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CURRENT PROBLEMS IN RESEARCH

Endocrine Pharmacology

This undeveloped field provides broad possibilities in experimental and applied therapeutics.

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The search for drugs to treat the ills of mankind is almost as old as the ills themselves. Modern applied pharmacology is a sophisticated extension of ancient practice. In addition to their use in the treatment of infectious diseases, it is customary to prescribe drugs to modify the function or dysfunction of the nervous, cardiovascular, respiratory, gastrointestinal, or renal systems. With the well-known exceptions of the antithyroid drugs, however, chemical agents foreign to the human body had, until very recently, virtually no established uses in regulating the manifold activities or diseases of the endocrine glands. The use of isolated secretions of endocrine glands—that is, hormones—in their natural or chemically modified state to treat disease is of course a common and useful practice. What has been strangely lacking, however, is a well-developed endocrine pharmacology involving knowledge and use of chemical nonhormonal compounds which can alter the secretion or action of hormones. The potentialities of this approach are particularly well illustrated by that large battery of drugs which, with a high and selective specificity, can block particular functions of the autonomic nervous system. This high-water mark in pharmacological achievement involves interference with the production or action of neurohumoral substances. Analogous possibilities exist in so far as the humors of the endocrine glands proper are concerned.

One reason for the limited advance in this field has been lack of concentrated, systematic effort. This in turn is due to the fact that the classic approaches to endocrinology have been spectacularly successful in the last few decades and that preoccupation with them preempted the time and energy of the students of this science. This classic approach has involved the following three phases, all of which have been, and still continue to be, productive.

1) *The identification, isolation, and synthesis of hormones and their therapeutic use in analogous deficiency syndromes.* This represents the first and self-evident approach to endocrine problems. Its prosecution has resulted in substitution therapies for diabetes mellitus, Addison's disease, myxedema, the menopausal syndrome, and many other disorders.

2) *The chemical modification of hormones to potentiate or prolong their activity.* Few hormones are now administered to patients in the natural state in which presumably they are released by the endocrine glands into the blood stream. Slight chemical modification of the natural compound may delay its rate of absorption from an injection site or delay its metabolic degradation in the body, or both, with the result that the frequency of administration can be greatly reduced. Hence we prescribe long-acting insulins, esters instead of the free alcohols of the steroid hormones, and so on. Similarly, slight chemical modification may inhibit the destruction of a hormone in the gastrointestinal tract and thus make its oral administration feasible and economical. Examples of this are the oral use of methyltestosterone instead of the natural testosterone and of ethinyl estradiol instead of estradiol. Such pharmaceutical manipulations, however, were not designed or intended to alter the biological activity of the hormone molecule but only to extend, enhance, and conserve it.

In one instance, that of stilbestrol and its derivatives, compounds which differ greatly from the natural estrogens produce effects essentially identical to those of the natural estrogenic hormones (*1*). Analogous substitutes for other types of hormones are not known to exist.

3) *The chemical modification of hormone molecules to alter their natural activity.* New developments of this type were introduced by the discovery of Fried (*2*) that 9α-halogenation of the adrenal cortical hormone, hydrocortisone, resulted in major alterations in the pattern of its biological activity. This has resulted in a flood tide of work (not to be reviewed here) in which chemically and biologically modified hormones have emerged from test tubes in profusion. It is now clear that chemical alteration of steroid hormone molecules can result in an accentuation of one biological activity and diminution of another. The same is apparently true of the polypeptide hormones (*3*). This makes it possible, both theoretically and in practice, to synthesize hormone-like substances with tailor-made properties to serve specific therapeutic or experimental needs. The most widely used

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substances of this type are the prednisolones and their successors, which are used in treating inflammatory diseases. New ones are surely coming, among them steroids which can control fertility in man (*4*). It is still true, however, that these chemical alterations of hormone molecules have produced no compounds with fundamentally new properties which were not present to some degree in the parent compounds. It is the ratio and magnitude of the different activities inherent in the parent compounds which have been altered.

Pharmacological Regulation of Endocrine Functions

This brings us to a newer and less well developed approach to the study of endocrinology, which is our main subject—namely, the use of drugs to control endocrine functions. While we are emphasizing here the potential practical applications of such work, any success would also be of equal or greater importance in the theoretical and fundamental studies of the nature of endocrine function. Witness the fruitful use of drugs in the study of neurological phenomena. The work outlined below is of a scattered sort, from many sources. It has seldom received comprehensive attention in the literature. Nevertheless, new work shows that this is a field in which systematic and profitable exploitation will be forthcoming, and one to which an increasing amount of attention will be given.

