which is elicited by the stimulus varies with the functional characteristics of the cells involved, as well as with the nature of the stimulating agent. Some systems show a broad sensitivity whereas others are highly specific and react only to certain stimuli. In the specialized chemoreceptor organs, such as the chemoreceptors of the carotid bodies or the olfactory sense organ, the cells are able to transduce the stimulus into a coded message that provides the central nervous system with information about the strength and nature of the stimulating agent. Though the cells of different tissues show widely different sensitivities and reaction patterns, they seem to have a great deal in common as regards the basic mechanisms of their responses. Knowledge about the function of the chemical sense organs may therefore be useful for the understanding of the action of chemical agents on biological systems in general and

the action of drugs in particular. Among the specialized chemo-sensitive systems in higher vertebrates, the olfactory organ may be of particular interest to the pharmacologist because of the close similarity that appears to exist between drug actions and the physiological processes that take place in the olfactory receptors.

The aim of this article is to present some fundamental facts and current concepts of the function of the olfactory system. Experimental data with direct bearing upon pharmacological aspects are scarce. The author has therefore chosen to give a broad presentation of the physiological and morphological approaches which have been made to evaluate the function of the olfactory organ. It is the hope of the author that the reader may extract out of this account what might be of particular interest from a pharmacological point of view.

II. THE OLFACTORY RECEPTOR ORGAN

1. Structure of the olfactory membrane. The olfactory receptors in man and higher primates are distributed in the mucous membrane covering the upper posterior part of the nasal septum and the opposite region of the wall of the superior concha. In lower mammals the topography of the olfactory area is more complicated, as the sensory cells are disposed over extensive portions of the nasal membrane covering an elaborate system of folds of the turbinal processes. Although the extent of the olfactory area varies greatly in different species, as does the development of their sense of smell, the structures of the sensory elements are essentially alike throughout the vertebrate phylum.

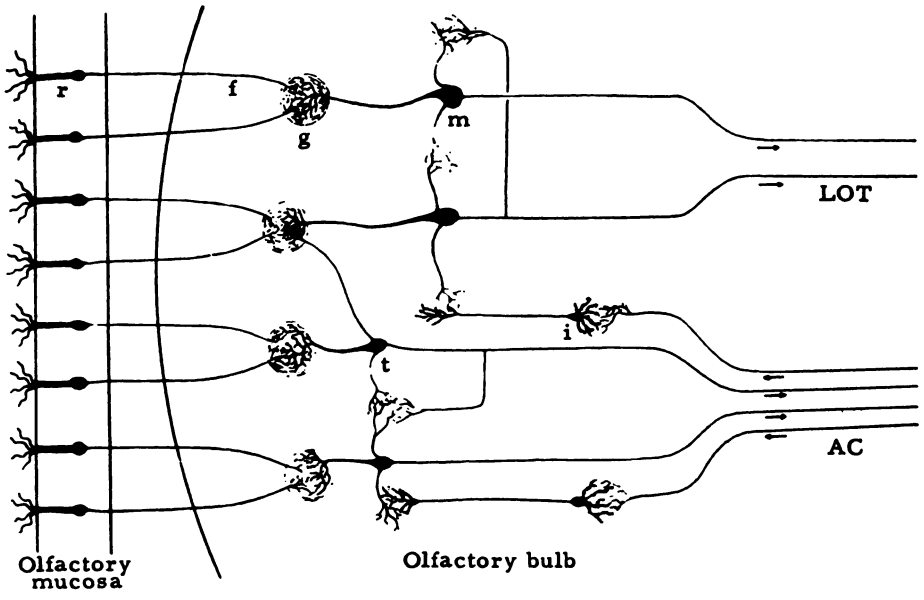

FIG. 1. Schematic diagram of the primary and secondary olfactory pathways: r, receptor cell; f, olfactory nerve fibre; g, glomerulus; m, mitral cell; t, tufted cell; i, granular cell; LOT, lateral olfactory tract; AC, anterior commissure.

As described in the classical papers by Eckhard (65), Schultze (201, 202), von Brunn (41), and van Gehuchten (78), the olfactory epithelium in vertebrates is built up of three kinds of cells: olfactory cells, sustentacular or supporting cells, and basal cells. The sensory cells are bipolar neurons with oval-shaped cell bodies. From the peripheral part of the cell body there extends a thin process, the olfactory rod or the dendrite, that terminates at the outer limiting membrane with a rounded enlargement, the olfactory vesicle. A number of exceedingly thin hairlike filaments protrude from the vesicle into the mucus covering the epithelium. The proximal part of the cell body tapers down into a fine process that continues as the olfactory nerve fibre and ultimately terminates in the olfactory bulb.

Recent electron microscopical studies by Bloom (35), Gasser (76), and de Lorenzo (141) show that the bipolar neurons are enwrapped throughout their course in the epithelium by the plasma membrane of the supporting cells and the basal cells. As pointed out by de Lorenzo this arrangement suggests that the supporting cell has a more important function than might be derived from its name. The plasma membrane of the receptor cell is about 150 Å thick and along its inner surface there are numerous granules and small vesicles. Most of the cytoplasm of the cell is found in the distal process, which also contains a great number of mitochondria concentrated close to the nucleus and to the olfactory vesicle. In the rabbit there are about 120,000 sensory cells per mm^2. Since the total area of the olfactory epithelium in this animal is about 4.5 cm^2 on each side, the total number of fibres conveying olfactory signals to the brain would be about 100 million (16, 129). An interesting function of the sustentacular cells is the active way in which they phagocytize the products of degeneration of the receptors when the latter disintegrate after ablation of the olfactory bulb. As shown by Le Gros Clark (130), removal of the olfactory bulb in the rabbit leads to a striking degeneration which reaches the height of its activity in about 48 hours. The debris is rapidly cleared away by the supporting cells, whose cytoplasm is seen to be filled with vacuoles containing the products of the degenerated receptors.

The most interesting structures from a functional point of view are the olfactory hairs, since they can be assumed to constitute the receptor elements. There is little agreement in the morphological literature as to the number and dimensions of these structures. The divergent statements may be explained partly by species differences, and partly by the fact that the hairs are difficult to demonstrate in histological preparations as they are easily disrupted by the fixation procedure. It also seems likely that in some studies ciliary processes of cells, other than the receptor cells, have been confused with olfactory hairs. At the marginal border of the sensory epithelium the receptor cells are intermixed with cells of the respiratory epithelium so that it may be difficult to distinguish between the processes of the two types of cells. It is also well known that the olfactory epithelium often undergoes metaplastic changes and is converted into an atypical epithelium with ciliated cells which may be mistaken for receptor cells. According to Hopkins (106), who examined the living olfactory epithelium

in the frog, there are two types of hairs. Some hairs had a length of 20 to 30 μ and showed a waving motion, while other hairs having a length of 75 to 200 μ were non-motile. A definite difference was observed between the motion of the cilia of the respiratory epithelium and that of the motile olfactory hairs. In the latter there was no coordination of movements of the hairs of neighbouring cells. It has been suggested that the motion of the hairs serves the function of making the olfactory membrane more efficient as receiving apparatus (130). In fixed material from man and rabbit the hairs are found to be only 1 to 2 μ long (69, 132). The electron microscopical studies of the hairs have revealed that they contain longitudinally oriented filaments arranged as pairs in a marginal ring around one pair in the center. According to observations of de Lorenzo (141) the central filaments are continuous with basal bodies which extend into the cytoplasm of the apical portion of the olfactory rod. An interesting finding is that cross-striations can sometimes be observed in the fibrils of the basal bodies. However, in contrast to ciliated structures elsewhere, the cytoplasm around the basal bodies in the olfactory rods seems to contain relatively few mitochondria. The hairs are oriented at right angles to the olfactory vesicle for a short distance and then bend off and form a feltwork covering the surface of the epithelium. This sheet of filaments forms the sensory membrane of the olfactory apparatus.

The olfactory nerve fibres emerge from the proximal part of the cell bodies. After the axon has left the cell it becomes ensheathed by the supporting cells and the basal cells. Then a number of axons are grouped together forming small fascicles which in the submucosa become enwrapped by the mesaxon of a Schwann cell. The fascicles are thereafter aggregated into small nerve bundles, fila olfactoria, which pass to the olfactory bulb. The morphology and arrangement of the axons exhibit several features pertinent to the understanding of the function of the olfactory organ. The early studies of Schultze (201, 202) and others showed that the olfactory axons are extraordinarily thin. Since their dimensions were found to be close to or beyond the resolving power of the light microscope, it has not been possible to determine their diameters accurately. Gasser's (76) and de Lorenzo's (141) electron microscopical studies disclosed that the olfactory nerve fibres have an average diameter of 0.2 μ with variations of 0.1 to 0.4 μ. The extreme fineness of the fibres may be illustrated by the fact that there are about 10 axons per μ^2 in a cross section of the olfactory nerve (76).

Unlike what is seen in other non-myelinated fibres, the olfactory axons of a fascicle are not ensheathed by individual mesaxons but share a common sheath. Since in addition to this the fibres are densely packed together there should be possibilities for an interaction between neighbouring fibres within a fascicle. It is likely that this arrangement may result in a synchronization of the discharge in the olfactory nerve. However, it is important to note that each fibre retains its individuality until it reaches the olfactory bulb. Since each bipolar cell gives rise only to one axon there is a one-to-one ratio between receptor cells and fibres. Another functionally important anatomical feature is that there are no synaptic connections between the bipolar cells in the mucosa. Each receptor cell with its axon therefore serves as a separate channel to the olfactory bulb.

There has been a great deal of discussion in the literature on olfaction as to whether or not there is a morphological differentiation of the sensory cells which might be associated with the discrimination of different odours. As has been pointed out by many histologists (123), the receptor cells differ in length of the dendrite, in size of the olfactory vesicle, and in number and length of their hairs. On the basis of the differences in length of the dendrite, Dogiel (60) has suggested that the sensory cells should be divided into olfactory rods and cones. Observations on the reaction of the receptors to lesions of the olfactory bulb suggest that there are two categories of bipolar cells (128, 129, 132). However, it would be premature to conclude that the observed structural differences have anything to do with the discriminative capacity of the receptors. Comparative studies on the structure of the olfactory epithelium in different species have shown that there is very little difference between animals with a well developed sense of smell and those with a less well developed one. It seems most likely, therefore, that if there are structural differences responsible for the differential sensitivities of the receptors, these differences have to be looked for at the molecular structure of the receptor membrane.

2. The olfactory pigment. The functional significance of the pigment that gives the mucosa its characteristic yellow colour has been the subject of a great deal of speculation. As early as 1870 it was suggested by Ogle (174) that the pigment might be associated with the absorption of some radiation from the odorous particles. The pigment would according to this hypothesis have a function similar to that of the photochemical substances in the visual cells. It has also been assumed that there is a correlation between the degree of pigmentation and the acuity of olfaction. This idea appears to derive from statements that albino animals in general possess a poorly developed sense of smell (17, 153, 174). The experimental data that have been presented as evidence of a poor olfactory sensitivity in albinos are fragmentary and unconvincing. In studies on the reactions of black, gray, and albino rats to olfactory stimuli, Keeler (118) observed behavioural differences which were interpreted as evidence of a depressing effect of the albino gene upon olfactory acuity. Recently, data have been presented which seem to refute this hypothesis. In 1957 Gruch (93) showed that there was no significant difference in olfactory acuity between albino and pigmented rats. This finding has been confirmed by Moulton (161) in carefully controlled experiments. It has further been reported that albino rats and rabbits have a normally pigmented olfactory membrane and that they give normal responses to odours when tested by electrophysiological methods (109).

