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CHEMICAL SIGNALS BETWEEN ANIMALS: ALLOMONES AND PHEROMONES

George M. Happ

I. INTRODUCTION

Air and water transmit a multitude of chemical signals, many of which are not by-products of human "civilization". A great variety of these air- and water-borne molecules, present at very low concentrations, carry specific information from one animal to another. Sensory receptors of the recipient animal may be astoundingly sensitive: only one molecule need hit certain sense cells to trigger an action potential (Kaissling and Priesner, 1970). Chemical ecology, the study of these signals and the interactions they mediate, is now a rapidly expanding field (Sondheimer and Simeone, 1970; Whittaker and Feeney, 1971).

Chemical interactions are both diverse and complex. As a whole, the chemical signals which act between organisms are termed *semiochemicals* (Law and Regnier, 1971). In multicellular organisms, the distinction between semiochemicals and hormones is usually clear: semiochemicals are exocrine secretions, produced by one individual and acting upon another. The signal (semiochemical) is the central element in a system consisting of producer–signal–recipient. When producer and recipient are of the same species, communication is intraspecific and the signal is known as a *pheromone* (Karlson and Lüscher, 1959; Karlson and Butenandt, 1959). When the signal acts between two different species, it is called an *alleochemic* (Whittaker, 1970; Whittaker and Feeney, 1971). Alleochemics may benefit the producer (e.g., by repelling a predator), or may be disastrous for the producer (e.g., by attracting a predator), or they may benefit both producer and recipient (e.g., floral scents which attract pollinating insects to nectar). Alleochemics which are adaptive for the producer are called *allomones* and those which are of adaptive advantage to the recipient are known as *kairomones* (Brown, 1968; Brown *et al.*, 1970).

This chapter is concerned with interspecific allomones and intraspecific pheromones, namely those chemical signals which have clear adaptive value to the animals producing them. In one species, several chemical signals may serve quite diverse functions, as illustrated by the mealworm beetle, *Tenebrio molitor.* Scent communication plays at least four roles in the reproduction of *Tenebrio.* The female produces a scent which attracts and sexually excites the male (Valentine, 1931; Tschinkel *et al.*, 1967, Happ and Wheeler, 1969). The male produces a scent which attracts females (Happ, 1969; August, 1971). A male which has "smelled" a female emits a scent which inhibits other males, i.e., makes them less responsive to the female attractant (Happ, 1969). Mature males, and to a lesser extent mature females, produce a scent which accelerates reproductive maturation in younger adult females (Happ *et al.*, 1970). Finally, adult *Tenebrio* possess glands (Roth, 1945) which may repel predators by means of defensive allomones, *p*-benzoquinones (Schildknecht, 1963).

Chemical signalling systems have been found in many phyla, as Wilson (1970) has noted, "they continue to turn up regularly in species when a deliberate search is made for them." Within the last 25 years, over 100 allomones and half as many pheromones have been chemically identified; the bulk of this research has involved insect material (Weather-

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ston and Percy, 1970; Law and Regnier, 1971). Insect studies have progressed especially rapidly for three principal reasons: (1) the dramatic improvements in analytic chemical techniques which now allow characterization of organic molecules present in microgram quantities, (2) the fact that chemical cues play a predominant role in many aspects of insect biology, and (3) the attractive possibility that natural chemical signals could be used to manipulate natural populations and thus contribute to control of insect pests. Yet insects are not unique; a vast number of observations on behavior and natural history indicates the importance of chemical signals in many animals, notably vertebrates see Wilson and Bossert, 1963, various papers in Seboek, 1968, Sondheimer and Simeone, 1970, and Johnston *et al.*, 1970, for references). Except for the studies of perfume chemists on animal musks (Lederer, 1950), relatively little information has been available on mammalian exocrine secretions. The present review will focus on two groups of animals: the terrestrial arthropods, where much biological and chemical data are available, and the vertebrates, where the importance of the chemical signals are acknowledged but the chemical data are, as yet, rather sparse. Of necessity, the choice of examples from the literature has been somewhat arbitrary, but I have attempted to indicate the diversity in both signal molecules and their functions.

II. CHARACTERISTICS OF CHEMICAL SIGNALS

In contrast to auditory or visual signals, chemical signals physically occupy space and are relatively persistent. Within the last 8 years, E. O. Wilson and W. H. Bossert have published a series of fascinating papers which elucidate many of the general features of chemical signal transmission (Wilson and Bossert, 1963; Bossert and Wilson, 1963; Bossert, 1968; Wilson, 1968, 1970; Wilson *et al.*, 1969). Crucial to their conclusions is a mathematical model of the system. I will attempt to describe its major features below, but the interested reader should consult the original papers (especially Bossert and Wilson, 1963) for fuller mathematical development.

Consider a simple system: a stationary animal on a flat surface begins to emit a pheromone into still air. Assume that the response to this signal is all-or-none, and thus a recipient will respond only when the pheromone concentration in his own vicinity exceeds threshold—this response threshold is designated as K (molecules/cm^3). As the pheromone diffuses out from the stationary emitter into ever-increasing volume of surrounding air, a concentration gradient appears, declining away from the emitter. At some distance from the emitter, pheromone concentration will be less than K, and no potential recipients will respond. However, there will be a certain volume (in the vicinity of the emitter) where pheromone concentration is at least K or exceeds K, and a response occurs. This volume is designated as the *active space*, and as Wilson (1970) has noted, "the signal is the active space."

The shape of the active space varies with three factors: (1) the position of the emitter, (2) air movement, and (3) the behavior of the emitter. If the emitter is at the top of a tall tree, the active space may be almost spherical, but when the emitter is on a flat surface, the active space will be essentially hemispheric, at least in still air. When the air is not still, the shape will be modified: in a constant wind, the hemispheric active space is smeared into a semiellipsoid. Finally, if the *emitter* is moving and marking the substrate with liquid pheromone, he leaves a trail of active space behind him which persists until the "marks" have evaporated.

The volume and life-span of any active space will vary with four parameters: (1) rate of pheromone emission into the air, designated Q and expressed in molecules per second, (2) the rate of diffusion characteristic of each molecular species, (3) the response threshold K, and (4) temporal factors, namely elapsed time since emission began and the duration of the emission. By a refinement of the diffusion equation, Bossert and Wilson (1963) have shown that these parameters are interrelated according to the following equation (for animals on a flat nonabsorbent surface).

$$K = \frac{Q}{2D\pi r}\, efrc\, \frac{r}{\sqrt{4Dt}}$$

where Q, D, and K are emission rate, diffusion coefficient, and threshold concentration, respectively, and where r is the "radius" of the active space (cm), t is the time from the beginning of emission (seconds) and where $efrc(x)$ is the complementary error function.

An increase in Q (emission rate) or a decrease in K (threshold concentration) will lead to a greater maximum volume for the active space. Wilson and Bossert (1963) have shown that the ratio between these two parameters

$$\frac{Q}{K} = \frac{\text{molecules emitted/second}}{\text{molecules/cm}^3\text{ at threshold}}$$

effectively describes not only the maximum volume but also the temporal characteristics of the signal. The Q/K ratio predicts both the lag-time

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Q/K	Maximum radius (cm
1	0.6
100	2
10,000	10
1,000,000	60

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required for expansion of the active space to maximum volume (which is equivalent to lag-time for signal transmission at maximum range) and the fade-out time after emission ceases. Wilson (1970) has calculated the volumes and temporal characteristics for a substance diffusing ($D = 0.1\ \mathrm{cm}^2/\mathrm{second}$) into still air (Table I).

It should be emphasized that *optimum* volume and duration of the active space are not synonomous with *maximum* volume and duration. Sex attractants emitted by female moths operate well over many kilometers (and the male moth can fly that distance upwind) but trail markers of ants must keep the following ants close to the original trail. In the case of the moth, Q/K is large and the calling female remains stationary. For the trail substance, the opposite holds. Natural selection has operated to maximize the efficiency of each signal system, including the properties of the molecular signal itself.

Neither nitrogen gas not glycogen would be effective as an air-borne chemical signal: such a signal must be volatile (which glycogen is not) and must be different from environmental noise (which nitrogen is not). A chemical signal must be of low molecular weight to be volatile, and yet of sufficient structural complexity to convey a signal of some specificity. There are an infinite number of organic compounds and a multitude of structural, geometric, and optical isomers of many. An upper limit on size is imposed by the volatility requirement and a lower limit by specificity. Wilson and Bossert (1963) propose a judicious compromise: air-borne pheromones will have 5–20 carbons and molecular weights from 80 to 400. As subsequent chemical studies have shown (see Sections IV,V) their predictions were amazingly accurate.

Given this variety of molecular signals, can the prospective recipient distinguish one from another? As noted below, discrimination is extremely precise in some cases. And at least in mammals, a very large number of distinct odors are recognized. Even in man, a notoriously

TABLE I

Q/K	Maximum radius (cm)	Time to reach maximum radius (sec)	Fade-out time (sec)
1	0.6	0.4	1
100	2	8	20
10,000	10	150	500
1,000,000	60	40,000	10,000

microsomatic species, Hainer *et al.* (1954) estimate that 10,000 odorants can be distinguished.

Transmission of a signal through aqueous media possess essentially the same sorts of problems, except that the rate of diffusion is usually much lower and one would expect the signal molecule to be rather polar in order to be water soluble. Wilson (1970) has made the calculations for such an aqueous medium: on the assumption that $D = 10^{-5}$ cm^2/second, he finds that for any given Q/K ratio, the volume of the maximum active space is similar to that in air but the time for expansion to maximum and time for fade-out are much longer.