Theoretically there are many ways in which drugs might modify endocrine function. From a practical standpoint, it would be more useful to have glandular inhibitors rather than stimulants because an excess of hormone usually can be obtained, when needed, by direct administration of the hormone in any quantity. Stated in the form of an outline (amplified below), some of the more obvious routes through which inhibition could be achieved are as follows.

1) A drug might "damage," reversibly or otherwise, the glandular secretory cells which produce hormones—through, for example, alloxan-like action on the pancreas or 1, 1-dichloro-2, 2-bis (*P*-chlorophenyl) ethane-like action on the adrenal (Fig. 1).

2) A drug might inhibit some specific (probably enzymatic) step in the biosynthesis of a hormone—through, for example, amphenone-like action on the adrenal cortex (Fig. 1).

3) A drug might block the stimulus, however remote, which causes glandular secretory activity—for example, sedative inhibitors of adrenocorticotrophin (ACTH) release (Fig. 1).

4) A drug might block the uptake of an essential raw material for hormone synthesis—for example, the uptake of iodine by the antithyroid drugs.

5) A drug might block the production of an essential precursor to hormone synthesis—for example, inhibitors of cholesterol synthesis which disturb steroid hormone production.

6) A drug might block the reaction of a hormone at a receptor site—for example, the spirolactone antagonists of aldosterone (Fig. 1).

In some instances it is certain and in others probable that drugs are now known which can and do achieve most of these effects. The fact that, with limited exceptions, they are not widely used is due to the need for better drugs. With the prototypes available, it should be possible to find them.

Drugs Which Inhibit Secretion of Anterior Pituitary Hormones

Work in recent years has clarified considerably the mechanisms by which the secretion of the several hormones of the anterior pituitary is regulated. This is accomplished, first, by the relatively slowly acting "thermostat" or "feedback" mechanism in which the pituitary trophic hormone stimulates secretion of a hormone by the target gland, and the hormone of the target gland in turn acts back to inhibit release of the pituitary trophin. This mechanism operates for most of the pituitary hormones which regulate other endocrine glands—for example, the gonadotrophins, thyrotrophin, and adrenocorticotrophin. It serves as a stabilizing system to prevent violent fluctuations in blood levels of the hormones concerned. There are, however, other regulatory stimuli which can override the feedback system and permit the sudden release of pituitary trophins, presumably to meet immediate or unusual needs. Most regulatory factors apparently operate as follows: neurohumoral cells in the hypothalamus can be stimulated to release or inhibited from releasing from their nerve endings humoral substances which are picked up by the hypothalamico-hypophyseal portal capillaries and delivered to the anterior pituitary. In the pituitary these neurohumors cause release of pituitary trophins, which in turn stimulate secretion of the target glands (*5*).

Such mechanisms have been implicated in the release of all anterior pituitary hormones except the growth hormone. The stimuli which impinge upon the hypothalamus to initiate this cycle of events are the subject of much current study and are not well understood. Apparently they may be either neural or blood-borne. Classic examples of their actions, however, are the release of pituitary luteinizing hormone after mating in some mammals and the quick release of adrenocorticotrophin in response to nonspecific stress. In any case, it is evident that a complex chain of events must transpire before the original stimulus (psychic, traumatic, humoral, pharmacological or otherwise) results in secretory response by the target gland involved. Theoretically, blocking of the response might be achieved at any link of the chain by a drug of sufficient specificity; the greater the length of the chain, the greater the vulnerability of the system to pharmacological blockade.

Gonadotrophins. The study of the influence of drugs on the secretion of gonadotrophins was initiated and developed largely by Markee, Everett, and Sawyer (*6*). They have skillfully used pharmacological tools to great advantage in a long series of studies to reveal important information about fundamental mechanisms in reproductive processes and, incidentally, about the drugs themselves. Thus, it could be shown that the secretion of luteinizing hormone in the rabbit, which causes ovulation under the stimulus of copulation, can be blocked by some (for example, dibenamine) but not all (for example, Regitine) antiadrenergics and by anticholinergics (such as atropine) as well. Studies to determine the time at which drugs had to be given after the stimulus of copulation in order to block ovulation led to the concept that a link blocked by anticholinergic drugs preceded one blocked by antiadrenergics in the presumably complex neural pathways involved.