A definite assessment of the possible role of the pigment in the function of the olfactory membrane can hardly be made until we know more about its localization and histochemistry. In most anatomical descriptions of the nasal mucosa the pigment is said to be localized in the Bowman's gland cells and in the supporting cells. By using different histochemical methods, Gerebtzoff and Shkapenko (82) have been able to demonstrate that the pigment is also present in the peripheral part of the sensory cells. Jackson (109) has expressed doubts about this finding and argued that the method used by Gerebtzoff and Shka-

penko did not permit a precise localization of the pigment. The presence of pigment in the supporting cells is of interest since the receptor dendrite is surrounded by the cytoplasm of the supporting cells. On the other hand, the presence of the pigment in the gland cells seems to be difficult to reconcile with the idea that the pigment is directly associated with the excitatory process.

Gerebtzoff and his collaborators (81, 82, 104, 187, 188) have carried out a detailed analysis of the chemistry of the olfactory pigment. The conclusion was drawn that the colour of the epithelium is due partly to chromolipids, and partly to non-lipid substances which are bound to lipids in the receptor cells and gland cells. Evidence was obtained which indicated that the pigment is present in the mucosa as a pigment-lecithin complex (81). Jackson (109) has suggested that the pigment may be a waste product of the lipid metabolism of the olfactory nerve fibres. According to him, the pigment is composed of phospholipids, probably lecithins and auto-oxidation products of phospholipids. The characteristic colour of the sensory epithelium was attributed mainly to the presence of the auto-oxidation products. Since these are unstable, Jackson considered a precise localization of the pigment as hardly possible by means of standard histochemical methods.

Because of its brilliant yellow colour the olfactory pigment has been supposed to be a carotenoid. If this were the case there might be a basic similarity in the function of the olfactory organ and the retina. This view was supported by the demonstration by Milas *et al.* (149) of vitamin A and carotenoids in the olfactory mucosa. However, later histochemical and biochemical studies have failed to confirm this finding (82, 188). It has been demonstrated by Le Magnen and Rapaport (138) that prolonged vitamin A deficiency reduces the olfactory discriminative capacity in rats. As pointed out by these authors, this does not imply that vitamin A is directly concerned with the function of the olfactory membrane.

According to a theory proposed by Wright (224), the pigment is supposed to serve as an energy acceptor in the process leading to the excitation of the olfactory receptors. As will be further discussed below, experimental observations as well as theoretical considerations (216) seem to render the proposed mechanism for stimulation improbable.

3. The enzymes of the olfactory mucosa. Histochemical studies have revealed the presence of a wide variety of enzymes in high concentrations in the olfactory mucosa. The following distributions of enzymes have been demonstrated (23, 24, 25, 37): glycerophosphatase, adenosine triphosphatase, hexosediphosphatase, 5-nucleotidase, 3-nucleotidase, esterase, and acid phosphatase in the basal cells; esterase and acid phosphatase in the receptor cells; small amounts of acid phosphatase and esterase in the supporting cells; esterase, lipase, and acid phosphatase in the Bowman's glands; glycerophosphatase, acid phosphatase, and esterase in the ducts of the Bowman's gland cells. In the human mucosa the glycerophosphatase is present in the sensory cells, the supporting cells, and the olfactory hairs, while in the rat's mucosa the enzyme is located mainly in the basal cells. Outside the olfactory region the epithelium contains very little or no glycerophos-

phatase. There is no histochemical evidence of amine oxidase, succinic dehydrogenase, or acetylcholinesterase (44). This last finding is of particular interest in view of the functional role that has been attached to acetylcholine as a chemical mediator in the initiation of the sensory discharge (126).

4. The electrical activity of the olfactory organ. The olfactory membrane develops a slow, negative, purely monophasic potential when stimulated with odorized air (179). The experimental data suggest that this response is analogous to the generator potentials recorded from other sense organs. It has been suggested that the olfactory response should be called the electro-olfactogram (EOG). The greater part of the study of this response has been carried out in the frog since the olfactory sense organ in this animal is of relatively simple structure. It lacks the turbinate system characteristic of higher vertebrates, and the entire olfactory area of the nasal mucosa can therefore easily be exposed and explored with the recording electrode. Now the frog is microsmatic, *i.e.*, it has a less well developed sense of smell compared with macrosmatic animals like the dog. It can therefore not be assumed *a priori* that the response obtained in the frog is also representative of macrosmatic species. However, studies on the EOG in the rabbit (10, 144, 182) and guinea pig (139) indicate that there are no essential differences in the electrical behaviour of the olfactory organs in macrosmatic and microsmatic species. Slow potential changes of similar nature coming from the olfactory receptors have also been demonstrated by Schneider (197) in insects. Studies in the frog have shown that the response can be obtained only in the regio olfactoria (175). When the electrode is moved to adjacent regions with respiratory epithelium, no response is recorded. It has been shown further that no appreciable response is obtained with pure air. This finding provides definite evidence that the olfactory receptors are not stimulated mechanically by the air current. In recording the olfactory response, stimulation with pure air may also be used as a test of the absence of potential changes of non-biological nature. This essential control seems to have been omitted by Mozell (165) who in a recent paper claimed that potentials similar to the olfactory receptor potential may be obtained from non-living tissues. This statement was later refuted by Kimura (121) who confirmed Ottoson's (179) findings and showed that no appreciable artifacts are obtained when appropriate electrodes are used. Whatever may be the ultimate explanation of the artifacts recorded by Mozell, it is essential that in studies of the olfactory organ non-biological potentials be clearly distinguished from the receptor potential (53).[1]

In the frog the response of the mucosa to a given stimulus varies from one region of the olfactory area to another (179). The greatest potentials are obtained from those parts of the mucosa where according to anatomical descriptions the sensory epithelium is particularly well developed. Evidence showing that the

[1] Note added by Dr. H. Davis: "A statement in my article in *Physiological Reviews* (1961) suggests the possibility of uncontrolled artifacts in Dr. Ottoson's experiments. I wish to retract this suggestion. A more careful reading of Dr. Ottoson's publications, supplemented by personal discussions, has completely convinced me that his experiments were in fact valid and well controlled."

potential comes from the receptor elements and not from the nerve fibres has been obtained in experiments where the mucosa was treated with cocaine. From studies of other sense organs, it is known that cocaine leaves the receptors unaffected while the fibres are blocked. When the nasal mucosa is treated with cocaine the EOG can still be obtained even after the impulse traffic in the nerve fibres has been extinguished. Observations pertinent to the question of the origin of the potential have also been made in experiments in which recordings were made with microelectrodes inserted to different depths in the sensory epithelium. It was then found that the response became successively smaller as the electrode was advanced into the epithelium. This shows that the potential originates in structures located close to the surface of the epithelium. It seems most likely that these structures are the olfactory hairs.

In most sense organs which have been studied electrophysiologically the quantitative relation between the effect produced in the sensory elements and the strength of the stimulus has been evaluated by analysis of the afferent discharge. Owing to the small dimensions of the olfactory nerve fibres it was until recently impossible to examine the relation between odour intensity and the activity elicited in the primary olfactory neurons. By measuring the amplitudes of the responses to stimuli of different intensities it has now been demonstrated (179) that the effect elicited in the olfactory receptors increases approximately logarithmically with increasing odour intensity. Of particular interest to the problem of the stimulus-response relationship in olfaction are the results recently obtained in psychophysical studies (67, 68, 112, 113, 157, 191). In an analysis of various methods of scaling the intensity of odours, Engen (67, 68) demonstrated that the method of magnitude estimation produced satisfactory results for a number of odorous substances. By using this method, Engen was able to show that the logarithmic values of subjective ratios increase linearly with the logarithm of the concentration values of the odorant.

The potential change in the olfactory mucosa has a comparatively slow time-course. In the frog, an air puff of a duration of about one second and of low odour strength gives a response that has a duration of 4 to 6 seconds. With an increase in odour intensity, the duration of the response becomes longer. It is noteworthy that there are considerable differences in the responses produced by different compounds. Amyl acetate, for instance, gives a response with a fast rising phase and a comparatively short-lasting falling phase, whereas oil of cloves gives a response the most typical feature of which is its prolonged fall. No systematic study has yet been done on the factors responsible for these differences. There seems to be reason to believe that the solubility properties of the stimulating substance are of decisive importance for the temporal course of the excitatory process in the mucosa. Other factors of great importance for the course of the response are the flow rate of the air current carrying the odorous particles to the olfactory membrane and the thickness and composition of the mucus covering the sensory epithelium.

Since the response obtained in gross recordings from the mucosa represents the summated activity of all excited receptors, no definite conclusion can be

drawn concerning the time-course of the electrical events in the individual receptors. The fact that changes in intensity of a stimulus are not followed by any marked changes in rise-time of the response (179) indicates that the rise-time in the individual receptors is relatively constant. As already mentioned, the rise of the potential differs from one substance to another. It seems conceivable that these differences reflect the differential rates at which the odorous substances, depending on their various physical properties, reach the individual receptors and activate them. It is also likely that the falling phase of the response reflects the restitution processes in the olfactory membrane. Its duration can be presumed to depend primarily on the time-course of the processes by which the original potential levels in the individual receptors are restored. These processes are most certainly influenced by the rate of elimination of the odorous material from the mucosa. As long as particles are left which are not taken care of, the receptors will be subjected to a persistent stimulation and repolarization will consequently be delayed.

5. Olfactory nerve activity. Recording of the electrical activity of the olfactory nerve in most mammals is difficult because of the inaccessibility and short length of the olfactory nerve fibres. Our present knowledge about the functional properties of the olfactory fibres therefore derives mainly from studies on amphibia and fish where the nerve can be reached more easily. The electrical properties of the olfactory nerve were first described in 1900 in the classical paper by Garten (75) who recorded the action potential of the olfactory nerve of the pike. This preparation was later used by Gasser (76) in a combined electrophysiological and electron microscopical study. He showed that the action potential of the olfactory nerve consists of only one single wave with a conduction velocity of 0.2 m/sec. The slow conduction conforms with the finding that the axons in the olfactory nerve have an average diameter of about 0.2 μ. The simplicity of the electrical response is consistent with the finding of a high degree of homogeneity of the fibre spectrum of the olfactory nerve. As shown by Ottoson (184) the action potential of the frog olfactory nerve has the same simple configuration. The conduction velocity of the frog olfactory nerve was found to be about 0.14 m/sec. In the opossum, MacLean *et al.* (143) found a conduction velocity of 0.4 m/sec. These findings demonstrate that the olfactory nerve fibres belong to the slowest conducting afferent systems in the body. On the other hand, the slow conduction of the olfactory fibres is compensated by the short distance the impulses have to travel to the brain. In the frog, for instance, the olfactory impulses reach the bulb within about 50 msec after having been initiated in the mucosa.

Studies of single unit activity in the olfactory nerve meet with great difficulties because of the small diameters of the fibres. Beidler and Tucker (33) have reported recordings from fine strands of the olfactory nerve in the opossum. These authors concluded that there is a close functional similarity between the olfactory and the trigeminal nerves. A promising method of recording the activity of single peripheral olfactory units has recently been developed by Gesteland *et al.* (83, 84). By using special low-resistance microelectrodes, these authors succeeded

in recording spikes from single cells in the mucosa. The same unit could sometimes be kept for more than two hours, and a thorough analysis of the sensitivity of the unit in question to different odours was therefore possible. It was found that different units behaved in different ways. Some were spontaneously active in the absence of stimulation, others were silent. The spontaneously active units either increased their firing when stimulated or were inhibited. The cells which showed no spontaneous activity fired with an irregular frequency when stimulated with odorized air. The relation between the activity of the receptors and that of the olfactory fibres has been studied by Kimura (121), who in recordings from small twigs of the olfactory nerve was able to demonstrate a close correlation between the receptor potential and the fibre discharge.