III. METHODS OF STUDY

The human nose is something of a handicap in studies of chemical signals which act in natural populations. Whereas in visual signalling, we can usually *see* something (ultraviolet and infrared cues excepted) and then record it on film, and in auditory signalling we can usually *hear* something (except ultrasonic signals) and record it on tape for analysis, when chemical signals are employed we often smell nothing. Defensive allomones are obvious exceptions. Formic acid is unpleasant to man, as it is to most animals. Commonly, a study of chemical signals begins with a chance observation that an animal responds in the absence of noticeable stimuli. The tasks then become: to determine whether the covert stimuli are chemical, to search for the molecule(s) responsible, and to define precisely their role in the behavioral or physiological changes of the recipient.

It may be relatively easy to demonstrate that a *chemical* signal triggers certain behavior. Elimination of auditory and visual cues is often not too difficult, and the recipient may then respond when exposed to a scented airstream or a liquid sample. It is sometimes reassuring to demonstrate that ablation of putative chemoreceptors or their axons, i.e., clipping off segments of an insect antenna or sectioning the olfactory bulb of a vertebrate, abolishes the response to the chemical stimuli; but this surgical insult may affect many other facets of nervous function, and the results must be interpreted with caution. In any case, for chemical isolation and characterization of the signal, it is necessary to have a suitable bioassay, preferably one which utilizes behavioral responses of intact organisms in reasonably natural situations.

Electrophysiological techniques, for example monitoring the electroantennograms of insects, have been employed profitably for bioassays, but eventually the purified chemical must be tested on intact animals. The major requisite is that the assay must be quantitative. To cite an example: in 1967, Wheeler and I isolated an homogeneous substance which attracted and excited male mealworm beetles, and we rather thought that we had found the natural sex pheromone. However, quantitative bioassay revealed that our "homogeneous substance" was 100 times *less* active than a partially purified extract of females. In fact, the "homogeneous substance" was dibutyl phthlate, a volatile contaminant introduced by Tygon tubing in our collection of female scent (Happ and Wheeler, 1969).

Given the quantitative bioassay, what usually follows is chemical drudgery—repeated purification and repurification, and biological ennui—bioassay of each fraction generated by the chemistry. (These procedures may be cleverly avoided in some cases by direct assay of a battery of known chemicals as demonstrated by W. Roelofs and his co-workers at Cornell). But in the usual routine, when the chromatography finally yields an apparently pure substance of high potency in the bioassay, modern spectral techniques (mass, infrared, nuclear magnetic resonance, and ultraviolet spectrometry) often allow identification. The power of these techniques cannot be overestimated, for they are sensitive to micro- and nanogram amounts. The structure determination must then be confirmed by careful comparison with an authentic sample. Especially with pheromones, which are often present in very small amounts, the authentic samples must be very rigorously purified, as a very minor contaminant may account for the biological activity. If the authentic sample is not available, it must be synthesized. Premature publication of pheromone structure on the basis of reasonable structural evidence only (but no synthesis) has led to unfortunate errors.

IV. ALLOMONES

In their recent review of alleochemics, Whittaker and Feeney (1971) define allomones as "chemical agents of adaptive value to the organism producing them" which do not act between members of the same species. Included within this broad definition are a host of chemical agents which will not be considered within the present chapter. Among those excluded will be counteractants (such as antibodies), venoms which are used to kill prey, escape substances (such as cephalapod inks), and substances which are primarily nutritive (such as vitamins provided by symbiotic bacteria). The following discussion will be limited to two classes of chemical *signals* which act upon another species: the repellents used for defense and the substances which regulate symbiotic interactions.

A. Allomones for Defense

Predators do not always succeed in capturing their potential prey: the presumptive meal may hide, flee, or counterattack. Among the most dramatic defensive weapons are the chemical ones: the notoriety of the skunk is founded on the overwhelming persuasiveness of its repellent spray. The millipede *Apheloria* responds to attack by emitting a mixture of benzaldehyde and hydrogen cyanide (Eisner *et al.,* 1963). Both the skunk and this millipede are distinctively colored, presumably so that in future encounters those predators which can learn (especially vertebrates) will heed the warning which these colors present. Chemical repellents are also found in fish, newts, frogs, and snakes, but among terrestrial and freshwater animals, arthropods have the most diverse chemical defenses (Roth and Eisner, 1962; Schildknecht, 1963; Cavill and Robertson, 1965; Eisner and Meinwald, 1966; Weatherston, 1966; Weatherston and Percy, 1970; Eisner, 1970; Schildknecht, 1970).

1. Small Repellent Molecules

In 1670, Fisher examined a distillate of formicine ants and detected an organic acid which was subsequently characterized as formic acid. As one of the simplest repellents, formic acid can serve to illustrate many of the characteristics of the substances found in defensive secretions. Because of its high acid strength ($pK_a = 3.77$), formic acid causes protein coagulation and is therefore cytotoxic. Ants squirt a finely dispersed stream of liquid acid at attackers, thus maximizing the chance that sufficient numbers of toxic molecules will be delivered to the assailant (see Eisner, 1970, for a dramatic photograph). Formic acid is of course a volatile substance (boiling at about 100°C) with a pungent odor; it is repellent in both the liquid and the gas phase.

Representative defensive allomones are shown in Fig. 1. Aliphatic acids and aldehydes are common; usually the acids (I–III, V) are short chain (C_1–C_5) while the aldehydes (IV, VI) are of intermediate length (C_4–C_8) and often α- β-unsaturated. Aliphatic alcohols are rare, but their sulfur analogs (VII, mercaptans) are utilized by mustelid mammals. Cyclic molecules include benzoquinones (VIII), phenols, benzaldehyde derivatives (IX, X), and an unusual chlorinated hydrocarbon (XI) apparently derived from injested herbicide. A number of defensive allomones are terpenoid (XII, XIII).

HCO_2H

Formic acid

(I)

CH_3CO_2H

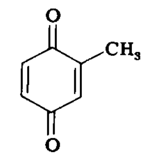
Acetic acid

(II)

$\overset{H}{CH_3C}=\overset{H}{C}-C\equiv C-C\equiv C-CH_2CH_2CO_2$

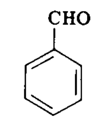
8-*cis*-Dihydromatricaria acid

(V)



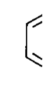
Toluquinone

(VIII)

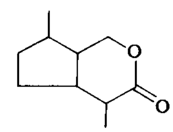


Benzaldehyde

(IX)



Benz



Iridomyrmecin

(XIII)

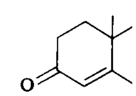


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Fig. 1. Representative defensive allom
scorpion, bugs; III, carabid beetles; IV,
roaches, bugs; VII, mustelid mammals
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al., 1971); XII, ants, bees, beetles; XII
XV, glomerid millipedes. Unless otherwi
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herbicide. A number of defensive

HCO_2H

Formic acid

(I)

CH_3CO_2H

Acetic acid

(II)

$CH_2{=}\overset{CH_3}{\overset{|}{C}}{-}CO_2H$

Methacrylic acid

(III)

$CH_2{=}\overset{C_2H_5}{\overset{|}{C}}CHO$

2-Ethyl acrolein

(IV)

$CH_3\overset{H}{C}{=}\overset{H}{C}-C\equiv C-C\equiv C-CH_2CH_2CO_2H$

8-*cis*-Dihydromatricaria acid

(V)

$CH_3(CH_2)_2\overset{H}{C}{=}\underset{H}{C}CHO$

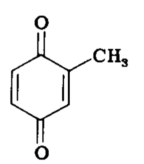
trans-2-Hexenal

(VI)

$CH_3(CH_2)_3SH$

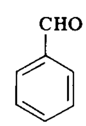
n-Butyl mercaptan

(VII)



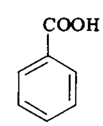
Toluquinone

(VIII)



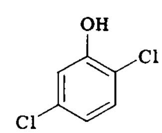
Benzaldehyde

(IX)



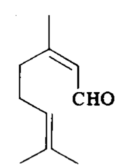
Benzoic acid

(X)



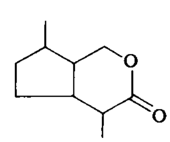
2,5-Dichlorophenol

(XI)



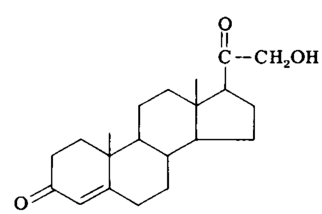
Citral

(XII)



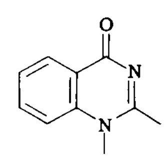
Iridomyrmecin

(XIII)



Cortexone
(21-Hydroxy-4-pregnene-3,20-dione)

(XIV)



1,2-Dimethyl-4(3*H*) quinazolinone

(XV)

Fig. 1. Representative defensive allomones. I, Ants, caterpillars, beetles; II, whip scorpion, bugs; III, carabid beetles; IV, cockroaches; V, cantharid beetle; VI, cockroaches, bugs; VII, mustelid mammals (Lederer, 1950); IX, millipede, ant (Eisner *et al.*, 1961; Blum *et al.*, 1969); X, dytiscid beetles; XI, grasshopper (Eisner *et al.*, 1971); XII, ants, bees, beetles; XIII, dolichoderine ants; XIV, dytiscid beetles; XV, glomerid millipedes. Unless otherwise indicated, references in Roth and Eisner, 1962; Schildknecht, 1963, 1970; Eisner and Meinwald, 1966; Weatherston and Percy, 1970; Eisner, 1970.