In the rat, which has a different type of reproductive cycle, the pharmacological relationships were also different. It was possible, however, to block the spontaneously occurring ovulation, pre-

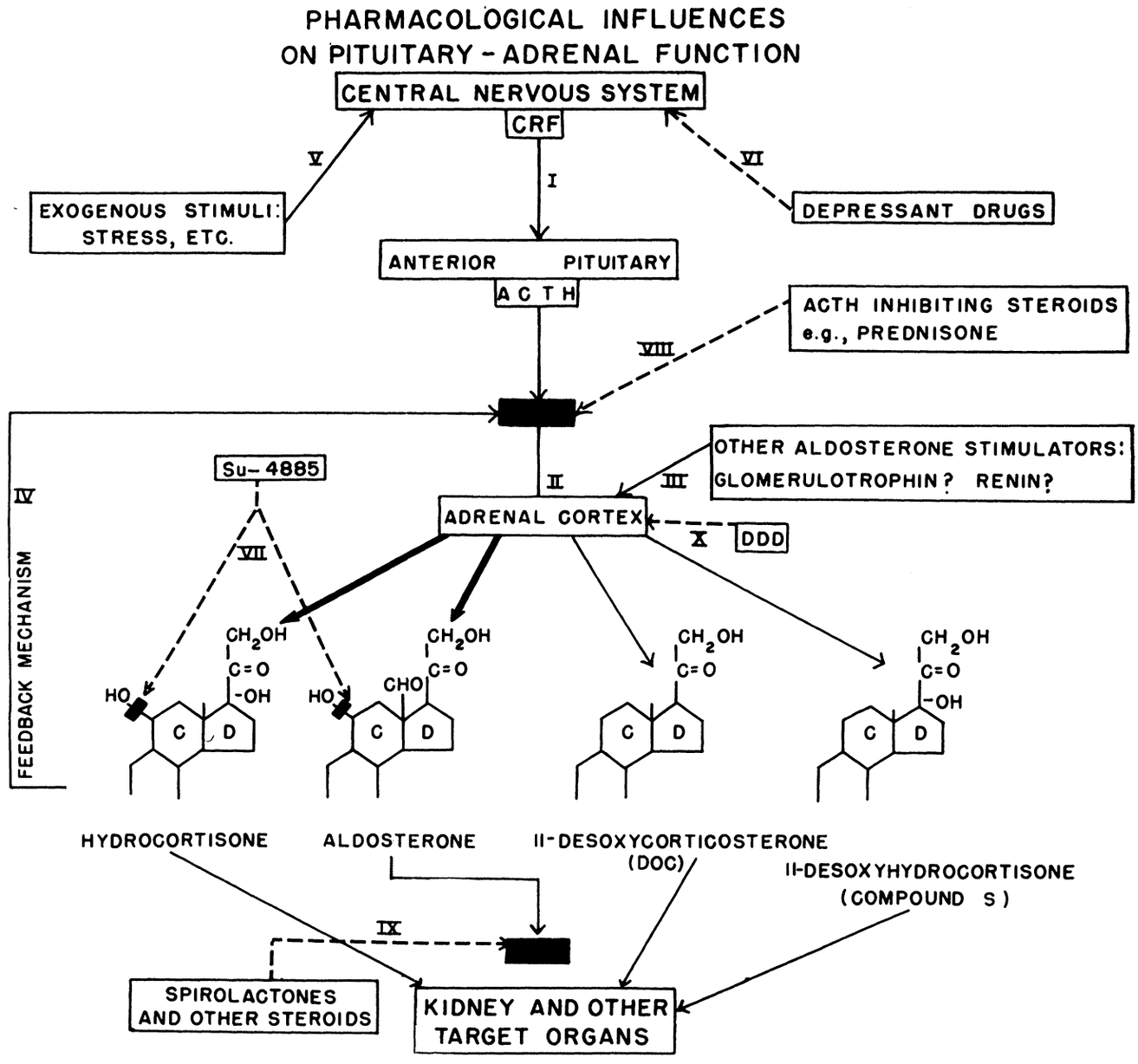

Fig. 1. A diagram illustrating some aspects of normal pituitary-adrenal function and the site of action of drugs which modify it. Physiological factors are illustrated by solid arrows, pharmacological ones by broken arrows. Inhibition or blockade is indicated by black boxes. *Physiological:* In the central nervous system a corticotrophin releasing factor (*CRF*) stimulates (I) the anterior pituitary to secrete corticotrophin (*ACTH*), which in turn causes (II) the secretion of the several adrenal hormones, only four of which are shown. Other humoral agents also influence (III) aldosterone secretion, but their identity is uncertain. Of the corticoids illustrated, hydrocortisone and aldosterone are the most important, the other two being produced normally in insignificant amounts. Hydrocortisone serves (IV) as the main natural inhibitor of ACTH secretion, thus providing a self-limiting regulatory system. It may act directly on the pituitary, the hypothalamus, or both (*101*). Exogenous stimuli (V) can, however, stimulate ACTH secretion, thus overriding the feedback mechanism (IV). Not illustrated is the possibility, for which some evidence exists, that the central nervous system exerts inhibitory as well as stimulating influences on ACTH secretion. *Pharmacological:* Depressant drugs (analgetics, tranquilizers, and so on) can inhibit (VI) the secretion of ACTH either by direct effects on the nervous system or by insulating it from exogenous sensory stimuli (V). Su-4885 acts (VII) primarily to inhibit the enzymatic hydroxylation of adrenal hormones at carbon-11, thus preventing or reducing the secretion of hydrocortisone and aldosterone. The lack of hydrocortisone eliminates the feedback mechanism (IV), permitting excess secretion of ACTH. Under these circumstances an excess of ACTH causes an outpouring of 11-deoxycorticosterone and 11-deoxyhydrocortisone. These are mineralocorticoids and their levels may rise sufficiently to cause sodium retention. If a steroid which inhibits ACTH (VIII) is given with Su-4885, all corticoid secretion is reduced and sodium diuresis and reduction of edema may occur. The spirolactones act (IX) as competitive inhibitors of aldosterone and block its effects on the kidney and at other sites. This results in sodium diuresis and a compensatory hypersecretion of aldosterone. The DDD-like compounds cause (X) cellular atrophy of the adrenal, lack of responsiveness to ACTH, and decreased secretion probably of all corticoids.