III. THE OLFACTORY BRAIN

The parts of the brain which are more or less directly involved in the transmission of olfactory signals are usually designated as the olfactory brain. Its main parts are the olfactory bulb, tract, and parts of the basal areas of the forebrain including the prepiriform and paraamygdaloid complex and parts

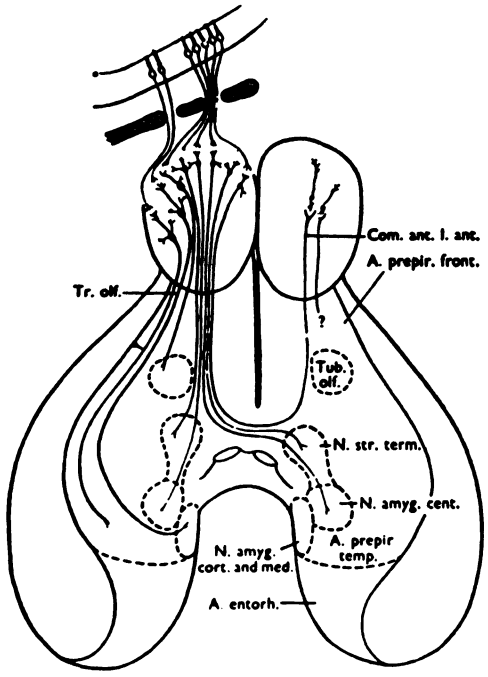

FIG. 2. Schematic diagram of the olfactory pathways in the mammalian brain: Tr. olf, olfactory tract; Com. ant. l. ant., anterior limb of the anterior commissure; A. prepir. front., frontal part of the prepiriform area; Tub. olf., olfactory tubercle; N. str. term., nucleus of the stria terminalis; N. amygd. cent., central amygdaloid nucleus; A. prepir. temp., temporal part of the prepiriform area; N. amygd. cort. and med., medial amygdaloid nucleus; A. entorh., entorhinal area. [Reproduced from Allison (15) with permission of the author and publisher.]

of the corpus striatum (189). There are species differences but these are small, as the morphology of the olfactory bulb and centres has remained relatively unchanged in the course of the evolution of the rest of the forebrain.

1. Structure of the olfactory bulb. This is the first relay station in the olfactory system. The fibres coming from the olfactory mucosa reach the bulb aggregated into small fasciculi which split up into thin strands. These form a plexus of densely interwoven fibres on the surface of the bulb. From this layer the fibres turn inward and enter into the glomeruli. From a functional point of view it is important to note that the afferent fibres do not branch until they have passed into a glomerulus. Since there are no synaptic connections between the receptor cells in the mucosa, and since the afferent fibre does not give off any collaterals during its course towards the bulb, it follows that each receptor cell with its axon functions as an independent unit.

The synaptic contact between the terminals of the incoming fibres and the dendrites of the secondary cells is restricted to the glomeruli. These are spherical structures formed by exceedingly thin endings of numerous incoming fibres and the ramifications of the dendrites of a number of secondary cells. Each glomerulus is encased in a capsule of periglomerular cells.

The secondary bulbar neurons are of two different types, the mitral cells and the tufted cells. The mitral cells have large triangular cell bodies and are arranged in a distinct layer. In higher vertebrates each mitral cell has only one main apical dendrite that follows a straight outward course. The dendrite does not branch until it has entered a glomerulus. The mitral cell also gives off accessory dendrites which connect nearby mitral cells and tufted cells. The tufted cells are somewhat smaller than the mitral cells. Like the latter, they have one main dendrite that terminates in a glomerulus. The axons of the mitral cells and the tufted cells pass into the deeper layers of the bulb. Here they gain myelin sheaths and become grouped together into small bundles.

Close to the periventricular layer in the bulb there are a number of strata of small cells with short axons which travel outward and terminate in contact with the dendrites of the mitral and the tufted cells. All layers of the bulb, except the periventricular layer, show severe shrinkage and the periglomerular tufted, mitral, and granule cells undergo transneuronal atrophy after destruction of the olfactory mucosa (147).

Counts of the number of afferent fibres coming from the mucosa have shown that there is a very high degree of convergence towards the glomeruli. It has been estimated that each glomerulus in the rabbit receives about 25,000 afferent fibres (16). The impulses from these fibres are transmitted through the synaptic connections in a glomerulus to 24 mitral cells and 60 tufted cells. The idea has been advanced that the structural arrangement of the synaptic connections between primary and secondary neurons in separate units represented by the glomeruli may serve an important function in olfactory discrimination (130). It was suggested that there is a concentration of fibres from functionally similar receptors onto particular glomeruli. This view is supported by observations on the responses of bulbar units to stimulation with different substances. Anatomical

studies have further confirmed that there is a topical localization in the sense that fibres coming from different areas in the mucosa are projected onto different parts of the bulb (128).

2. Efferent bulbar pathways. The fibres leaving the bulb are grouped together into two main pathways: the olfactory tract and the anterior limb of the anterior commissure. It is now recognized that the olfactory tract is mainly, if not entirely, formed by the axons of the mitral cells while the fibres of the anterior limb of the anterior commissure come from the tufted cells.

The olfactory tract seems to be a purely efferent pathway (14, 15), whereas the anterior limb of the anterior commissure also includes fibres travelling to the bulb. The fibres of the olfactory tract end in the prepiriform and in the periamygdaloid areas, and to a less extent in the olfactory tubercle and the anterior olfactory nucleus (131). The fibres of the tufted cells form a deep projecting system, the termination of which has been traced bilaterally to the stria terminalis and the central amygdaloid nucleus. Hence, the olfactory system possesses two distinct routes with respect to the course of the axons of the secondary neurons: a cortical one conveying the impulses from the mitral cells, and another subcortical route transmitting the signals from the tufted cells. It has been suggested that the cortical system is responsible for the fine discriminative functions and that the subcortical system is concerned with crude discrimination (14). Another interesting aspect on the function of the two pathways has been advanced by Le Gros Clark (130), who suggested that they correspond to the specific and the diffuse afferent connections of other sensory systems. This view is supported by observations which indicate that parts of the amygdaloid nuclei may be regarded as homologous to the brain stem reticular formation.

3. The olfactory cortex. Most of the olfactory tract fibres terminate in the prepiriform and periamygdaloid areas. These areas constitute the primary olfactory cortex and are anatomically homologous to other sensory areas of the cerebral cortex. In general, the organization of the olfactory cortex is considerably less complex than in other sensory cortical areas. The incoming fibres approach the olfactory cortex from the surface and establish axo-dendritic connections in the outer layer of the cortex with the dendrites of the pyramidal cells. As a consequence of this arrangement, the connections of the afferent fibres become restricted to one single type of cell. In the deeper layers of the cortex different types of cells are found which provide the anatomical basis for complex integrative functions (127).

Knowledge about the tertiary olfactory connections is still far from complete. A multitude of pathways and connections have been described which are considered to convey olfactory signals to different parts of the brain. In most vertebrates two main routes can be distinguished: the one carrying impulses to the hypothalamus, the other to the habenular nuclei. There seems to be reason to believe that the entorhinal area, which in man occupies the gyrus entorhinalis, represents the secondary olfactory area corresponding to the peristriate and parastriate areas in the visual system. It has been assumed that this area is concerned with associative functions in receiving impulses, not only of olfactory

origin but also from other parts of the brain as well, and conveying these signals to the hippocampus. The hippocampal formation has for a long time been held as an olfactory centre. However, it is now generally agreed that the hippocampus is only indirectly associated with olfaction (36, 39).

4. The electrical activity of the olfactory bulb. As was first described by Gerard and Young (79) the olfactory bulb exhibits a persistent activity in the absence of manifest stimulation. In recordings from the surface of the bulb the spontaneous activity appears as irregular waves (4, 140) which are accompanied by a discharge of impulses in deeper layers (2, 4, 7, 10). The continuous activity in the bulb is not maintained by an afferent inflow of impulses since it persists after section of the olfactory nerves or complete destruction of the olfactory mucosa. The intrinsic activity also remains or is sometimes enhanced after section of the nervous connections between the bulb and the forebrain.

The potential changes which appear when the mucosa is stimulated with odorized air are of three main types: 1) a slow sustained potential, 2) oscillatory waves, 3) impulse activity. The slow potential (182, 183) together with the superimposed waves, the induced waves (4), can be obtained in recordings from the surface or outer layers of the bulb, whereas the spikes appear in the deeper layers (2).

The general characteristics of the slow potential suggest that it is homologous to the persistent potentials recorded from sensory areas of the cerebral cortex (21). Experimental evidence indicates that the response comes from the dendritic network in the glomeruli, while the induced waves appear to be produced by synchronous activity in neurons of secondary order. By simultaneous recordings from the bulb and the olfactory mucosa in the frog, it has been possible to study the general relationship between the receptor and the bulbar activity. It has been found that changes in stimulus strength produce almost identical changes in amplitude and time-course of the two potentials. This observation is of interest since it shows that the events in the sense organ are faithfully reproduced in the first synaptic relay station as far as the activity at this site is represented by the slow bulbar response. Comparisons of the response in the mucosa and the bulb have further shown that the induced waves in the bulb are not governed by the oscillatory potentials which sometimes are superimposed upon the receptor response. The results obtained in studies on the peripheral and bulbar electrical responses suggest that the sequence of events involved in the initiation and transmission of olfactory signals is the following: olfactory particles which are brought into contact with the receptors produce, by intermediate mechanisms, a change in the receptor membrane. This alteration leads to the development of the receptor potential which spreads electrotonically in the nerve fibres and elicits the afferent discharge. The afferent inflow to the bulb results in the production of a slow synaptic potential in the glomeruli. This potential closely follows the peripheral response and gives rise to the discharge in the neurons of secondary order. As the stimulus intensity is increased, more and more bulbar neurons are thrown into synchronous activity, which is reflected as regular waves superimposed upon the slow potential change.

The function of the bulb has also been studied by using electrical stimulation

of the receptors instead of natural stimuli. The bulbar response in the frog to an electric shock of 0.2 msec duration applied to the mucosa consists of a purely monophasic negative potential of a duration of about 150 msec (184). The response is built up of two components with distinctly different properties. The first component lacks a true refractory period and summates to a sustained potential under repetitive stimulation. The second component on the other hand has a comparatively long refractory period and is not able to follow stimulation at frequencies of 1/sec without undergoing a reduction in height. Further, the second component is sensitive to the action of barbiturates and is blocked when the bulb is invaded by antidromic impulses. It has therefore been concluded that the first component is of synaptic origin and that the second component represents the activity in neurons of secondary order. It appears likely that the first component of the electrically produced response corresponds to the slow bulbar potential evoked by natural stimulation, and that the second component is generated by the structures producing the induced waves. Later studies by Orrego (175 to 178) in the turtle and by Iwase *et al.* (108) in the cat have confirmed the results obtained in the frog and further extended the knowledge about the function of the olfactory bulb. Takagi and Shibuya (213, 214) have reported the finding of slow "off" responses in the olfactory bulb and in the mucosa. No other authors have reported similar observations.