The acids, aldehydes, quinones, and aromatic compounds are all reactive general toxicants which are effective against a broad spectrum of predators. Albeit by rather different mechanisms, both the aldehydes and the acids are protein fixatives. Whereas the acids are nonadditive fixatives in the sense of Baker (1958), the aldehydes can be regarded as additives which bond to nucleophilic groups (amines, thiols, etc.) of proteins. The α,β unsaturation in both the aldehydes and quinones would favor such addition reactions.

Acids such as formic and acetic, which are relatively polar, often must penetrate layers of integumental lipids before they can exert cytotoxic effects. A variety of interesting adaptations ensure penetration of these acids. In the whip scorpion, *Mastigoproctus giganteus*, the defensive glands produce a mixture of 84% acetic acid, 5% caprylic (octanoic) acid, and 11% water (Eisner *et al.*, 1961). Eisner and his co-workers nicely demonstrated that the caprylic acid disrupts the lipoid epicuticle of arthropods and thus allows the more irritating and cytotoxic acetic acid to penetrate. An analogous mixture, namely formic, methacrylic, or tiglic acids accompanied by a hydrocarbon is found in the defensive secretions of many ground beetles (Schildknecht, 1970). The ant *Acanthomyops claviger* uses both mechanical and chemical means to disrupt epicuticle; its mandibles scratch the attacker; its mandibular gland secretion (citral and citronellal) is applied, and formic acid is sprayed on this site (Ghent, 1961).

Many defensive secretions are mixtures, apparently because intermediate polarity properties of the secretion as a whole are optimum for broad-spectrum repellency. The defensive secretion of the tenebrionid beetle *Eleodes longicollis* has at least seven components in the nonpolar phase including three benzoquinones, caprylic acid, and three hydrocarbons (Eisner and Meinwald, 1966). That of the bug *Nezara viridula* is a mixture of 20 molecular species, but mostly aliphatic aldehydes (Gilby and Waterhouse, 1965). When one component predominates, it is usually reactive, of intermediate polarity, and often has detergent action. Phenolic compounds usually have alkyl chains which increase their toxicity over that of phenol itself (Sexton, 1963). The bacteriostatic and fungistatic activities of phenols are due in large part to their physiochemical characteristics, especially their tendency to "orient at an oil–water interface and so perhaps by this means to interrupt life processes" (Sexton, 1963).

The general toxicity of many of these allomones raises an interesting problem: How can a living system produce and store such potent toxicants without poisoning itself in the process? For some animals, the answer lies in spatial separation of the final steps in the biosynthesis of the toxic end product—an adaptation that Eisner (1970) has called the "reactor gland." In the defensive glands of *Apheloria* (which emit hydrogen cyanide and benzaldehyde) and of *Brachinus* (which ejects a mixture of benzoquinones and hydrocarbons at 100°C), the living secretory cells produce a relatively nontoxic precursor which is stored in a glandular reservoir. When the precursors pass into an outer cuticular compartment, they are enzymatically converted into the defensive toxicant (Schildknecht and Holoubek, 1961; Eisner *et al.*, 1963; Schildknecht *et al.*, 1968; Aneshausley *et al.*, 1969; Schildknecht *et al.*, 1970). Most defensive glands lack such large cuticular reaction compartments, but the same general strategy may be employed within each secretory cell unit. Each secretory cell is drained by a fine efferent cuticular ductule in many glands, and as Eisner *et al.* (1964) suggested, the ductule and cavities associated with it could serve as serially arranged reaction chambers. Histochemical evidence on quinone production in tenebrionid defensive glands supports Eisner's suggestion (Happ, 1968). Even where such a system of cuticular ductules is lacking, as in the defensive gland of the osmeteria of papilionid caterpillars, the cuticle over the secretory cells is complex and riddled with fine labyrinthine channels (Crossley and Waterhouse, 1969) and these many canaliculi could function as micro reaction compartments.

A considerable variety of predators have been tested in the laboratory and in the field in order to establish clearly the effectiveness of defensive secretions. Many are antimicrobial as well as antipredator. For references to some of these studies, see Eisner (1970).

Topical application of the defensive allomone to the predator is most often the case. An acrid mist may be ejected a distance of several feet and aimed directly at the site of attack, as in the whip scorpion (Eisner *et al.*, 1961) or the secretion may ooze from a gland orifice and then be wiped directly onto the point of attack, as in a soldier beetle (Eisner, 1970). The blind snake *Leptotyphlops* coats itself with an emulsion of fatty acids and glycoprotein from its cloacal sac which effectively repels attacking army ants (Gehlbach *et al.*, 1968; Watkins *et al.*, 1969; Blum *et al.*, 1971b).

A topically applied blatant chemical insult obviously deters predators, but the effect of the defensive allomone may be more subtle. Fatty acids produced by the blind snake and citral produced by ants are scarcely general toxicants, yet they do repel predators. They may function by acting primarily on chemoreceptors to mask the effects of food stimuli. Dethier and Chadwick (references in Dethier, 1963) have shown that a sugar solution may be rendered unpalatable to blowflies by addition of various small organic molecules. An increase in length of the alkyl chain increased inhibitory efficiency. No one has done a systematic study of known defensive allomones (and closely related molecules) to determine which predators might be discouraged by this sort of sensory (as opposed to cytotoxic) mechanism.

Defensive allomones may also act in the gas phase, forming a repellent active space as the volatile molecules diffuse into the surrounding air. In certain bugs, a zone of specialized "fuzzy" cuticle lies adjacent to the orifice of the defensive gland, and secretion trapped within this space slowly evaporates, creating a small active space which moves with the bug as it leaves the site of an attack (Remold, 1962). Even if the concentration is quite low, the active space could still bias predator behavior, making attack less likely. Who would fail to detour around the active space left by a frightened skunk?

2. Steroids and Alkaloids

Steroids and alkaloids found within defensive secretions are usually nonvolatile pharmacologically active agents. In the skin secretions of Amphibia are the most potent of neurotoxins, including salamandrin (Habermehl, 1966), bufotalin (Meyer, 1952), tetrodotoxin (Woodward, 1964) and batracotoxin (Tokuyama *et al.*, 1969). These defensive allomones apparently serve to teach vertebrate predators to avoid the aposematically colored urodeles and anurans which produce them. Their chemical structures and pharmacological effects have been the subject of recent reviews (Bücherl *et al.*, 1968–71).

The steroids expelled from the prothoracic glands of dytiscid beetles, and the quinazolinones in the defense secretions of glomerid millipedes, are less understood from a pharmacological point of view. Most of the dytiscid steroids (including testosterone) are pregnane derivatives (XIV) and they are present in surprising quantities: a Mexican *Cybister* can store as much as 1 mg of 12-hydroxy-4,6-pregnadiene-3,20-dione. Both the crude prothoracic secretions and the purified steroids are anaesthetic and sometimes lethal to fish and amphibians (Schildknecht, 1970). Glomerid millipedes expel a proteinaceous fluid which contains 1-methyl-2-ethyl-4(3H)-quinazolinone and the related 1,2-dimethyl derivative (XV). The quinazolinones have a bitter taste to man, and a delayed general toxicity to birds, mice, and spiders (Schildknecht *et al.*, 1966, 1967; Y. C. Meinwald *et al.*, 1966; Eisner, 1970).

Perhaps the most surprising defensive substance to be reported is colymbetin, a small nucleoprotein (MW > 700), produced in the defensive glands of a water beetle (*Colymbetes fuscus*). When colymbetin was injected into rats, a drastic reduction on blood pressure occurred (Schildknecht and Tacheci, 1971).

B. Allomones Promot

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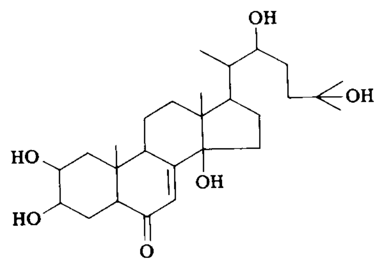
B. Allomones Promoting Symbiotic Associations

Symbiotic associations have long fascinated biologists and the respective contributions of each partner to the success of the association have been cataloged by many ingenious investigations (see Henry, 1967). In a few cases, the allomones which regulate these associations have been identified, but this vast field still awaits systematic biochemical study.

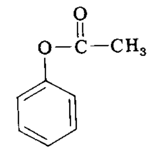
Probably the most dramatic demonstration of an allomone acting between symbiotic partners comes from the classic work of L. R. Cleveland on the wood roach *Cryptocercus* and its intestinal flagellates. The cellulose-digesting flagellates are obligate anaerobes in the hindgut of the cockroach, whose cuticle (including that of the hindgut) is shed at each molt. Before the molt, the flagellates encyst and thus survive exposure to oxygen. The signal for encystment is a chemical (ecdysone) which is also the molting hormone of the insect. In this case ecdysone is both a hormone and an allomone (Cleveland *et al.*, 1960).