sumably dependent upon a release of luteinizing hormone mediated by the central nervous system (*7*) as in the rabbit, by a variety of drugs (such as atropine, dibenamine, barbiturates, morphine, SKF-501, chlorpromazine, and reserpine) if they were administered at certain time-limited stages of the estrus cycle. Specifically this was between 2 and 4 P.M. on the day of proestrus (*8, 9*). Electrophysiological studies showed again that although several of these drugs seemed to have common actions in the central nervous system, no single common pattern of response was seen. This suggests strongly that the inhibition of ovulation achieved was effected at different sites. In the hen, ovulation can be blocked by drugs, but pharmacological details seem to differ from those seen in mammals: the barbiturates are inactive, but atropine and SKF-501 work (*10*). A drug used for the treatment of infectious diseases in birds [2-amino, 5-nitrothiazole (Enheptin)] causes dramatic gonad atrophy and sterility in chickens, apparently due to gonadotrophic inhibition (*11*). In mammals, however, this type of action is only transient if it is present at all (*11, 12*).

Studies with the newer tranquilizing drugs are of particular current interest. It is clear that reserpine, for instance, can affect anterior pituitary function in such a way as to inhibit estrus, menstruation, and fertility (*13, 14*) and modify the decidual response, which is dependent on the secretion of pituitary luteotrophins (*15*).

Interestingly enough, this inhibitory effect on certain gonadotrophins is not carried over to the lactogenic hormone of the pituitary, the release of which is certainly not inhibited by reserpine (*13*), but instead in some species (including man) and under some conditions is stimulated to the extent that lactation is induced. This was first seen in isolated clinical cases and was subsequently demonstrated unequivocally in animals (*16, 17*). A still different pattern of effects, discussed below, occurs in the release of ACTH, which may be either stimulated or depressed.

Syrosingopine, a compound derived by chemical modification from reserpine, is much weaker than the latter in influencing the release of gonadotrophins and lactogen (and ACTH) from the pituitary (*17–19*) and in causing tranquilization-sedation, although it is as effective as reserpine in reducing blood pressure in laboratory animals. Unlike reserpine, it reduces catecholamine levels much more at peripheral than at central sites (*20*). Hence it may be inferred that the endocrine effects of *Rauwolfia* alkaloids are mediated primarily in the brain.

Chlorpromazine has, in general, endocrine effects much like those of reserpine, but minor differences suggest that different mechanisms of action are involved.