As was first demonstrated by Adrian (2), a regular discharge of impulses can be obtained from units in the inner core of the bulb at each inspiration of room air. If an odorous substance is added to the inspired air the discharge becomes more intense. In the rabbit the spikes are usually not obtained until the electrode has reached a depth of about 1.5 mm below the surface of the bulb. It is most likely that the spikes come from mitral cells or their axons. Studies on the discharge evoked by different substances have provided information of particular interest for the problem of olfactory discrimination (5, 164, 166). It has been shown by Adrian (5) that there are large differences in the spatial pattern of excitation produced by different substances. In the rabbit the threshold for water-soluble substances is lower in the anterior part of the bulb, whereas lipid-soluble substances appear primarily to excite units in the aboral parts. There seems to be reason to believe that the spatial pattern of excitation is due to a differential distribution of different substances in the nasal cavities. Differences have also been found between neighbouring units in the sense that one unit may be sensitive to a substance which does not excite an adjacent unit. Studies on the behaviour of a number of units towards different substances have indicated that odorous substances might be divided into a limited number of groups according to their excitatory effects. On the basis of his observations on the excitation patterns of different substances, Adrian (7) has suggested that the spatio-temporal patterns of incoming discharge may give information as to quality of smell as it does with quality of sound.

Walsh (219) has reported that there are bulbar units which do not respond to olfactory stimulation of the olfactory mucosa. Some of these units fire synchronously with the respiratory cycle. Recent observations indicate still another type

of unit (61, 228). These cells fire spontaneously in the absence of obvious stimulation. When the mucosa is stimulated with odorized air the discharge of these units decreases or is completely blocked. At the present time no information is available about the morphological identity of these cells.

Adrian (4) has reported interesting observations on the interaction between the induced activity in the bulb and the intrinsic activity at different depths of anaesthesia. When the intrinsic activity is suppressed, as in deep urethane anaesthesia, the olfactory signals are transmitted without interference. In moderate anaesthesia the intrinsic activity is intense enough to interfere with the transmission of the incoming signals. In light anaesthesia again the olfactory signals are able to overcome the intrinsic activity. These changes have been interpreted as due to a changed tonic influence from higher centres.

5. Central regulative effects upon the input from the olfactory organ. There is at present a body of evidence showing that the afferent input from the sense organs can be influenced by the activity of certain brain centres. The centrifugal effect is generally exerted upon the transmission from primary to secondary neurons, though it may also occur at higher levels. In the case of the cochlea, the muscle spindle, and certain skin receptors the centrifugal regulation is exerted directly upon the end organs.

In the olfactory system the centrifugal control is exerted upon the transmission of the olfactory signals in the first relay station. There does not seem to be a direct peripheral influence, since no efferent fibres have been demonstrated passing from the olfactory bulb to the receptors. Changes in olfactory sensitivity secondary to vascular changes mediated by autonomic nerve fibres are well known but cannot be regarded as expressions of a direct central regulatory control of the activity of the end organs.

As described above, the olfactory bulb receives fibres from basal telencephalic areas and from the opposite bulb. Ramón y Cajal (46) who first described this fibre system, suggested that the centrifugal fibres may influence the transmission of olfactory impulses through the glomeruli. Direct evidence of a central regulation has been obtained by Kerr and Hagbarth (120). As demonstrated by these authors, stimulation of basal encephalic areas causes a reduction of the spontaneous activity of the bulb and a reduction or abolition of the bulbar response to olfactory stimulation. Similar effects were also obtained by high-frequency stimulation of the anterior commissure. There seems to be reason to believe that the olfactory centrifugal system exerts a tonic influence as do the centrifugal systems operating on the input from other sense organs. This view is based on the finding that section of the anterior commissure, which includes the centrifugal fibres, is followed by an augmentation of the amplitude of the olfactory response. Observations on the effect of a light anaesthesia upon the bulbar response have also been interpreted as evidence of a tonic influence. The efferent bulbar system also includes fibres coming from the opposite bulb and taking their origin in the tufted cells. Experimental evidence strongly suggests that the units in the one bulb may influence the activity of the units in the opposite bulb through this commissural system. Walsh (220) has shown that a short-lasting electrical

shock to one bulb evokes a long-lasting potential in the opposite bulb. This potential summates when repetitive stimuli are applied. These observations have been confirmed by Kerr (119), who demonstrated further that the synchronized activity induced in the one bulb by weak, ipsilateral, olfactory stimulation was depressed when strongly odorized air was passed into the contralateral nostril. It was also demonstrated that repetitive stimulation of the anterior commissure depressed a concomitant retrograde lateral tract response if the frequency of the commissural stimulation was sufficiently high (above 50/sec) to produce the summated potential.

The demonstration of an inhibitory effect mediated by the commissural fibres from basal forebrain areas clearly shows that the excitability of the olfactory afferent relays within the olfactory bulb might be influenced in a manner analogous to the influence of the brain stem reticular system upon the input from other sensory systems. Besides being under the influence of higher centres, the bulbs may exert a mutual depressive effect through the commissural interbulbar connections. It is conceivable that the olfactory feed-back system may serve to depress the input of irrelevant information during focus of attention, as has been shown to occur through feed-back loops in other sensory systems.

It has recently been reported by Hernández-Peón *et al.* (103) that auditory or gustatory stimuli may produce activation in the olfactory bulb. Since electrical stimulation of the reticular formation was found to give a similar effect, it was suggested that the olfactory bulb is influenced from the brain stem during arousal. According to this view the centrifugal effect would provide a mechanism by which the efficiency of the olfactory apparatus could be enhanced. The exact mechanism of this regulatory control remains to be analyzed.

6. Electrophysiological studies of central olfactory connections. The projection of olfactory tract fibres to higher olfactory centres has been studied by numerous workers in investigations on the distribution of responses evoked in various parts of the olfactory system by natural or electrical stimulation.

As described by Adrian (2), olfactory stimulation gives rise to a train of regular waves in the pyriform lobe. Similar potentials were later reported by MacLean *et al.* (142) to be produced also by gustatory and noxious stimulation. By using electrical stimulation of the olfactory bulb, Fox *et al.* (73) showed that single shock stimuli produced responses in the prepyriform cortex, the anterior olfactory lobe, the pyriform lobe, and the olfactory tubercle. The response of the pyriform lobe was a negative wave preceded by a spike potential. The sign of the wave is noteworthy since the initial response of other sensory areas when activated comparably consists of a positive wave. This difference is most likely due to the fact that the olfactory tract fibres approach the olfactory cortex from its surface, whereas the afferent signals of other sensory systems are relayed from thalamic centres to the cortical layers. It was further found that the responses from the pyriform lobe and the olfactory tubercle were composed of two negative waves, the first of which was augmented by repetitive stimulation while the second one was blocked under the same procedure. It was suggested that the late wave comes from the transcortical connections between the prepyriform

and pyriform cortices. The finding of a response of the olfactory tubercle is of particular interest since it has been questioned whether this structure belongs to the olfactory system. Studies of fibre degeneration after extirpation of the olfactory bulb have given contradictory results. An explanation might be that there are marked species differences. In mammals with a particularly well developed olfactory system, fibre connections between the olfactory bulb and the olfactory tubercle have been definitely established (208). According to Allison (15) the antero-lateral part, and only this part, of the olfactory tubercle receives olfactory tract fibres. The restricted distribution of the tract fibres might perhaps account for the failure of Rose and Woolsey (194) to obtain responses from the olfactory tubercle. The observations of Fox *et al.* (73) have been confirmed and extended by Kaada (115). He showed that the distribution of the negative surface potential evoked by stimulation of the olfactory bulb closely coincides with the cortical distribution of olfactory tract fibres as mapped by Meyer and Allison (148). Kaada also suggested that the positive potential that is obtained in areas surrounding the primary olfactory cortex represents the activity of areas analogous to secondary areas in other sensory systems. Arduini and Moruzzi (19) have presented evidence indicating that the olfactory system may exert influence upon cortical activity. They found that odorized air produced generalized arousal reactions in "cerveau isolé" preparations in cats. Since visual stimuli were ineffective, the authors concluded that olfactory signals represent the most active sensory modality. It was further observed that the intensity as well as the duration of the arousal reaction was less marked in the "cerveau isolé" preparation than in the spinal preparation. This finding was interpreted as indicating the convergence of olfactory and reticular ascending impulses upon cephalic areas of the activating system. As shown by Arduini and Moruzzi (20), low frequency stimulation of the thalamus produces recruiting responses in the olfactory bulb. Since these responses are not obtained after transection of the olfactory peduncle, they can be assumed to represent a genuine thalamically induced synchronization of bulbar structures. It was also demonstrated that the wave-component of the response could be blocked by bulboreticular stimulation.

As mentioned earlier, anatomical data indicate that the hippocampus is not directly concerned with olfactory functions. From electrophysiological investigations it is known that the hippocampus responds to a variety of stimulus modalities. Thus, it has been demonstrated by several investigators (89, 90, 91, 92) that the deeper parts of the hippocampal formation contain units which can be activated by visual, auditory, tactile, and olfactory stimuli. The long latencies of the responses indicate that the afferent impulses pass through several synapses before reaching the hippocampus. There is no evidence of a localization of the responses for different modalities. Recent studies by Cragg (50) show that the olfactory influence on the hippocampus varies greatly from one species to another. By comparison of the olfactory responses with those obtained by stimulation of various other afferent nerves, Cragg arrived at the conclusion that the olfactory influence upon the hippocampal formation is rather dominant in some species,

while in others only a minor part of the hippocampus is concerned with olfactory functions.

IV. FUNCTIONS OF THE OLFACTORY SYSTEM

1. Olfactory discrimination. a. Peripheral analytical mechanisms. It is generally held that different odours are recognized because of the presence in the olfactory mucosa of differentially sensitive receptors. This concept seems to be based mainly on the well-known fact that after the nose has become adapted to one odour so that the sensation of smell has vanished, other odours can still be perceived. In the last decade more direct experimental evidence has been obtained that strongly suggests the existence of receptors with specific sensitivities.

In studies on the discharge in the bulb, Adrian (7) found units which were sensitive to one particular substance in concentrations that had no effect upon neighbouring units. The observations indicated that there were considerable differences in the sensitivities of the individual units. Further evidence has been obtained in studies on the selective fatigue in the frog olfactory organ (179). It was shown that the sensitivity of the olfactory receptors to different substances could be reduced selectively. This finding conforms to what has been found in cross adaptation studies in man (156) and to the demonstration by Guillot (95, 96, 97) of a selective insensitivity to certain odours in subjects with partial anosmia. Still other evidence on this point has been obtained in recordings of the impulses in small twigs of the olfactory nerve and from single units in the mucosa. Gesteland *et al.* (83, 84) found units with a specific sensitivity to certain substances. It is of particular interest to note that they found a unit that responded to nitrobenzene but not to benzaldehyde. Using ethyl butyrate, camphor, coumarin, carbon disulfide, and pyridine as test stimuli, Gesteland (83) was able to demonstrate five different types of receptors. One type of receptor responded to camphor and was unaffected by any of the others. Each of the remaining four receptor types showed a marked increase in firing rate for one of the stimuli and a marked inhibition to another, and was unaffected by the remaining stimuli. Thus, type number two was excited by ethyl butyrate and inhibited by coumarin. The third type was excited by coumarin and inhibited by pyridine. The fourth type was excited by carbon disulfide and inhibited by ethyl butyrate, while type number five was excited by pyridine and inhibited by camphor. In all, Gesteland was able to demonstrate six types with distinct sensitivity properties. It seems most likely that there are more types. Each receptor type apparently has a broad spectrum of different odours to which it is sensitive. For a particular receptor type there were clearcut differences in the pattern that each compound evoked. The method developed by Gesteland *et al.* seems to open new and fascinating possibilities of analyzing the chemical sensitivity of single olfactory receptors.