Nowhere are the symbioses between two insect species more diverse and richly documented than within insect societies. In his comprehensive and very readable monograph, E. O. Wilson (1971) has graphically described the many gradations which occur between species of social insects ranging from casual association to parasitism. Many of these must involve, at the very least, a tolerance or habituation of one species to the pheromones of another. Even more bizarre are the nonsocial species which exploit the insect societies at some point in their own life cycles. These social parasites placate their hosts with secretions, which Wilson has termed "appeasement substances." The appeasement substances are often produced by a special set of epidermal glands. In *Termitella,* a staphylinid beetle which lives in the nests of nasute termites, Pasteels (1968) has painstakingly described two glandular systems: the "primary" which is common in free-living and symbiotic staphylinids, and the "secondary" which is unique to the social parasites and produces the appeasement substances. Hölldobler (1971) describes analogous glandular specialization in *Atemeles,* a staphylinid found in ant nests. When an ant worker approaches an *Atemeles,* the beetle bends the tip of its abdomen toward the ant and the ant feeds on the appeasement secretion. Next, the ant licks the "adoption gland" on the lateral margins of the beetle's abdomen, and finally, the ant carries the beetle into its nest.

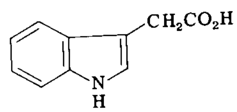
Attine ants, certain termites, and many scolytid beetles may transport, culture, and consume ectosymbiotic fungi. For each insect species there is a characteristic microflora, usually consisting of only one or two species



α-Ecdysone
(XVI)



Phenylacetic acid
(XVII)



Indolylacetic acid
(XVIII)

$$CH_3(CH_2)_6-\underset{}{\overset{OH}{\overset{|}{C}H}}-CH_2-CO_2H$$

Myrmicacin
(β-hydroxydecanoic acid)
(XIX)

Fig. 2. Allomones promoting symbiosis. XVI, Woodroach, Cleveland *et al.*, 1960; XVII, XVIII, and XIX ants, Maschwitz *et al.*, 1970; Schildknecht and Koob, 1971.

of fungi. The purity of the fungal culture maintained by these insects is intriguing, and at least for attine ants, an explanation is at hand. The ants mechanically remove alien spores from the fungus garden (Weber, 1955), provide proteolytic enzymes and amino acids which the symbiotic fungi require for optimum growth (Martin, 1970) and, according to a recent report, regulate the growth of microflora by allomones. The metapleural glands of *Atta* produce phenyl acetic acid, β-indolyl acetic acid, and β-hydroxydecanoic acid (Fig. 2) (Maschwitz *et al.*, 1970; Schildknecht and Koob, 1971). Schildknecht and his colleagues envision the role of each compound as follows: Phenylacetic acid is an antibiotic which prevents the growth of bacteria and some fungi in the fungus garden. Indoleacetic acid is, of course, a plant hormone and it is thought to promote mycelial growth of the symbiotic crop. "Myrmicacin" (β-hydroxydecanoic acid) is an inhibitor which prevents the germination of extraneous spores in the fungus garden. Growth of the symbiotic fungi is unaffected by either phenylacetic acid or myrmicacin. Myrmicacin is also found in several other ant genera,

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V. PHEROMONES

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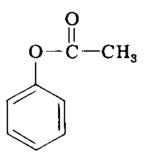
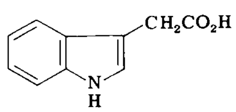


Phenylacetic acid
(XVII)



Indolylacetic acid
(XVIII)

$-CO_2H$

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notably a harvester ant (*Messor*) which collects and stores large numbers of seeds in special chambers of its nest. These seeds do not sprout during storage, apparently because Myrmicacin prevents germination.

Many scolytid beetles transport fungi within a special cuticular compartment, the mycangium (Francke-Grossman, 1967). In many species of beetle, the mycangium is a selective culture chamber; even though weed fungi can be readily isolated from the body cuticle, only the symbiotic species proliferate within the mycangium (Barras and Perry, 1972). The growth of fungi is apparently regulated by secretory cells which surround the mycangial lumen. In *Gnathotrichus* a distinct cycle of secretory activity is correlated with the period of fungal proliferation (Schneider and Rudinsky, 1969). There are two morphological types of secretory cells in the southern pine beetle, and it may be that one cell type nourishes the symbiotic crop while the other inhibits the growth of alien contaminants (Barras and Perry, 1971; Happ *et al.*, 1971).

V. PHEROMONES

Pheromones act within a defined context: between individuals of a single species. On the basis of their modes of action, pheromones can be divided into two general classes: (1) *releasers* which trigger a relatively rapid behavioral response and (2) *primers* which produce a more gradual and prolonged shift in the physiology of the recipient (Wilson and Bossert, 1963). Releasers act mainly through the nervous system, while the mechanism of primer action usually involves the endocrine system as well. Although some authors (e.g., Bronson, 1968) have objected to the ethological implications of the word "releaser," it seems to me that such a minor semantic shortcoming hardly justifies the substitution of a new term for one which is already in general use. As treated in the present chapter, releasers affect behavior, either by evoking an immediate stereotyped response or they act in concert with other stimuli to bias the behavior of the recipient.

Communication systems are found in all animal species, although they are most highly developed in social forms. Within insect societies and within local populations of vertebrates, odor signals play many specific roles; at least a score of situations can be listed for mammals (Mykytowycz, 1970). For the purposes of this chapter, releaser pheromones will be discussed under four general headings: (1) alarm, (2) recruiting, (3) reproductive, and (4) recognition. In each case, selection has influenced both the rate of emission of the signal and the response threshold of the target organisms to favor optimum efficiency of the signal system.

A. Alarm Substances

Alarm substances communicate the presence of danger. The classic demonstration of such a chemical signal stems from the work of Karl von Frisch on the minnow *Phoxinus* (von Frisch, 1941). Von Frisch removed one minnow from a normal school, and after slightly injuring the minnow, returned it to the school. The school promptly dispersed. In a series of experiments, von Frisch demonstrated that the stimulus for dispersal was a water-borne chemical substance (Schreckstoff), and that the intensity of the response to this signal varied with its concentration and also with the physiological state of the recipient. Analogous alarm substances have been found in many fish species (Bardach and Todd, 1970). In each case, they are liberated after injury, and Pfeiffer (1962, 1963) has argued that the likely sources in some species are the club cells of the epidermis. Aside from von Frisch's (1941) data which indicate that Schreckstoff retains its potency after 5 minutes of boiling but is partially inactivated by longer boiling, almost nothing is known of the chemical nature of these substances.

Alarm substances (variously known as fright substances, warning substances, fear substances, etc.) have been found in other vertebrate groups. Tadpoles of the toad *Bufo vulgaris* produce a substance (perhaps steroidal) which elicits the fright reaction in other *Bufo* tadpoles (Eibl-Eibesfeldt, 1949; Hrbacek, 1950). Cloacal secretions may evoke an alarm reaction in snakes (Burghardt, 1970). When red foxes are alarmed, they release a mixture of short-chain carboxylic acid from their anal glands (Albone and Fox, 1971). Among rodents, alarm substances have been demonstrated in the urine of traumatized house mice (Müller-Velten, 1966), laboratory rats (Valenta and Rigby, 1968), and golden hamsters (Sherman, unpublished). It is surprising that few chemical characterizations of vertebrate alarm substances have been attempted, for since the evasive behavior is repeatedly and easily evoked, a quantitative bioassay for monitoring chemical fractions during purification could certainly be devised.

Among social insects, alarm substances are widely used to signal the presence of an intruder into the nest (Maschwitz, 1964, 1966; Butler, 1967; Blum, 1969; Gabba and Pavan, 1970; Stuart, 1970; Wilson, 1971). In at least some ant species, the alarm substance serves two roles: at low concentrations it attracts other workers while at higher concentrations it produces a state of high excitement and releases attack behavior (Wilson, 1958; Moser, 1970). Thus the alarm substance acts not only to alert other workers to the presence of danger but also to recruit other workers for a collective defense effort. Alarm substances are often

$CH_3(CH_2)_9CH_3$ (

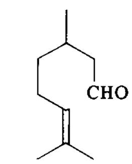
Undecane

(XX)

$(CH_3)_2CHCH_2CH_2O\overset{O}{\overset{\|}{C}}CH_3$ CH_3

Isoamyl acetate Tet

(XXIII)



Citronellal

(XXVI)

Fig. 3. Representative alarm pher
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workers while at higher concentra-
itement and releases attack behavior
the alarm substance acts not only
ence of danger but also to recruit
se effort. Alarm substances are often

$CH_3(CH_2)_9CH_3$
Undecane
(XX)

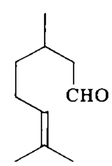
$CH_3(CH_2)_5C(=O)CH_3$
2-Heptanone
(XXI)

$CH_3(CH_2)_2CH(CH_3)C(=O)CH_2CH_3$
4-Methyl-3-heptanone
(XXII)

$(CH_3)_2CHCH_2CH_2OC(=O)CH_3$
Isoamyl acetate
(XXIII)

$CH_3(CH_2)_{12}CH_2OC(=O)CH_3$
Tetradecyl acetate
(XXIV)

$CH_3{-}S{-}S{-}CH_3$
Dimethyl disulfide
(XXV)



Citronellal
(XXVI)

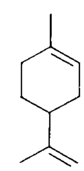

Limonene
(XXVII)

Fig. 3. Representative alarm pheromones. XX, Formicine ants; XXI, bees, dolichoderine ants; XXII, myrmicine ants; XXIII, honeybees; XXIV, formicine ants (Bergstrom and Löfqvist, 1968; Regnier and Wilson, 1971); XXV, ponerine ants; XXVI, formicine ants; XXVII, termites. Unless otherwise indicated, references in Blum, 1969; Gabba and Pavan, 1970; Wilson, 1971; Law and Regnier, 1971.

emitted concurrently with defensive allomones, and may facilitate the penetration of toxicants through cuticular barriers (Ghent, 1961).

In order to effectively communicate danger and to accurately pinpoint its locus, an alarm substance must be volatile and the active space should be moderately small. Wilson and Bossert (1963) predicted that most alarm substances would have molecular weights of 100–200 and their Q/K ratios would be intermediate (10^2–10^4) so that the active space is about 10 cm in radius and that it expands and fades out within minutes. At least twenty alarm substances of insects have been identified (Blum, 1969) (see Fig. 3). Many appear to meet the criteria set forth by Wilson and Bossert (1963). C_6–C_8 ketones (XXI, XXII) or esters (XXIII, XXIV) predominate in the social Hymenoptera while termites utilize terpenoid hydrocarbons (XXVII). Often a mixture of several substances, produced by several glands, individually or collectively evoke alarm behavior (Regnier and Wilson, 1968).

Alarm pheromones are sometimes exploited for offense. Robber bees

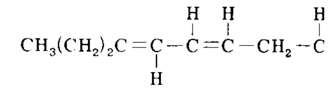
(*Lestrimelitta limao*) obtain their protein by plundering the nests of other stingless bees (*Trigona* spp.) (Moure *et al.*, 1958). Citral (Fig. 1, XII), produced by the mandibular glands of *Lestrimelitta* workers when they attack a nest of *Trigona*, attracts other *Lestrimelitta* and pervades the nest of *Trigona*. Citral also causes disorientation and dispersal of the *Trigona*, and thus allows *Lestrimelitta* to plunder the nest without serious opposition (Blum, 1966). An analogous situation is found in slave-maker ants (*Formica sanguinea*). As *F. sanguinea* raid other colonies to obtain slave workers, the raiders expel their alarm pheromones (a mixture of decyl, dodecyl, and tetradecyl acetates). The mixture, dubbed "propaganda substances," produces apparent panic in the workers of the colony under attack and thus any organized defense is precluded (Regnier and Wilson, 1971).

Danger to one species is often danger to many. The alarm vocalizations of many species of passerine birds are almost identical, and thus different species alert one another (Marler, 1959). Alarm pheromones also act interspecifically: Maschwitz (1964) has shown that common alarm substances are often found throughout genera or even subfamilies of social Hymenoptera. Rodent alarm pheromones have yet to be analyzed in this regard. Only three species of rodents have been studied and the experiments were confined to artificial laboratory situations. In the wild, alarm pheromones most probably affect dispersal and therefore they are density-regulating. If species-specificity is low, then the sharing of a chemical signal must influence interspecies interactions as well. The possibility deserves investigation.

B. Recruitment Pheromones

Chemical signals are employed by worker castes of social insects to guide their nest mates to a food source. These signals are of two kinds: stationary scent marks at the site of the food and chemical trails which lead to it (Gabba and Pavan, 1970; Blum, 1970; Moser, 1970; Wilson, 1971; Stuart, 1970).

Trail substances are common in ants and termites. The trail is laid by workers returning to the nest from a food source. The details of the trail laying behavior vary with the particular biology of each species. In fire ants the gland producing the trail substance is associated with the sting (Wilson, 1962) while in termites, the trail substance is produced by sternal glands (see Stuart, 1970 for references). The trail substance left behind the returning forager forms an active space which guides outgoing foragers. At least in fire ants, the Q/K ratio is quite small so that the active space is narrow and, unless other returning



cis-3, *cis*-6, *trans*-8-Dodec

(XXVIII)

H

Fig. 4. Trail substances. XXVIII, Ter
(Hummel and Karlson, 1968); XXX, a

foragers reinforce the original tr
onds (Wilson, 1962). Hangartne
of the ant *Lasius fuliginosus* ac
the active space of the trail and a
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Very few trail substances hav
Hummel and Karlson (1968) hav
bon ($C_{11}H_2O$) and hexanoic ac
Zootermopsis and Moore (1966
($C_{20}H_{32}$) plays this role for *N*
have shown that *cis*-3, *cis*-6, *tr*
probably the trail substance of *R*
et al. (1971) have identified 4-
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follow a trail which contains les
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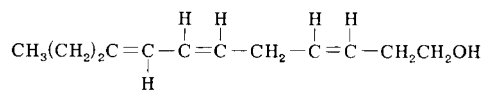
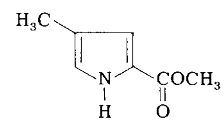
Although trails are rare in flyi
(Meliponi) are exceptions. As e
(1958, 1960), foragers returning
3 meters to mark tufts of vege
their mandibular glands. Outgoi
and returning recruits reinforce



cis-3, *cis*-6, *trans*-8-Dodecatriene-1-ol
(XXVIII)

$CH_3(CH_2)_4CO_2H$

Hexanoic acid
(XXIX)



4-Methylpyrrole-2-carboxylate
(XXX)

Fig. 4. Trail substances. XXVIII, Termite (Matsumura *et al.*, 1968); XXIX, termite (Hummel and Karlson, 1968); XXX, attine ants (Tumlinson *et al.*, 1971).

foragers reinforce the original trail, the trail evaporates within 100 seconds (Wilson, 1962). Hangartner (1967) showed that outgoing foragers of the ant *Lasius fuliginosus* actually weave from side to side within the active space of the trail and apparently turn back toward the original trail whenever the concentration of the pheromone falls below *K*.

Very few trail substances have been identified (Fig. 4). In termites, Hummel and Karlson (1968) have implicated a non-terpenoid hydrocarbon ($C_{11}H_{20}O$) and hexanoic acid (XXIX) as the trail substance for *Zootermopsis* and Moore (1966) belives a diterpenoid hydrocarbon ($C_{20}H_{32}$) plays this role for *Nasutitermes*. Matsumura *et al.* (1968) have shown that *cis*-3, *cis*-6, *trans*-8 dodecatrienol (XXVIII) is most probably the trail substance of *Reticulitermes*. Very recently Tumlinson *et al.* (1971) have identified 4-methyl-pyrrole-2-carboxylate (XXX) as the trail substance of the leaf-cutting ant *Atta texana*. Ant workers will follow a trail which contains less than 10^{-13} gm/cm (3.48×10^{8} molecules/cm). One-third milligram is sufficient to lay a trail around the earth! Unlike the short-lived trails of *Solenopsis* (Wilson, 1962), those of *Atta* persist for several days (Moser, 1970).

Although trails are rare in flying insects, certain South American bees (Meliponi) are exceptions. As elegantly shown by Lindauer and Kerr (1958, 1960), foragers returning from a food source pause every 2 or 3 meters to mark tufts of vegetation with droplets of secretion from their mandibular glands. Outgoing foragers follow the aerial odor trail, and returning recruits reinforce the scent marks. Blum and associates (cited in Blum, 1970) have recently identified some of these secretions. In *Trigona postica,* ten methyl ketones, benzaldehyde, and two hydrocarbons are present. In *T. tubiba,* eight of the methyl ketones are lacking. It is quite possible that the collective effect of several molecules allows workers to distinguish trails of their own species.

Are other trail pheromones species specific? The answer is unclear and is complicated by the fact that results in the laboratory (where many species follow one anothers' trails) seem in conflict with the field data, which suggest species and even nest specificity. It may be that in addition to the primary trail pheromone, each nest has its own dialect due to minor components (Blum, 1970).

Although the dance language of honeybees seems to be the major communication system used for recruitment over some distance (von Frisch, 1967), pheromones play a role in short-range attraction. When a worker honeybee has located a good food source, she often exposes her abdominal Nasanov gland and fans her wings. The acylic terpenes emitted from this gland, which include geraniol, citral (both isomers), geranic acid, and nerolic acid, attract other foragers (Boch and Shearer, 1962; 1964; Butler and Calam, 1969). According to Butler and Calam (1969), citral is the most attractive constituent.

C. Sex Pheromones

Scents influence reproductive behavior in many species. The chemical signals may act either as attractants which bring the sexes together or aphrodisiacs which trigger specific aspects of precopulatory or copulatory behavior.

The most studied communication systems are those of nocturnal Lepidoptera. In a typical situation, a stationary female exposes a gland in her abdomen from which attractant molecules diffuse into the surrounding air. Air movements cause the active space to form a scent plume extending downwind from the female. When pheromone concentration exceeds the threshold for the males, they fly to the female. It seems unlikely that the males find the female by following a concentration gradient per se, but rather they orient by anemotaxis, i.e., merely flying upwind. By a very convincing series of experiments with flightless male silkmoths which ran along a surface to find "calling" females, Schwinck (1958) showed that the orientation to females is a two-step process: at low concentrations of pheromone, the males run upwind, and at high concentrations they search randomly. Thus anemotaxis accounts for long-distance orientation while random search apparently suffices when females are nearby.

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rientation to females is a two-step
ıeromone, the males run upwind,
ch randomly. Thus anemotaxis ac-
while random search apparently

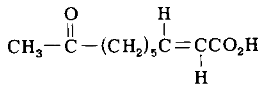
Females emit their signals only in the proper context: females call only in the early hours of the evening and female *Polyphemus* moths call only in the presence of 2-hexenal, a volatile constituent of their food plant (Riddiford, 1967). The majority of the attractants which have been isolated are long-chain alcohols, esters, or acids (Fig. 5). Most often, a single molecular species appears to constitute the signal and the differences between species may appear slight. For example, two species of gelechid moths utilize 9-tetradecenyl acetate (XXXIII) as a sex attractant, but one species produces the *trans*-isomer and the other the *cis*-isomer. Furthermore, each isomer attracts only conspecific males and inhibits the response of the other species to its own isomer (Roelofs and Comeau, 1969).