On the basis of observations made in studies on the activity of bulbar units, Adrian has advanced a theory (3, 5, 6, 7, 9, 10) according to which olfactory discrimination depends on 1) the existence of different types of receptors with a differential sensitivity to different odours, 2) the distribution of excitation in

the olfactory membrane, and 3) the temporal pattern of excitation. The hypothesis that spatial factors are involved was based on the observation that the threshold for water-soluble substances is lower in the anterior part of the bulb whereas for lipid-soluble substances it is lower in the posterior part. It was suggested that these differences were due to a differential distribution in the nasal cavities of different substances. Other factors, such as the composition of the surface film and the velocity of the air current, were assumed also to affect the distribution pattern. However, even if there is a differential distribution of different substances in the olfactory membrane it seems doubtful that the spatial pattern is of essential importance in olfactory discrimination. The olfactory mucosa in man and higher primates forms a flat sheet and the distribution of different substances must therefore be even. Nonetheless, man has a rather high olfactory discriminative capacity. Finally, it has been reported that the discrimination is not changed when odorized air is introduced in the nose by the retronasal route (133).

In addition to the spatial differences in the bulb, there is also a distinct differentiation in time relations of the responses evoked by different substances. Some substances produce a discharge with a rapid onset and fast decay whereas others give rise to a slowly developing and gradually vanishing discharge. It is interesting to note in this connection that the receptor potential shows similar differences in time-course. Amyl acetate gives a receptor response with a fast rising phase and a rapid decline. At the mitral cell level the same substance gives a discharge that starts abruptly and has a short duration. These findings show that the general temporal pattern of excitation in the receptor organ is preserved at the level of the secondary neurons. We do not know at the present time what factors determine the time-course of the excitatory processes in the receptors. It seems quite likely that the vapour pressure and the solubility properties of the stimulating substance are of importance, but other factors such as the steric configuration of the molecule may also be relevant. The fact that the time-course of excitation varies for different substances does not necessarily imply, however, that these differences are associated with the discriminating mechanisms.

b. Central mechanisms. It has been suggested by Le Gros Clark (129) that there is a rearrangement of the fibres coming to the bulb in the sense that fibres from receptors with similar sensitivity properties are directed to particular glomeruli. The discrete character of the glomeruli with sparse interconnections is assumed to provide the anatomical basis for the segregation of the impulses from receptors of different types. The fact that each mitral cell sends its main dendrite only to one glomerulus is thought to add to the preservation of the integrity of each particular input channel. This hypothesis is supported by Adrian's observation of the differential sensitivity of different mitral units. As pointed out by Le Gros Clark, the hypothesis does not require that the specificity applies to all glomeruli. Even if only a small fraction of the glomeruli in the bulb possess a functional specificity of the type outlined above, they should well account for the required discrimination.

Ablation studies have failed to demonstrate the existence of any particular cortical region serving finer discriminative functions. As shown by Swann (212), up to 85% of the cortex of rats can be removed without any deleterious effect upon learned olfactory habit involving simple olfactory discrimination. Cats are still able to locate food by olfaction after bilateral removal of the neocortex (26). In studies on the effect of lesions of subcortical structures, Swann (211) found that destruction of various parts of the archipallium, including the hippocampal complex, pyriform lobes, septum, and amygdaloid nucleus, was without any significant effect as to the retention of olfactory habit. He showed further that interruption of the main pathways to and from the archipallium, including the fornix, projection fibres of the amygdaloid nucleus, fimbria, habenula, and olfactory bundles in association with the corpus callosum did not interfere with olfactory discrimination. Of the pathways leaving the bulb, the lateral tract was not essential to olfactory discrimination while the anterior limb of the anterior commissure appeared to be crucial. Later studies by Brown and Ghiselli (40) failed to reveal any central structure, cortical or subcortical, that was essential for the olfactory discrimination habit. These authors arrived at the conclusion that the mechanisms underlying olfactory discrimination consist of two or more equivalent subcortical complexes. When one of these is destroyed the function is carried out by the other. No delimitation of the particular subcortical complexes involved was suggested. In criticism of this work, Allen (13) has argued that the odours used by Brown and Ghiselli were effective over both the trigeminal and the olfactory nerves. Allen (11, 12, 13) showed that destruction of the piriform amygdaloid areas abolishes negative conditioned reflexes, simple olfactory discrimination being retained. Lashley and Sperry (125) found that discrimination was not disturbed by interruption of the radiation of the anterior nuclei. Masserman *et al.* (146) have reported that bilateral lesions of the dorsomedial nucleus of the thalamus in cats produced amnesia for preoperative learned behaviour with greater impairment of the olfactory response than in those of any other modality. The operated animal showed a tendency to generalize certain intense olfactory experiences without discrimination.

As is evident from the foregoing discussion, the knowledge about the mechanism underlying olfactory discrimination is still incomplete. The experimental evidence accumulated in the past years strongly supports the view that there exist receptors with specific sensitivity. However, so far we know nothing about the kind of specificity exhibited by the receptors in terms of physical or chemical sensitivities.

2. Olfactory adaptation. It is a generally held notion that the olfactory receptors are rapidly adapting sense organs. This belief seems to derive from the common experience that an odour which at first is felt as strong rapidly weakens and soon becomes almost imperceptible. This rapid disappearance of the sensation of smell is generally attributed to a presumed inability of the receptors to respond to prolonged iterative or continuous stimulation. This idea has recently been challenged by various experimental observations, particularly of the electrical activity in the bulb and the sensory epithelium.

The first direct evidence showing that the olfactory receptor adapts relatively slowly was presented by Adrian in 1950 (4). He showed that there is a distinct discharge from the mitral cells in the rabbit at each inspiration without any appreciable adaptation for more than one hour. This observation clearly showed that in contrast to what was generally believed, the olfactory receptors are not easily fatigued. Further evidence on this point was obtained in recordings of the receptor response of the sensory mucosa (179). It was demonstrated that repeated stimulations at short time intervals produced responses which after an initial decline remained almost constant in height during the subsequent stimulations, provided weak stimuli were used. Strong stimulation produced a pronounced reduction of the response. It was also demonstrated that a continuous stream of air gave a response that declined from its initial peak to a level that was maintained almost constant for the rest of the stimulation.

The demonstration of the comparatively slow adaptation of the olfactory receptors suggests that the phenomenon of olfactory fatigue has a central origin. A recent comprehensive study by Stuiver (209) on the various factors determining the course of adaptation has provided further evidence supporting this view. Adrian has suggested that the progressive weakening and disappearance of the olfactory sensation in man may be attributed to the fact that the intrinsic activity gradually regains control over and suppresses the transmission of the incoming signals. This view is strongly supported by the observation of a competitive interaction between the intrinsic activity in the bulb and the incoming signals.

3. Olfaction and nutrition. It is a well established fact that in most mammals the sense of smell plays an important role in the search for food and selection of an adequate diet. As shown by Harris *et al.* (100) in their classical work in 1933, rats depleted of vitamin B almost invariably select the adequate diet when offered the choice of two diets, one devoid of the vitamin, the other containing the vitamin in some distinct form. If no cue was offered, for instance when the vitamin was added as a minute amount of a highly potent concentrate, the rats were unable to make the correct choice. There appears to be good evidence that the differentiation between the vitamin-deficient and the vitamin-containing diet is made on the basis of olfactory discrimination. It was noted by Harris *et al.* that before the rats started to eat, they gave a cursory sniff to each of the two diets offered and then proceeded to eat the vitamin-containing food. The correct choice could also be made if some other distinct character was given to the vitamin-containing diet, for instance by addition of some inert material. Rats not depleted of vitamin ate the two diets indiscriminately until they began to suffer from vitamin deficiency. Then they began to show preference. If the number of diets offered was made sufficiently large, the rats were unable to make the correct choice.

It has been concluded from these and similar experiments (204) that the ability of rats to make the correct choice does not depend on instinct but on the experience of the beneficial effect of the vitamin-containing food. The differentiation is made on the basis of an association of this effect with some distinctive character, particularly the odour, of the diet in question. The importance of the sense of

smell in the selection of food is demonstrated further by the observation (34) that transection of the olfactory nerves in dogs is followed by a transient aphagia. The animals chew food or any material offered and then reject it. Transection of the trigeminal or glossopharyngeal nerve is not followed by any similar effect.

The observations of Harris *et al.* have been confirmed and extended by several investigators (192, 203, 217, 218, 229). Some authors, however, have arrived at the conclusion that the sense of smell is not indispensable (218). Definite evidence on this point now seems to have been provided by the comprehensive and important work of Le Magnen (133 through 137). In a series of carefully controlled experiments this author was able to show that the rats in their choice of an adequate diet may be guided by olfactory cues. It was shown, for instance, that rats when given a free choice between two diets select the one the odour of which from previous experience is associated with a full caloric food. Deprived of olfactory cues the rats may make the correct choice on the basis of gustatory, tactile, or visual discrimination. Comparative studies on the relative significance of the different modes of differentiation indicate that olfactory guidance is more important than gustatory, visual, or tactile ones.

When offered two or more equivalent diets, one of which has been flavoured, rats eat indiscriminately (203). As shown by Janowitz and Grossman (111), the amount of food eaten daily by dogs is not significantly modified by giving alcohols or bitters shortly before the regular feeding. In studies on whether or not rats can be induced to ingest non-nutrients when these are flavoured Adolph (1) found that flavours did not provoke any change in the intake of non-nutrient material provided the flavouring substance itself had no appreciable caloric value. If, however, flavours with nutrient values were added to the inert material, the amount ingested increased, the increase being closely related to the caloric value of the flavouring material.

Though the importance of olfaction in the selection of food has been recognized for a long time, the influence of the olfactory system upon the mechanisms regulating the quantitative food intake has only recently been demonstrated. Le Magnen has reported interesting observations on food intake of rats offered differently flavoured diets (135, 136). Four types of flavoured diets were used, and the rats were given these over a period of 32 days to become used to each of them. Only one type of diet was offered at a meal. At the end of this period the amount eaten at each meal was constant for each type of diet offered. The rats were then given meals during which the four types of food were presented in a sequence that was changed for each meal. The observation was now made that the amount eaten during such a "mixed" meal was considerably greater than that when the single-flavoured meal was given. In another series of experiments the same author demonstrated that addition of a flavour to the diet may provoke a transient reduction of food-intake. However, the rats soon became used to the odorized diet and thereafter ate the same amount as of the non-odorized diet. The rats were then fed on this diet for 14 days. At the end of this period they were again offered the non-odorized food. This change from odorized to non-odorized food was followed by a considerable increase in intake. Some of the animals increased their intake by 50% for a period of about three days and

then gradually returned to the earlier level of intake. These observations strongly suggest that olfaction may play an important role in the quantitative regulation of food intake.

Goetzl and Stone (86, 88) have reported that olfactory acuity in human subjects shows diurnal variations which are closely related to the ingestion of food. They found that meals were preceded by a period of increased acuity and followed by a period of decreased olfactory sensitivity. It was suggested that these changes represented a direct measure of the desire for food before a meal and the sensation of satiety afforded by intake of a meal. In another series of experiments Goetzl and Stone (87) found that amphetamine, in addition to its well-known effect on the intensity of the sensation of appetite, also produced a decrease in olfactory acuity. They considered that this finding supported their suggestion that the sense of smell is important in regulating the sensation of appetite and satiety. It was further reported (85) that bitters ingested during freely selected meals are capable of preventing postcibal decrease of olfactory acuity. The experiments by Goetzl *et al.* have been subjected to sharp criticism. It has been argued that essential controls have been ignored and that no data are presented showing the statistical reliability of the reported finding. Janowitz and Grossman (110) found only minor variations in olfactory acuity during the day. According to their findings, there is no consistent relation between these variations and satiety sensation or appetite. In measuring the olfactory acuity in a series of normal and obese subjects, Guild (94) found diurnal variations in olfactory acuity related to the intake of meals. The variations in the two groups were essentially alike, though the obese patients had a significantly higher threshold than the normal subjects. Amphetamine was found to inhibit the precibal increase in both the obese and normal subjects. The occurrence of rhythmic variations in olfactory acuity was later confirmed by Hammer (99) in studies on the relation of odour, taste, and flicker-fusion thresholds to food intake. He found that odour and taste acuity were high before lunch and low after lunch. The curve for flicker-fusion showed the same general variations as taste and odour thresholds. Hammer arrived at the conclusion that food intake is not the only factor responsible for these changes.