Although one might expect that every species would emit its own unique molecular signal, such is not the case. Often, signal ambiguity is avoided in spite of chemical overlap because the species are temporally, geographically, or ecologically isolated. In other species, minor synergistic chemicals apparently prevent signal ambiguity (Brady *et al.*, 1971).

Upon reaching the female, the male may release an aphrodisiac which induces the female to mate. In noctuid moths, the aphrodisiac is liberated from special scent brushes everted from the male's abdomen (Birch, 1970). In noctuids the molecules are small and highly volatile, for example, butyric acid or benzaldehyde (Alpin and Birch, 1970). Birch (1970) showed that after surgical removal of the brushes, the females were unresponsive and mating was unsuccessful.

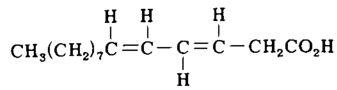
For many day-flying butterflies, visual cues mediate long-distance attraction of the sexes and many specific stages in the courtship sequence. However, for the queen, the monarch, and other danaid butterflies, an aphrodisiac pheromone is required for successful copulation. The aphrodisiac is produced in the eversible hair pencils of the male and dusted onto the antennae of the female (Brower *et al.*, 1965; Pliske and Eisner, 1969). The molecule which seduces the female queen is a ketonic pyrrolizidine (methyl 1,2,3-dihydro-1*H*-pyrrolizidin-1-one, XL) (Meinwald *et al.*, 1969; Pliske and Eisner 1969).

Sex attractants of several coleopterans have been chemically characterized. The female black carpet beetle (*Attagenus*) attracts the male by emitting megatomic acid (XXXII) (Silverstein *et al.*, 1967), a substance rather like those produced by many female Lepidoptera. Four attractant substances are produced by female *Trogoderma*, two of which have been identified as a C_{16} alcohol and a methyl ester of the corresponding C_{16} acid (Rodin *et al.*, 1969). The male boll weevil (*Anthomonas*) produces a mixture of two terpenoid alcohols (XXXVIII, XXXIX) and



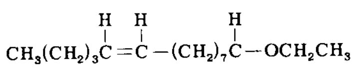
Honeybee queen substance
(*trans*-9-keto-2-decanoic acid)

(XXXI)



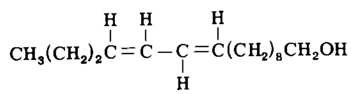
Megatomic acid (*trans*-3, *cis*-
5-tetradecadienoic acid)

(XXXII)



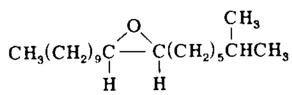
cis-9-Tetradecyl acetate

(XXXIII)



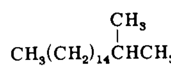
Bombykol (*trans*-10, *cis*-
12-hexadecadien-1-ol)

(XXXIV)



Disparlure (*cis*-7, 8-epoxy-
2-methyl octadecane)

(XXXV)

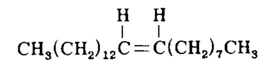


2-Methyl heptadecane

(XXXVI)

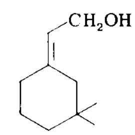
Figs. 5 and 6. Representative sex pheromones. XXXI, Honeybee queen; XXXII, female black carpet beetle; XXXIII, female gelecid moth; XXXIV, female silkmoth; XXXV, female gypsy moth; XXXVI, female arctiid moths (Roelofs and Cardé, 1971); XXXVII, female housefly (Carlson *et al.*, 1971); XXXVIII and XXXIX, male boll weevil; XL, male danaid butterflies; XLI, male muskdeer (Lederer, 1950). Unless otherwise indicated, references in Law and Regnier (1971).

two aldehydes which act synergistically to attract the females (Tumlinson *et al.*, 1969) (Fig. 6). In the scolytid beetle, *Ips confusus*, male feces contain a mixture of three terpene alcohols which attract both sexes and all three are required for full biological activity (Silverstein *et al.*, 1966). Although Vite (1967) has pointed out that these substances are not true sex attractants (since they primarily promote aggregation), mating occurs within these aggregations and I will therefore include them in this section. In other scolytids of the genus *Dendroctonus*, a series of terpenoid compounds, produced by males or females, promote the aggregations and thus allow mating (see Silverstein, 1970 for references). The most interesting feature of these coleopteran pheromones is that, at least for several species, the signal is a medley of several substances.



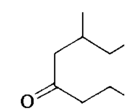
cis-9-Tricosene

(XXXVII)



cis-3, 3-Dimethyl-$n^{1,\beta}$
cyclohexane ethanol

(XXXIX)



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Sex pheromones have been iden
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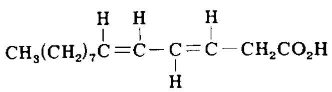
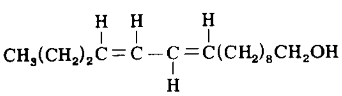


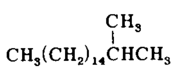
Megatomic acid (*trans*-3, *cis*-5-tetradecadienoic acid)

(XXXII)



Bombykol (*trans*-10, *cis*-12-hexadecadien-1-ol)

(XXXIV)



2-Methyl heptadecane

(XXXVI)

ıones. XXXI, Honeybee queen; XXXII, gelecid moth; XXXIV, female silkmoth; .le arctiid moths (Roelofs and Cardé, et al., 1971); XXXVIII and XXXIX, ;; XLI, male muskdeer (Lederer, 1950). and Regnier (1971).

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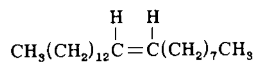
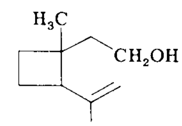


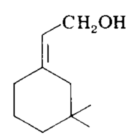
cis-9-Tricosene

(XXXVII)



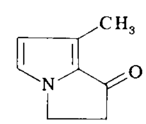
cis-2-Isopropenyl-1-methylcyclobutane ethanol

(XXXVIII)



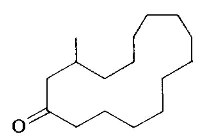
cis-3, 3-Dimethyl-$n^{1,\beta}$ cyclohexane ethanol

(XXXIX)



2, 3-Dihydro-7-methyl-1*H*-pyrrolizin-1-one

(XL)



Muskone

(XLI)

See legend on page 170.

Sex pheromones have been identified for many other insects, including houseflies (*cis*-9-tricosene (XXXVII); Carlson *et al.,* 1971) and honeybees (9-keto-2-decenoic acid (XXXI); Gary, 1962). Assembly scents (esters, alkanones, alcohols, hydrocarbons) which attract conspecifics of both sexes are produced by the mandibular glands of male bumblebees (Kullenberg *et al.,* 1970). Aphrodisiacs have been reported for numerous insect species, for example "seducin" produced by some male cockroaches (*Nauphoeta cinerea*) (Roth and Dateo, 1966).

Although it is known that many vertebrates possess sex pheromones (principally aphrodisiacs), relatively little chemical information is available. A number of fish (Bardach and Todd, 1970; also Losey, 1969; Rossi, 1969; Gandolfi, 1969) produce aphrodisiacs. Newts apparently possess sex attractants (Twitty, 1955). The musk glands of male alligators produce yacarol, a mixture of compounds including citronellal (Lederer, 1950), which may be attractive to females (Burghardt, 1970). The complex mammalian secretions used by the perfume industry, including muskone from male musk deer (XLI), civetone from male civet cats, and beaver castoreum (Lederer, 1950) may well be sex pheromones or territorial markers. Most of the putative mammalian sex pheromones have a musky odor and are large cyclic compounds, either steroids (such as the "boar taint substance") or cycloketones (muskone and civetone). The proposition that man may have similar pheromones has been delightfully argued by Comfort (1971a, b). Unfortunately, there is little experimentally derived data on the exact roles of these musky scents in the reproduction of any mammal.

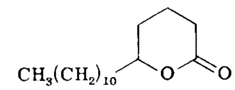
Many female mammals indicate their physiological readiness to mate by emitting characteristic scents (Gleason and Reynierse, 1969; Le Magnen, 1970; Mykytowycz, 1970). Recently, Michael, Keverne, and their co-workers have shown that vaginal secretions of receptive female rhesus monkeys contain an aphrodisiac pheromone which they call "copulin." Copulin production is estrogen-dependent, and thus copulins are not present in ovariectomized females (Michael and Keverne, 1970). Topical application of estrogen-stimulated vaginal secretions on to the sexual skin of ovariectomized females renders these females attractive to males which respond by mounting, ejaculation, or masturbation. Ovariectomized females were used routinely for bioassay of gas-chromatographic fractions from vaginal secretions, and the copulins have been identified. They comprise a mixture of a short-chain acids, namely acetic, propionic, isobutyric, isovaleric, and isocaproic (Michael *et al.*, 1971; Curtis *et al.*, 1971).

D. Territoriality and Recognition Scents

Pheromones are widely used to mark territories in mammals (Gleason and Reynierse, 1969; Mykytowyctz, 1970; Ralls, 1971). With the exception of the musky scents exploited by perfumery (Lederer, 1950), little is known of their chemical nature. These scents may be deposited in dung or urine or they may be produced by special glands, for example, the chin glands of rabbits (Mykytowycz, 1970).

It is often difficult to distinguish between scents which label a territory, scents which signal social status, and scents which allow individual recognition. In mammals, a medley of exocrine products may play all three roles.

The "colony odors" of ants, bees, and wasps have long been recognized but have resisted precise chemical characterization to date. Perhaps this



5-Hydroxydecanoic acid lactone

(XLII)

Fig. 7. Recognition pheromones. XL
XLIII, male black-tailed deer, (Brownl

is because these odors are actuall
is influenced by diet and micro
social status is also mediated l
and 9-hydroxy-2-decanoic acid
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In many vertebrates, mother-yo
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E. Prim

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Primers may be produced by
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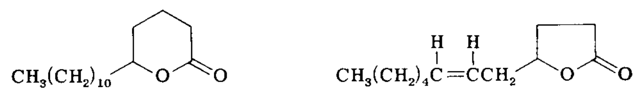

5-Hydroxydecanoic acid lactone

(XLII)

cis-4-Hydroxydodec-6-enoic acid lactone

(XLIII)

Fig. 7. Recognition pheromones. XLII, Oriental hornet queen (Ikan *et al.*, 1969); XLIII, male black-tailed deer, (Brownlee *et al.*, 1969).

is because these odors are actually medleys, and the scent of each colony is influenced by diet and microhabitat (Wilson, 1971). Recognition of social status is also mediated by pheromones; 9-keto-2-decanoic acid and 9-hydroxy-2-decanoic acid produced by queen honeybees causes settling of worker swarms (Butler and Simpson, 1967), while δ-*n*-hexadecalactone (Fig. 7, XLII) produced by a queen hornet (*Vespa orientalis*) attracts workers and stimulates them to build new queen cells at the appropriate season (Ikan *et al.*, 1969).

In many vertebrates, mother-young recognition is dependent on chemical cues (Gleason and Reynierse, 1969). Within a local population, social status is often correlated with urination; for example, the urine of male mice contains a pheromone that increases aggression in other males. The urine from dominant male mice is more potent than that from submissive ones (Mugford and Nowell, 1970).

Only one known vertebrate recognition scent has been chemically identified: *cis*-4-hydroxydodec-6-enoic acid lactone (XLIII) produced by the tarsal glands of male black-tailed deer (Brownlee *et al.*, 1969; Müller-Schwarze, 1969). The female deer lick and nuzzle the tuft of hair associated with the tarsal gland and apparently distinguish between individuals on the basis of the tarsal scent. Several components are present in the natural secretion, and the lactone is merely one. For a maximum response from the female, at least four components are necessary (Müller-Schwarze, 1969).

E. Primer Pheromones

The actions of primer pheromones are more covert than are those of the releasers discussed above, for primers regulate physiological functions of a recipient. Primers may inhibit, accelerate, or synchronize reproductive maturation and/or reproductive cycles in the target organisms. Primers may be produced by either or both sexes and may operate on males or females. For the desert locust (*Schistocerca gregaria*), mature males give off a scent which accelerates reproductive maturation of young males (Loher, 1961), and mature mealworm beetles of both sexes emit a scent which increases the rate of ovarian growth in young females (Happ *et al.*, 1971).

The development of the various castes in insect societies is largely regulated by pheromones. The mandibular glands of queen honeybees produce 9-keto-2-decanoic acid and 9-hydroxy-2-decanoic acid which inhibit both the growth of ovaries of worker bees and the building of queen cells by the workers (Butler and Fairey, 1963; Butler and Callow, 1968). In a series of elegant experiments, Lüscher and his co-workers have shown that several pheromones regulate differentiation of worker termites into reproductives in *Kalotermes flavicollis*. In the termite colony, there is normally only one functional reproductive of each sex. Each royal male or female produces an inhibitory pheromone which prevents reproductive maturation of pseudergate workers of the same sex. In the absence of the appropriate inhibitor, a pseudergate molts several times and transforms into a replacement reproductive. In addition, the royal male produces a pheromone which accelerates transformation of pseudergate females. The pheromones are passed by contact, from the royal pair to pseudergates and thence between pseudergates (Lüscher, 1961).

Although primer pheromones are suspected in many mammalian species, they have been clearly demonstrated in only one order, Rodentia. At least four distinct roles are played by primer pheromones in mice (Wilson, 1970; Whitten and Bronson, 1970). The *Lee–Boot effect* is a suppression of estrous and the development of pseudopregnancy in over 50% of the females when four or more females are grouped together and a male is not present (Lee and Boot, 1955). The *Whitten effect* is the induction or acceleration of the estrous cycle in the female mouse when she is exposed to an odor from male urine. This effect is most clearly seen in groups of females (after the Lee–Boot effect), (Whitten, 1958). The *Bruce effect* is a failure of implantation and rapid return to estrous in a female mouse which has been exposed to the odor of a strange male whose odor is unlike that of her stud (Bruce, 1960). The *Ropartz effect* describes the adrenal hypertrophy which occurs when isolated mice are exposed to the odor of other mice (Ropartz, 1966, 1968). Most of these investigations have utilized laboratory mice, and demonstration of similar effects in laboratory rats has been difficult. However, many of the experiments have been repeated with deermice (*Peromyscus*) and thus the phenomena may be widespread among rodents (Bronson and Eleftheriou, 1963; Bronson and Marsden, 1964; Bronson and Dezell, 1968).

The physiological effects of these pheromones are usually statistical, and attempts to develop quantitative bioassay techniques have been discouraging (Whitten and Bronson, 1970). The lack of reliable assays probably accounts for the fact that none of the molecules have been identified. The adaptive significance of these pheromones is unclear, although both the Lee–Boot and Ropartz effects may contribute to the well-known stress syndrome observed in cases of very dense rodent populations (Wilson, 1970; Whitten and Bronson, 1970).

F. Pheromone Perception

Airborne pheromones are detected by primary olfactory sense cells in the antennae of mandibulate arthropods and the nasal epithelia of vertebrates. An analysis of the primary transduction at the receptor and the processing of information in the central nervous system is prerequisite to an understanding of the characteristics of the signal system. The analysis is far from complete.

Both behavioral studies, such as those cited earlier, and the capacity of the appropriately educated human nose attest to the fact that vertebrates can distinguish a large number of specific odorants. The discriminative powers are extremely refined: some pairs of enantiomeric isomers differ in their smell (Russell and Hills, 1971; Friedman and Miller, 1971; Leitereg *et al.*, 1971). Neurophysiological investigations of the vertebrate nasal epithelium and its primary receptor cells provide only slight insight into the olfactory process. In their excellent study of olfaction in the frog, Gesteland *et al.* (1965) recorded from a large number of individual receptors; specific odorants produced shifts in the rather irregular background firing of each unit. Each individual unit is odor-selective, i.e., sensitive to a certain set of molecular species and, within this set, some molecules increase the frequency of action potentials while others inhibit depolarizations. The units are highly heterogeneous, and could not easily be grouped into distinct classes. Downstream, the primary fibers terminate in the glomeruli of the olfactory bulb. On anatomic grounds, one can argue that the dendritic field of the mitral, tufted, and plexiform cells within the bulb are capable of filtering and consolidating the signals from the primary fibers. If a few molecules are to trigger a behavioral response, some sort of signal amplification is probably necessary. Recently, Nicoll (1971) has obtained neurophysiological evidence that recurrent axons from mitral and tufted cells run back into the external plexiform layer and within this layer excite other mitral or tufted cells. Positive feedback via the recurrent axons could be the basis of signal amplification.

In vertebrates, relatively few studies have concerned pheromone reception *per se,* and those few have been primarily concerned with a demonstration that olfaction was involved in the response to the molecules. Anosmic minnows do not react to Schreckstoffe (von Frisch, 1941), nor do anosmic female mice exhibit the Lee–Boot or Whitten effects (Lee and Boot, 1956; Whitten, 1965). Repeated topical application of male urine on to the nostrils of intact female mice produces the Whitten effect (Marsden and Bronson, 1964). Male rhesus monkeys may be rendered reversibly anosmic with noseplugs; when the noseplugs are in place, the males do not resond to the female copulins (Michael and Keverne, 1968).

A recent study by Pfaff and Gregory (1971) employed putative crude pheromone (namely the urine of female rats) in an attempt to analyze coding in the olfactory bulb and medial forebrain bundle of normal and castrated male rats. It had previously been shown that urine from "estrous females" evokes more intense male exploratory behavior than does that from ovariectomized females (Pfaff and Pfaffmann, 1969). Pfaff and Gregory (1971) were unable to detect units in the olfactory bulb or preoptic area which responded *exclusively* to estrous female urine, but 24% of the units in the olfactory bulb and 58% of the units if the preoptic area did respond differentially to urine of estrous and ovariectomized females. Perhaps the difference between the areas reflects the signal amplification suggested by Nicoll (1971).

Electrophysiological studies of pheromone reception in insects have met with considerable success. The neural response to pheromone stimuli has been monitored on three levels: at the individual olfactory sensillum over the antennae as a whole, and in the antennal lobe of the brain. The most extensive studies are those of Dietrich Schneider and his associates on the antennae of the domestic silkmoth *Bombyx mori* (see Schneider, 1969, 1970 for references).

When whole antennae of male *Bombyx* were exposed to bombykol, the sex attractant of the female, Schneider detected a slow potential shift of a few millivolts—termed the electroantennogram (EAG). The magnitude of the EAG is proportional to the logarithm of bombykol concentration and apparently the EAG represents the summed generator potentials of many receptor cells. Microelectrode studies of individual receptor cells revealed that they fall into two classes: odor specialists which react only to the pheromone, and odor generalists which respond to a variety of scents but differ widely from one another. Many odor specialists are present, at least 25,000 on each antenna (Kaissling and Priesner, 1970). By using tritiated bombykol, it has been possible to estimate accurately how many molecules of bombykol are necessary

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at each receptor for a unit response, and how many units must be affected to trigger a behavioral response. At behavioral threshold, 200–300 molecules of bombykol are available to 25,000 cells. By application of Poisson statistics, it was calculated that 99% of the units were stimulated by only a single molecular hit (Kaissling and Priesner, 1970). EAG's in response to pheromones have been recorded in other Lepidoptera as well in cockroaches and bark beetles (Payne, 1970 and references therein).