Observations by Reid (190) indicate that olfactory stimuli may also affect the blood sugar level. A dog was deprived of food for 21 hours and thereafter allowed to sniff and taste minimal quantities of finely minced flesh. It was found that the sniffing and tasting caused a fall in blood sugar. This observation suggests that the output of insulin may be influenced by olfactory and gustatory mechanisms. There are also indications that olfaction may be associated with the function of the pituitary gland. Nováková and Dlouhá (173) have recently reported that a condition closely like diabetes insipidus is produced in rats after severance of the olfactory bulbs. This effect did not become apparent until about 20 days after the operation and could therefore not be due to the exclusion of olfactory signals. As a tentative explanation, Nováková and Dlouhá suggested that removal of the olfactory bulb may produce degeneration of fibre connections with hypothalamic nuclei.

Sundsten and Sawyer (210) have recently presented evidence of the presence

in the olfactory bulb of elements sensitive to changes in osmotic pressure of the blood. They found that intracarotid injections of hypertonic saline in dogs induce high-amplitude potential waves. The response was still obtained after section of the olfactory peduncle and after the olfactory membrane had been treated with procaine to block receptor activity. Since the potential change could be evoked by hypertonic glucose as well, Sundsten and Sawyer concluded that the effect did not depend on specific receptors for sodium chloride but rather on osmosensitive elements. Interesting observations indicating an olfactory influence upon the hypothalamus have recently been reported by Miline (151, 152), who found that changes appeared in the supraoptic nucleus and in the paraventricular nucleus of rats exposed to strong odours.

4. Factors influencing olfactory sensitivity. It has been shown in investigations on olfactory acuity in man that the capacity for odour detection varies greatly from time to time in the same subject. These variations might be explained as due to alterations in the functions of the nasal membrane or to changes within the central nervous system. Though it cannot be excluded that the observed variations may be at least partly of central origin, for instance as a result of an alternating activity in the centrifugal olfactory system, it seems more likely that they are produced by local changes in the nasal mucosa. This view is substantiated by observations of Schneider and Wolf (200) in a comprehensive study on the relation between olfactory acuity and local nasal membrane functions. In measuring olfactory perception in eight subjects over an extended period of time, these authors found a close relationship between olfactory acuity and the degree of swelling, wetness, and colour of the nasal mucosa. A moderate degree of swelling was found to be associated with good acuity while a pale and relatively shrunken membrane was associated with poor acuity, as was also a highly swollen membrane. The authors suggested that the warmth and humidifying effect accompanying a moderate swelling facilitate olfactory stimulation. In view of the great number of factors which by direct or reflex action may influence the turgescence, blood flow, and secretion of the nasal membrane, it is not surprising that olfactory acuity varies greatly. It is, for instance, well known that engorgement of the nasal mucosa is provoked by inhalation of irritating vapours, dust, or particles of substances to which the subject is sensitive. Cooling of the body surface leads to a marked vasoconstriction and general ischemia of the nasal mucosa.

It is generally recognized that there exists a relationship between nasal and genital functions (70). The tissues covering the middle and inferior turbinate bones and part of the nasal septum are anatomically very similar to the cavernous tissue of the genital organs. It has been reported that vascular engorgement of the nasal mucosa accompanies menstruation and pregnancy. It seems to be generally assumed that these alterations are due to hormonal influence upon the nasal tissues. Experimental observations by Mortimer *et al.* (158, 159, 160) on monkeys support this view. They found that administration of oestrogenic hormones produces a reddening and swelling of the nasal mucosa. It is therefore likely that the changes in olfactory sensitivity which often occur during preg-

nancy might be explained as hormonal effects upon the olfactory mucosa. Congestion, swelling, and increased secretion of the nasal mucosa have been observed also after administration of androgens (98). Direct evidence of a hormonal influence upon the function of the olfactory organ has been obtained by Schneider *et al.* (199), who found that olfactory acuity in hypogonadal women was increased during oestrogen administration and decreased during androgen administration.

Observations have been reported which indicate that the administration of certain drugs may produce an increased olfactory sensitivity in dogs. In studies on conditioned reflexes in dogs Myznikov found (169) that caffeine and other drugs increased the olfactory discriminative capacity. This effect was confirmed in later studies by Krushinsky and Fless (124) who showed that daily administration of a drug for a long time was accompanied by a reduction in olfactory acuity. Disturbances of olfaction have been reported to occur after transnasal use of drugs. It has been reported by Seydell and McKnight (205) that anosmia may develop after instillation of tyrothricin intranasally. Streptomycin when given in high doses has also been reported to produce anosmia (47). Treatment with prednisone and ACTH has been found to produce remission of the sense of smell in patients with anosmia due to intrinsic allergic rhinopathy (18).

Skouby *et al.* (207) have studied the effects of acetylcholine, acetyl-*beta*-methylcholine, menthol, and strychnine on olfactory sensitivity in man. It was found that topical application of acetylcholine, acetyl-*beta*-methylcholine, or menthol lowered the threshold by 21 to 50%. Strychnine produced an initial increase in threshold that lasted for about 10 minutes and was followed by a decreased threshold. Control experiments demonstrated that saline alone produced a consistent increase of up to 400%. Skouby *et al.* concluded that the observed effects were due to a direct action of the drugs on the receptor cells. In view of the demonstration by Schneider *et al.* that changes in the local conditions of the mucosa may produce pronounced changes in olfactory acuity, it cannot be excluded that the threshold changes found by Skouby *et al.* might be indirect effects.

5. Haematogenic olfaction. It is well known that many substances when injected intravenously give rise to olfactory sensations. Theoretically this effect may be elicited either at the level of the peripheral receptors or through a direct action of the injected substance upon central olfactory structures. A direct excitation of the end organs can be assumed to occur either by the substance's being carried to the olfactory membrane by the blood, or alternatively through odorous particles that have been eliminated in the lungs or the nasal membranes. Bednár and Langfelder (29) were the first to attempt to analyze the mechanism of haematogenic olfaction. They found that intravenous injection of substances such as neo-salvarsan or camphor elicited an odorous sensation that appeared a few seconds after the injection and lasted for 1 to 2 minutes. The sensation was usually described as very intense and with a rapid onset. It appeared also after complete obstruction of the nose. Repeated injections of the same substance were followed by a gradual weakening of the sensation, whereas the sensitivity

to other substances was unaffected, *i.e.*, the olfactory fatigue was clearly specific. Taste sensations were occasionally observed in connection with the injection of arsenicals. From these observations the conclusion was drawn that haematogenic olfaction is due to activation of the olfactory receptors through the odorous substances' being carried to the *regio olfactoria* by the bloodstream. This view was also supported by the finding that no sensation of smell could be produced by the intravenous route in patients with ozaena. This finding was later confirmed by Hennebert (102) and van Dishoeck and Versteeg (59). However, the latter authors were unable to obtain haematogenic olfaction in normal subjects when the olfactory cleft was obstructed. After an injection of camphor, olfactory sensation was found to be absent as long as the patient was able to hold his breath but appeared at the moment of the first expiration. When ether was injected, some of the subjects reported a slight sensation also when the breath was held. From these observations van Dishoeck and Versteeg concluded that haematogenic stimulation is most likely produced by odorous particles which are eliminated in the lung and reach the nose with the expired air. The effect of ether was explained as due to diffusion of this substance through the nasal membrane. As further support of the idea that haematogenic olfaction is produced only by the expired material, the authors reported that no sensation of smell was obtained with camphor in laryngectomized patients. However, in a study on olfaction in such patients, Marco *et al.* (145) found that half of these patients experienced a sensation of smell when a solution of essence of lavender was injected intravenously. A direct stimulation of the receptors by the material carried to the mucosa was considered as unlikely. To support this notion, Marco *et al.* quoted old observations that no sensation is produced when a solution of an odorous substance is instilled into the olfactory cleft. They concluded therefore that haematogenic olfaction arises as a result of stimulation of the olfactory centres. This conclusion was considered to be substantiated by the observation that changes in respiratory rate still could be produced by injection of odorous substances in dogs whose olfactory nerves had been cut (49). The problem of where the stimulus acts has been approached in recent experiments on rabbits (181). It was found that intravenous injection of substances such as methylacetate, coumarin, or pyridine elicited an increased activity of olfactory bulbar units. The fact that this effect was obtained in animals breathing through a tracheal cannula shows that the stimulating particles have not to be carried to the olfactory mucosa by expired air in order to excite the receptors. On the other hand, no excitatory effect was observed after the olfactory nerves had been cut. It therefore seems most unlikely that haematogenic olfaction can be attributed to a direct stimulation of central nervous structures. The most plausible explanation seems to be that the stimulating substance is carried to the mucosa by the blood and gives rise to an inflow of afferent impulses in the olfactory nerve fibres by direct excitation of the end organs.

6. Comparative and behavioural aspects. The significance of the sense of smell to the mode of life and general reactions to environmental changes in different species is intimately associated with the development of the olfactory system

relative to the development of the other parts of the brain. In fish and amphibians the greater part of the cerebral hemisphere is under olfactory influence. In spite of the fact that the olfactory influence apparently is very dominant in the amphibian brain, there is no evidence that olfaction is of decisive importance, for example, in the frog. In order to attract the frog the food must be in motion, but it does not seem to be chosen or rejected because of its odour (193). In fish the behavioural significance of olfaction is more apparent. Evidence has been obtained that olfactory recognition plays an important role in both feeding and avoiding reactions in fish. It has also been shown that the migrating species are guided to their home waters by olfactory cues (101). The olfactory acuity is extremely highly developed in some species (172, 215).

Though the organization of the olfactory system is fairly constant in all vertebrates, its functional importance is clearly very different in different species. The dog is generally thought to possess an exceptionally well developed sense of smell. This view is supported by experimental observations by Neuhaus (171) which indicate that the olfactory acuity in the dog is one million to one thousand million times greater than in man. These figures are considerably higher than those arrived at by Moulton *et al.* (162). In carefully controlled experiments in two dogs, these authors found that the dog has an olfactory sensitivity for butyric acid up to a hundred times greater than the lowest threshold reported in the literature for this compound in man. The threshold data obtained by Moulton *et al.* seem to be in agreement with the idea presented by Adrian that the olfactory acuity of the dog is in the same range as that of man. Adrian (8) suggested that the superiority of the dog to man with respect to olfactory capacity is probably much more due to a greater power of discrimination than to a lower absolute threshold of the end organs. As has been emphasized by Becker *et al.* (28), great caution has to be taken, when olfactory thresholds are measured, to exclude non-olfactory cues which might be utilized by the animals. Eayrs and Moulton (64) have recently developed a technique by means of which threshold measurements can be made under well controlled experimental conditions. The ability of dogs to follow human tracks has been studied by Kalmus (116) who found that dogs can distinguish fairly reliably between the body odours of different individuals other than identical twins. The view that domestic species have a lower olfactory sensitivity than the wild ones is not supported by the data obtained in laboratory experiments. As shown by Gruch (93), olfactory acuity is approximately the same in wild and domestic rats.

It has been demonstrated by Masserman *et al.* (146) that odours may become considerably more determinant in monkeys made experimentally neurotic than they are in normal animals. It was shown that previously neutral olfactory stimuli produced severe anxiety and phobic and escape reactions after having been presented a few times together with a snake. At the same time the animals became hypersensitive to nearly all forms of olfactory stimuli and tended to avoid unfamiliar odours for up to three months.

Many insects seem to depend almost entirely on olfaction for location of food,

mating, and finding sites for oviposition. Honeybees are able to distinguish members of their own colony from bees belonging to other colonies by odour (74). Kalmus and Ribbands (117) have obtained evidence suggesting that the characteristic odours of the members of a colony are not genetically inherited but due mainly to diet.

Some insects possess abdominal scent glands producing sexual attractants. In certain species the male may be attracted over a distance of a mile by the odour emitted from the gland of the female. If the male is deprived of his antennae or if the female is kept in a well sealed glass jar where she can be seen but not scented, the male does not orient towards the female. Butenandt *et al.* (45) have shown that the attractant of *Bombyx mori* is an unsaturated primary alcohol. By using the amplitude of the slow electrical response of the antennae as a quantitative measure of the stimulating effect of the attractant, Schneider (198) was able to show that female glands of *Bombyx* had a considerably greater effect than the glands of *Saturniid* on the male *Bombyx*. On the other hand *Bombyx* gland attractants had no effect upon the antennae of the *Saturniid* males. Wharton *et al.* (221, 222) have developed a method for quantitative measurements of the behaviour of the American cockroach to the odorous attractant of the female. By using the wing lift as a criterion of response, these authors were able to demonstrate that the percentage of responses was proportional to the logarithm of concentration of the attractant.

V. MECHANISMS OF STIMULATION

1. Relation between olfactory stimulatory effectiveness and physico-chemical properties of odorous compounds. Numerous attempts have been made to find a correlation between the physical or chemical properties of odorous compounds and their action on the olfactory membrane. Reviews on the vast literature in this field clearly disclose the diversity of ideas that have been advanced (32, 80, 114, 153).

For a long time it was thought that the initiation of the nervous discharge was due to chemical processes, and that the odour quality was determined by certain functional groups. Because of the failure of the chemical theories to explain, for example, why many saturated compounds are odorous or why different compounds may produce very similar odours, attention has been focused upon the possibility of a correlation between physical properties and odour.

It is generally agreed that in order to activate the olfactory receptors a substance must be volatile, it must to some extent be soluble in water, and it must possess a certain degree of lipid-solubility. Information about the influence of the physical properties upon the stimulatory potency of odorous compounds comes mainly from studies on the olfactory effects of homologous substances. In such series there is a gradual change in vapour pressure and solubility properties as the series is ascended, while the chemical properties remain unaltered. In 1892 it was shown by Passy (186) in studies on olfactory acuity in man that primary aliphatic alcohols are increasingly potent as the series is ascended. This observation was confirmed by Backman (22) in an extensive analysis of the olfactory detectability in man of a great number of substances.

The odorant potency of different series of homologous compounds, including primary aliphatic alcohols, aldehydes, and fatty acids, has more recently been studied in different animals and by different techniques. It has been demonstrated by Dethier and Yost (58) on insects that the rejection thresholds for alcohols decrease logarithmically with increasing chain length. The higher members, especially octanol and decanol, showed irregularities but did not depart significantly from a straight line. A similar relationship between chain length and threshold for stimulation was also demonstrated for aldehydes. These observations were confirmed and extended by Hughes (107) in studies on tsetse flies and blowflies. It has further been demonstrated that the relation between the olfactory effect upon the nasal mucosa of the frog and the chain length of alcohols and aldehydes is almost identical with that in insects (181). Later studies by Moulton and Eayrs (163) on the ability of rats to detect alcohols have provided further evidence of the logarithmic increase of odour intensity as the series is ascended. The striking similarity between the results obtained in different species and with different techniques is noteworthy. Quite recently Higashino *et al.* (105) have reported observations which are at variance with the results mentioned above. In recordings from the frog olfactory mucosa, these authors found that the odorant potency of saturated vapours of homologous alcohols increased from C_1 to C_6 and then decreased for the higher members. With lower concentrations they obtained curves with different slopes and maxima. In a study of olfactory detectability in two dogs, Moulton *et al.* found that the threshold in one dog decreased logarithmically as the formic acid series was ascended; in the other dog this relation was discontinuous though the general trend was the same.

Since the physical properties, including vapour pressure and water- and oil-solubilities, of the members in a homologous series change in a regular manner, the increase in odorant potency with increasing chain length might be related to any of these properties. Backman (22) thought that the solubility properties were decisive, and suggested that the action of odorous substances depends on their oil–water partition coefficients. In studies on tarsal receptors in blowflies, Chadwick and Dethier (48, 56) observed that the curve relating chain length to odorant potency had a dual course. Since the break in the curve was found in the region where infinite solubility in water was lost, it was concluded that the limiting system in contact chemoreception involved a two-phase system (54). It is interesting to note that in the curve relating chain length to olfactory effect in man (157) and in the frog (181), there is an inflexion in the same region. As will be further discussed below, this strongly supports the view that the solubility properties play an important role in the action of odorous substances on the olfactory receptors.

To be odorous a substance must have a certain vapour pressure. Now the relative saturation of the vapour of a substance in the vapour phase represents its thermodynamic activity. Since the thermodynamic activity of a compound is the same in all phases in an equilibrium system, the activity at the locus where the biological action is exerted can be determined by measuring the activity in the external phase. The thermodynamic scale can therefore be applied only to

processes in which an equilibrium is reached. It has been suggested (38, 71) that thermodynamic activities should be used as a measure of the potencies of certain compounds. Supposing that the processes associated with the action of odorous compounds on the olfactory receptors represent an equilibrium system, the potencies of different substances might then be analyzed in terms of thermodynamic activities.

In studies on human olfactory thresholds, Gavaudan *et al.* (77) found that in terms of thermodynamic activities the odorant potencies of alcohols increased from C_1 to C_4 and then decreased for the higher members. In studies on the potencies of alcohols in producing repellence in insects, Dethier and Yost (58) found that thresholds for alcohols of intermediate chain length (C_4 to C_8) were approximately equipotent when expressed in thermodynamic activities. A similar relation between thermodynamic activities and thresholds was later demonstrated also for aldehydes. Dethier (55) therefore suggested that homologous compounds of intermediate chain length and of equal thermodynamic activities have equal odorant potency. This view is supported by measurements of the response evoked in the frog olfactory mucosa by substances of equal thermodynamic activities. It was shown by Ottoson (180, 181) that the alcohols of intermediate chain length and equal thermodynamic activities were approximately equally potent, while the three first members in the series were less active. It was suggested that solubility properties might account for the differences in potency of the alcohols of short and intermediate chain length. In testing olfactory acuity in rats, Moulton and Eayrs (163) found that the alcohols with 5 to 11 carbon atoms were almost equipotent. Essentially similar results were obtained in man when olfactory thresholds for alcohols were expressed as activities. Hence, all the studies in which the thermodynamic analysis has been applied to olfactory data indicate that within a certain range of chain length the odorant potency of homologous compounds closely follows thermodynamic activity. The fact that some of the members in the series studied do not conform to this trend clearly shows that other factors also influence the action of a substance on the olfactory receptors.

2. Olfactory theories. Most of the old theories of olfaction regard the initiation of the nervous discharge as the result of chemical reactions between the odorant particles and the olfactory receptors. In 1906, Woker (223) proposed that the odour intensity of a substance is linked to the degree of unsaturation of the compound. A direct relation between chemical structure and odour was later suggested in a number of theories. Durrans (62) thought that the presence of free valencies was the main factor. In 1920, Ruzicka (195) suggested that activation of the olfactory receptors occurs as the result of reactions between what he called osmoceptors in the olfactory membrane and certain functional groups such as —OH, —CHO, —CO, —COOR, —CN, NO_2, and N_3 in the odorant molecule. Though Ruzicka attached great significance to the presence of these groups, he also attributed an important function to the steric configuration of the molecule. Ruzicka (196) later modified his theory and proposed that the odoriferous groups trigger enzymatic reactions which are the direct cause of the

initiation of the nervous discharge. Chemical reactions are thought to be responsible for the elimination of the odorous material from the olfactory membrane.

A number of theories attribute an important function of the excitatory process to adsorption of the odorant molecules on the surface of the receptor membrane. The classical theory in this category was advanced by Zwaardemaker in 1921 (230). He suggested that the excitatory action of an odorous substance is determined by its lipid solubility and the rate at which it is adsorbed on the receptor membrane. The quality of odour was supposed to be determined by odoriferous groups in the molecule. A similar view has been advocated by Moncrieff (153 through 157), who suggested that in order to activate the olfactory receptors a substance must have a molecular configuration that is complementary to certain sites in the receptor membrane. Discrimination of different odours was postulated to depend on selective adsorption at different membrane sites. In studies on the adsorption properties of the nasal mucosa, Moncrieff showed that the olfactory membrane renders some kinds of odorized air odourless (155). The finding that substances with similar odour behave in a similar way to different adsorbents was considered as further support of the theory.

A profile-functional group concept has been developed by Beets (30, 31, 32), who suggested that the external shape of the molecule is the decisive factor in olfaction. According to Beets' theory the action of the molecule is determined by the affinity of the molecule to the receptor membrane and the ability of the molecule, when adsorbed, to trigger off impulses. The affinity was assumed to depend on the presence of functional groups, while the excitatory effect was attributed mainly to the outward shape, the profile, of the molecule. It was suggested that molecules which impinge upon the mucosa pass through a transitional stage which involves orientation of the molecule. The tendency towards orientation was assumed to depend on the number and character of the functional groups, and it was thought that the profile, after the orientation of the molecule, would fit into a receptor site. Quality of odour was assumed to be determined by the separate influences of the functional groups and the profile of the molecule, while activation was attributed to the energetic change in the receptor membrane accompanying the adsorption of the molecule. This idea conforms to the notion which now appears to be generally accepted, *viz.*, that the initial event in the excitatory process involves adsorption of the odorous particles on the receptors, and that this process is specific in the sense that the stimulating molecules have to fit into certain sites in the membrane (170). As pointed out by Moncrieff, this hypothesis does not imply that there have to be as many sites as there are different molecular configurations. It is more likely that there is a limited number of different types of receptor sites and that the molecules are mainly, but not exclusively, adsorbed to the site that matches with their form. However, even if we accept the idea that the primary event in the olfactory process consists in adsorption of odorous particles on the receptor membrane, the question of the direct cause of the depolarization of the end organs still remains to be answered.

Ehrensvärd (66) has suggested that changes in phase boundary potentials

may be responsible for the receptor activation. His theory is based on observations of potential changes produced by organic compounds in a system of a solution of potassium chloride / a solution of an organic compound / a solution of potassium chloride. The first phase in this model is thought to correspond to the mucus of the olfactory mucosa, the second phase to the receptor membrane, and the third phase to the cytoplasm of the receptor cells. Ehrensvärd found that the concentrations of odorous compounds necessary to produce potential changes in this system are of the same order as those required to give olfactory sensations. The potential measured was of the order 10 to 20 mV, but differences of more than 100 mV were seen.