To my knowledge, recording from the antennal lobes has been successful with only two species, the American cockroach (Yamada, 1971) and the mealworm beetle (Freundlich and Happ, unpublished). In the male mealworm some of the units (presumably at least second order) in the antennal lobe responded differentially to the scents of male and of female beetles, while certain of the units in the cockroach antennal lobe were specialists for partially purified pheromones.

How specific are the specialist receptor cells? For *Bombyx*, the behavioral threshold concentration for bombykol (hexadeca-10-*trans*, 12-*cis*-dien-1-ol) is at least two orders of magnitude lower than the related *cis-trans* isomers (Schneider, 1963). Theories to explain the mechanisms by which primary sense cells detect odorant molecules are numerous, but the most recent debate has concerned two alternatives: the vibrational theory advocated by Wright (1966) and the stereochemical theory espoused by Amoore (1964). The bulk of the evidence on pheromone perception in insects favors the stereochemical interpretation. Potency of structural analogs is well correlated with the similarity between the size and shape of the analog and that of the natural pheromone (Amoore *et al.*, 1969). Blum *et al.* (1971a) screened 99 ketones (C_2–C_{13}) for their effectiveness in releasing the alarm response in the harvester ant *Pogonomyrmex badius*. Two of the 99 were maximally potent: 4-methyl-3-heptanone, the natural pheromone identified by McGurk *et al.* (1966), and 4-methyl-3-hexanone. Structural similarities are obvious. Furthermore, deuteration of these substances, which shifts their vibrational spectra, has no effect on their biological activity, and this fact argues against the Wright theory. Other studies using analogs of alarm substance in honeybees (Boch and Shearer, 1971) and a trail substance of termites (Tai *et al.*, 1971) also support the Amoore explanation.

When both the natural pheromone and an analog are presented simultaneously, the analog can inhibit or act synergistically with the natural pheromone. Roelofs and Comeau (1971a) have demonstrated such interaction between *cis*-11-tetradecenyl acetate and a series of analogs of this attractant for male red-banded leaf rollers (Torticidae: Lepidoptera). Both synergists and attractants are similar to the natural pheromone, and in fact, all chemicals which are attractant or attractant-modifying elicit strong EAG's (Roelofs and Comeau, 1971b). It may be that the modifiers affect the time course of sensory adaptation or central habituation to the natural pheromone, i.e., inhibitors accelerate habituation while synergists prolong habituation (Roelofs and Comeau, 1971a).

In a fascinating paper, Riddiford (1970) reported that after antennae of male saturniid moths (*Anthera pernyi*) had been exposed to tritiated female scent, a saline wash of the antennae contained a radioactively labeled protein. This protein might serve to convey the attractant through overlying fluid to the sense cell, or it might be the "receptor protein" on the surface of the cell membrane.

VI. EXOCRINES AND ENDOCRINES

Chemical regulatory systems are ubiquitous. Semiochemicals occur not only in metazoans but also in protozoans (Siegel and Cohen, 1962; Starr, 1968). Most probably, chemical signals between unicellular organisms appeared early in the evolution of living systems, and as Wilson (1970) has suggested, "pheromones are in a special sense the lineal ancestors of hormones." Among the lower plants, chemical signals between reproductive cells have been classed as hormones (Raper, 1970) or pheromones (gamones) (Müller *et al.,* 1971). In these forms, the distinction is largely a matter of the taste of the experimenter. Both in their origins and in their interactions, one can see the close relationships between the internal and the external signal systems.

Hormones act within a single organism, pheromones between genetically similar organisms (of the same species), and allomones between genetically dissimilar organisms. The internal system should be relatively free of noise, since sender–molecule–milieu–target are all part of a closed system and are co-adapted for efficient communication. Chemical noise is inevitable in the external milieu through which pheromones and allomones are transmitted. For pheromones and symbiotic allomones, the selective pressures operate on both the producer and the target organism to favor an appropriate diffusible molecule which is emitted at reasonable rates by the producer and is discriminated at optimum distance by the target. For defensive allomones, selection operates on the producer to favor signal efficiency and on the target to favor mechanisms which allow the signal to be ignored. Thus the most common defensive allomones are general toxicants.

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Similar carbon chains form the skeletons of the signals which constitute allomones, pheromones or hormones. The same molecule may function in two of the categories, for example ecdysone (a symbiotic allomone and molting hormone of the cochroach *Cryptocercus*) and citral which acts as a defensive allomone, an alarm substance, a recruitment substance, and a propaganda substance in ants. In spite of the almost unlimited structural diversity theoretically possible for chemical signals (see Wilson and Bossert, 1963), only a few classes of molecules are commonly utilized: aliphatics, terpenoids, peptides (hormones), and in a few cases, small cyclic compounds. The explanation of this conservatism, "biochemical parsimony" as Blum (1969) has termed it, is probably two-fold: first, a sort of Hendersonian "fitness" (Henderson, 1958) of those molecules which diffuse properly, and second, the fact that it is easier for cells to make some carbon skeletons than others. It is simpler to modify a pre-existing pathway than to develop an entirely new one. When unusual carbon skeletons are found (e.g., iridomyrmecin) their biogenesis from intermediates in pre-existing pathways can be predicted.

Some generalizations about the molecules employed as allomones and pheromones are possible. In general, the requirements of volatility and reasonable specificity, enunciated so clearly by Wilson and Bossert (1963), have been supported by the chemical identifications over the last decade. For the most part, defensive allomones are distinguished by a functional group (often carbonyl) which renders the molecule reactive and toxic. The more specific pheromones, such as sex attractants, tend to be less reactive and to have a certain structural rigidity. Sex attractants are often terpenoid or *unsaturated* fatty acid derivatives. As Clayton (1970) has suggested, the unsaturation introduces structural rigidity which makes the geometric shapes of these fatty acid derivatives, like that of terpenes, quite highly defined. Such speculation is of course consistent with the stereochemical theory of olfaction (Amoore, 1964), and the discrimination of *cis-trans* isometers from one another (Schneider, 1963). In spite of the fact that only a few chemical classes are utilized, many distinct signals are possible because of the specificity of the biochemical pathways which produce them, and also the specificity of the receptors which detect them.

An increasing number of chemical signals are proving to be medleys of several substances. Theoretically this allows an increase in information if the various molecular species all diffuse at a common rate. One might expect medleys to be more common at close range (copulins of rhesus monkeys or tarsal scent of deer) than at great distances.

Pheromones influence the endocrine system and endocrines influence both pheromone output and receptivity to pheromones. The pheromone regulation of endorcine activity is most dramatically seen in the effects of primer pheromones. Both in social insects (Wilson, 1971) and in mice (Whitten and Bronson, 1970), odors control endocrine gland size and the effects of the pheromone may be prevented by hormone injections. It is also apparent that physiological state, including endocrine activity, affects emission. In cockroaches (Barth, 1961), saturniid moths, (Riddiford and Williams, 1971), mealworm beetles (Menon, 1970), and rhesus monkeys (Michael and Keverne, 1970), a certain endocrine state is prerequisite to pheromone production. Also, an increase in the behavioral response of insects to sex pheromones often accompanies reproductive maturation (Shorey *et al.*, 1968; Happ 1971), and this increased responsiveness apparently stems from shifts in the central nervous system, since the EAG's of mature and immature males are indistinguishable (Payne *et al.*, 1970). A direct correlation between hormone levels and olfactory sensitivity has been demonstrated in man by Le Magnen (1948, 1950). Le Magnen has shown that the synthetic compound exaltolide is odorless to men and children but strongly musky to women, and the sensitivity of women to exaltolide varies with the stage of the menstrual cycle. In addition, estrogen-treated men can smell exaltolide. Vierling and Rock (1967) have confirmed many of Le Magnen's results.

If the odorous steroids found in mammalian urine are functional pheromones, the origins of these steroids, their delivery, and their titer epitomize physiological economy. The steroids may well originate as by-products of circulating hormones; thus little or no special biochemical or cytological machinery is necessary for their production. The steroids are not exported through an independently derived gland, but merely pass into the nephron and are not reabsorbed. If the level of circulating hormones is related to the titer of odorous steroids in urine, then the coordinating link between endocrines and exocrines is built into the system.

Chemical ecology is yet in its infancy. The importance of chemical signals between organisms is increasingly apparent, and the structures of many signals have been established. Many more signals remain to be characterized and many of their roles need more precise definition. The field of chemoreception and subsequent processing of the information is scarcely understood. Much more information is needed on the ways in which external and internal chemical signals interact with each other. Finally, the potential importance of exocrine signals as regulators of population density, acting for example as epideitic pheromones (Corbet, 1971), and the contribution of such signals to the stability of an ecosystem are largely matters of appealing conjecture.

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ENDOCR

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I. INTRODUCTION

The study of the influence of
storage, and release of hormones
of research over the last two deca
the delicate control exerted by
hypothalamus, over the endocrine
lous detail. Attention is now turni
regulatory effects of hormones o
system. Recent evidence indicate
the nervous system is deeply sens
tini, 1971), and certainly it is to
neuron will be regulated by hor
demonstrably sensitive to minute