Bungenberg de Jong and Saubert (43) have developed a theory based on interesting observations on the influence of organic non-electrolytes upon coacervate systems. They found that coacervates of phosphatides or oleates were sensitive to vapours of a great number of organic compounds, while coacervates of proteins or hydrocarbons lacked this property. The sensitivity of the phosphatide or oleate coacervates was explained by the fact that besides being hydrophilic these coacervates are also lipophilic because of the presence in the molecules of long-chain hydrocarbons. The observed effect consisted in a vacuolization of the coacervate when exposed to the vapour of the odorous substance or after removal of the vapour. This effect was attributed to a decrease or increase in the distance between the phosphatide or oleate molecules, and was described in terms of shrinking or swelling. Shrinking was thought to depend on the action of the active (odorous) substance as a cohesive agent upon the hydrocarbon chains in the molecule of the coacervate and was assumed to be mediated by van der Waals forces. It was noted that some substances caused shrinking, others swelling. One and the same substance could produce both of these changes: shrinking in low, and swelling in high concentrations. Aromatic hydrocarbons had a strong shrinking effect. Aliphatic hydrocarbons also produced shrinking though their effects were weaker. It was further found that introduction of hydrophilic groups counteracted the shrinking effect of the hydrocarbon chain and caused a reversed change, *i.e.*, swelling, when the hydrocarbon chain was short. In the series of homologous primary aliphatic alcohols the first three members produced swelling, whereas the higher members, from butanol to heptanol, caused shrinking. It is of particular interest to note the striking conformity of the observations with the results obtained in olfactory studies in different species. As already mentioned, it has been demonstrated in man (22), frog (181), rat (163), and insects (58) that the first three members in the series of primary aliphatic alcohols have a considerably lower stimulatory potency than the higher members. On still another point there is an interesting similarity between the observations on the coacervate system and biological olfactory data. Bungenberg de Jong and Saubert reported that branching of the hydrocarbon chain had a marked effect. While *n*-butanol, for instance, produced shrinking, tertiary butanol caused swelling. This finding conforms to observations in insects (57) and in the frog (181) showing that branching of the chain of hydrocarbons leads to a reduction of olfactory stimulatory potency.

It has been suggested by Bungenberg de Jong and Saubert (42) that the phosphatide or oleate coacervate may serve as a model of the olfactory membrane. If we assume that the change produced in the receptor membrane by odorous particles is similar to that observed in the coacervate model, activation of the receptors would be linked with shrinking of the membrane. If it is further assumed that the membrane contains pores, as has been postulated by many authors (*cf.* 168), the shrinking would result in a widening of the pores and thereby in permeability changes. The odorant potency of a substance would accordingly be determined by the degree of shrinking produced. If shrinking is counteracted by swelling, for instance due to introduction of hydrophilic groups, the olfactory effect will be weaker. As pointed out by Bungenberg de Jong and Saubert, the coacervate model also resembles the olfactory receptor system, insofar as the changes are reversible and the stimulating particles reach the active membranes through a water phase. The theory provides primarily an explanation of the mechanism of stimulation.

A pore membrane as model of the olfactory receptor membrane has also been proposed by Mullins (167, 168), who suggested that the membrane is formed of macromolecular cylinders arranged in a regular hexagonal pattern with pores at the junctions between any three cylinders. Such a membrane can be presumed to show a considerable degree of specificity in terms of interaction between the walls of the pores and the molecules brought into contact with the membrane. Davies and Taylor (51, 52) have developed a theory that regards the initiation of the olfactory nervous discharge as produced by localized permeability changes in the receptor membrane. In using the erythrocyte membrane as a model for their study, these authors showed that a large number of odorous substances act as accelerators of haemolysis by saponin. For many substances they found a linear relation between the logarithms of the haemolytic accelerating powers and the olfactory thresholds. The fact that haemolytic accelerators produce leakage of potassium ions across the red cell membrane was considered as further support of the idea that the adsorbed odorous molecules excite the olfactory receptors by dislocating or "puncturing" the membranes. The olfactory threshold for different odorants was postulated to depend on their adsorption energies in passing from air to lipid-aqueous interfaces, and on shapes, sizes, and flexibilities of the odorous molecules.

A number of theories attribute the action of odorous substances to molecular vibrations. Dyson (63) has suggested that the odour of a substance is related to a characteristic molecular vibration pattern. According to his theory, which is concerned primarily with the mechanisms of differentiation of odour qualities, in order to be odorous a substance must have a certain vapour pressure, be soluble in lipids, and have one or more Raman shifts between 1400 and 3500 cm^{-1}. The reason for limiting the frequency range for olfactory stimulation to 1400 to 3500 cm^{-1} appears to be that most strong odours have Raman shifts within this range. Dyson introduced the term "osmic frequencies," and suggested that the quality of odour of a substance was determined by its particular osmic frequency pattern. This theory, as well as other similar vibration theories,

would explain why some substances with different chemical constitution have similar odours, and also why stereoisomers may have different odours. In criticism of Dyson's theory it has been argued that Raman shifts above 1000 cm^{-1} are generally related to the presence in the molecule of particular groups. The theory would therefore not be essentially different from the chemical theories which attribute odour to such groups. Since these theories have proved to be untenable, Dyson's theory would be equally unsatisfactory. Wright (224) has suggested that instead of searching for a correlation between odour and molecular vibration in the band above 1000 cm^{-1}, one ought to look at the low-frequency vibrations since they reflect movement of the whole molecule. This idea has been elaborated in detail by Wright (225, 226, 227). The theory proposed by him attributes a significant function to the olfactory pigment. He suggested that the pigment molecules act as energy acceptors and that the triggering of the nerve impulses occurs by de-excitation of the pigment molecules. According to this theory there would be a close resemblance between the excitatory processes in the visual cells and those in the olfactory receptors. The type of odour would be determined by the particular vibration frequencies of the molecule, and the threshold concentration by the closeness of coupling of the odours and pigment molecules.

If the olfactory pigment had the function postulated in Wright's theory, one would expect odorized air to produce a bleaching of the olfactory mucosa. This has not been found to occur. No obvious colour change can be observed when strongly odorized air is passed over the exposed olfactory membrane in cats or rabbits (180). This finding does not refute Wright's theory, since the discoloration may be too slight to be discerned by visual observation. If stimulation occurs as proposed in Wright's theory, one would further expect the mucosa to fluoresce under ultraviolet light when stimulated with odorized air. As reported by Jackson (109), extracts of the olfactory tissue do not fluoresce until they are separated and applied to chromatographic paper. The distribution of the pigment also seems to speak against the presumed function of the pigment. As shown by several investigators, the pigment is located mainly in the gland cells and in the supporting cells, whereas the receptor cells appear to contain only little pigment.

A vibrational theory that has attracted great interest and caused much discussion was advanced by Beck and Miles in 1947 (27, 150). On the basis of observations on honey bees, these authors suggested that the olfactory receptors emit infrared radiation. It was assumed that odorous particles entering the nose absorb some of this radiation and thereby cause a loss of energy of the receptors. This energy loss was thought to initiate the nervous discharge. The receptor elements were postulated to radiate selectively, depending on differences in size and shape. Different odorous substances would, by virtue of their infrared absorption properties, affect the receptors differentially. This theory has been criticized on theoretical grounds. Various experiments have also been designed to test its validity. In human experiments Schkapenko and Gerebtzoff (206) found that no sensation of odour was produced when a closed polyethylene tube filled with odorized air was inserted up to the nose as closely as possible to the olfactory region. It has also been demonstrated that odorized air at body temper-

ature produces sensation of smell (72). Another piece of evidence against the theory has been obtained by Ottoson (179), who showed that odorized air failed to activate the olfactory membrane in the frog if the mucosa was covered with a thin plastic membrane. The membrane used transmitted a great proportion of the infrared radiation within the range supposedly involved, and would therefore not have prevented the receptors from being stimulated if excitation occurs as postulated in Beck and Miles' theory. The finding that no stimulation was produced in this experiment also provides definite evidence that the olfactory organ is not stimulated unless the odorant particles are brought into contact with the olfactory receptors.

A number of theories assume the participation of enzymes in the activation of the olfactory receptors. Kistiakowsky (122) has suggested that odorous molecules impinging upon the mucosa inhibit the enzymes and thereby trigger off the nervous discharge. According to this hypothesis, different odorous substances should be distinguished by virtue of their specific inhibitory action on one particular enzyme system. The intensity would depend on the amount of enzyme inhibited. Since the gustatory region of the tongue contains very much the same enzymes as the olfactory mucosa, the theory would also account for the gustatory mechanisms.

Baradi and Bourne (23, 24) have tested the enzyme theory experimentally by measuring the concentration of enzymes in the olfactory mucosa after substances with different odours had been added to the substrate solution. They found a certain degree of specificity insofar as that the enzymes were inhibited differentially by different substances. On the basis of these observations the authors suggested that excitation of olfactory and gustatory receptors occurs as a result of ionic changes which are produced by the reactions between the enzymes and a stimulating substance. If the enzymes play the presumed role in the excitatory process, one would expect to find them localized particularly to the olfactory hairs. However, the hairs seem to contain less enzymes than the other structures in the olfactory mucosa. The failure to demonstrate enzymes in the hairs may be explained by the fact that these structures are extremely fragile and therefore easily destroyed by the fixation procedure. It has been argued against this theory that many substances which are known to be strong enzyme inhibitors are odourless. Furthermore, it has been found that treatment of the olfactory mucosa with cholinesterase inhibitors such as neostigmine, eserine, and Paraoxon (diethyl-4-nitrophenyl phosphate, Mintacol) does not block the olfactory response (185). It does not seem likely therefore that the enzymes studied are directly responsible for the activation of the olfactory receptors. This does not, however, imply that they do not participate in the excitatory process, or that other enzymes may not be more directly involved.

If the enzymes are at all involved in the olfactory process it appears more plausible to assume that they are concerned with the elimination of the odorous material. This part of the olfactory process is usually overlooked, though it must be of utmost importance for the function of the receptors. It has been demonstrated, for instance, that the receptors are able to respond to repeated

stimulation for up to one hour without any appreciable sign of fatigue. This would not be possible if the odorous material were not eliminated very efficiently after each stimulation. This elimination could be mediated by the bloodstream. The olfactory area has a rich vascular supply that would make possible a rapid removal of odorous material. However, it seems to be equally probable that part of the material is disposed of by the enzymes in the mucosa.

VI. CONCLUDING REMARKS

The sense of smell is often said to be the most neglected of our senses. This is only partly true. As shown by the enormous literature on olfaction, there has been a considerable interest attached to problems concerning the function of the olfactory system, and the amount of data which have been collected is at the present time immense. In spite of all attempts at evaluation of the processes by which smell is perceived, the basic mechanisms of olfaction are still unknown. The difficulties encountered in controlling the stimulus parameters and in recording the activity of single primary olfactory units have undoubtedly been the major obstacles to progress of research on olfaction. The fact that unequivocal and precise data are hard to obtain has made olfaction a field for speculations and hypotheses, often with no or little experimental evidence. Actually, more theories seem to have been proposed for olfaction than for any other sensory function.

Research work in the last decade has changed the situation. Adrian's investigations on the activity of the olfactory bulb have provided important contributions to the understanding of the mechanism underlying olfactory discrimination and have given an impetus to further electrophysiological studies on the function of the olfactory system. The demonstration of the receptor potential of the olfactory organ has yielded information about the functional characteristics of the olfactory organ and has expanded the possibilities for quantitative measurements of the effect evoked by odorous substances in the end organs. Furthermore, our knowledge about the action of different substances has been considerably extended through the work by Dethier and collaborators on insects and by Moulton and collaborators on rats, as well as by the results obtained in recent psycho-physical investigations. The conformity of the results obtained suggests that the basic functional properties of the olfactory receptors are essentially alike in different species. It also shows that olfactory problems may be successfully approached with widely different techniques. The method for recording the activity of single units recently developed by Gesteland *et al.* represents a promising methodological advance in olfactory research. A detailed analysis of the specific sensitivity of single receptors no longer seems to be an unattainable reality.

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