It is a curious fact that very scanty manifestations of such actions of reserpine and chlorpromazine have been obtained in the millions of patients treated with these drugs. One reason may be that the dosage required to obtain anything other than subtle evidence of activity is larger than dosages usually used in medical practice; such effects are more frequently seen in psychiatric practice, where large doses are conventionally used (*21*). This means that these drugs will probably never be effective therapeutic agents for the controlled and purposeful regulation of reproductive functions in man. These findings do, however, point clearly to the fact that such pharmacological regulation is possible. Drugs which act more specifically would be of great potential use, both in clinical medicine and in animal husbandry, in treating reproductive dysfunction and in controlling —particularly in inhibiting—fertility. In this connection the hoped-for application of the gonadotrophin-inhibiting effects of extracts of the *Lithospermum* plants, a heritage from the American Indian, have not yet been realized.

Despite their gonadotrophin-suppressing action, as seen in the rat (*8*), the use of barbiturates and other anesthetics as inhibitors of ovulation has not had, and probably will not achieve, practical application.

Recent reports show that different monoamine oxidase inhibitors, including the "psychic energizer" iproniazid, in relatively high dosage, can suppress gonad function and produce sterility in rats (*22*). It is probable but not certain that the major effect involves a selective inhibition of certain gonadotrophins, perhaps the interstitial cell-stimulating hormone.

In conclusion, it is of interest that all of the drugs mentioned above, believed to affect reproductive functions in mammals through modification of gonadotrophin secretion, are drugs which act on the autonomic or central nervous systems. Generally they act on some aspect of the metabolism of the neurohumoral catechol amines. Here similarity ends, however, because sites and details of their action vary widely. This emphasizes again the point that the chain of neurohumoral influences in the control of reproduction is a long one, with many points of pharmacologic vulnerability.

Gonad hormones. Studies have been continued over many years in an attempt to find steroids which, by competitive inhibition or otherwise, would antagonize the action of the natural hormonal steroids. With the exception of the recent work on antialdosterones discussed below, these efforts have been largely fruitless. The natural estrogens and androgens themselves may show either antagonistic or supplementary effects when given together, the result being dependent upon the end point chosen. A few nonhormonal steroids can interfere with the action of natural ones to a moderate degree (*23, 24*). Perhaps the recent finding of an antiandrogenic activity of A-norprogesterone represents the greatest success in this direction (*24*). In general, however, such work has not contributed greatly either to experimental or to clinical endocrinology.

The recent discovery of the antiestrogenic action of the new nonsteroidal compound, 1-(*p*-2-diethylaminoethoxyphenyl)-1-phenyl-2-*p*-methoxyphenyl ethanol (Mer-25), provides a tool of much greater potential importance. In rats, mice, monkeys, chicks, and rabbits, it will block the action of endogenous or exogenous estrogens, either steroidal or nonsteroidal, with remarkable effectiveness (*25*). The mechanisms of action are not known. In addition, in the rat it causes degeneration of fertilized eggs in the oviducts, even when given after mating, and thus prevents pregnancy (*26*). Whether this is a consequence of its antiestrogenic action or a separate effect is not certain (*27*). The potentials of a compound with these properties in the treatment of reproductive disorders and of tumors and in fertility control are great. The danger is, however, that such compounds, like the estrogenic doisynolic acid derivatives and some adrenal cortical inhibitors, tend to have a high degree of species specificity. They may work in man as in animals, but enthusiasm must be tempered until that is demonstrated to be the case. In fact, there is an ominous lack of reports of activity of Mer-25 in man.

One of the first effects of sex steroids

on the uterus seems to be the release of histamine (*28*), to which some later reactions are presumably secondary. Also, histamine is apparently involved in other hormone-triggered uterine events, such as the formation of deciduomata. Antihistamine drugs can, therefore, block some actions both of the estrogens and of progesterone in animals (*28, 29*). As yet there has been no practical application of this interesting fact. Ergotoxine can block estrus cycles, pseudo-pregnancy, and pregnancy in rats by means which are not clear (*30*).

A considerable variety of chemical compounds, such as the antimitotic drugs, alkylating agents, and antimetabolites, can interfere with the activity of the germinal epithelium or other aspects of the reproductive process and produce sterility. Such work has been extensively reviewed by Jackson (*31*) and Nelson (*4*); it does not appear that endocrine mechanisms are primarily involved.

Drugs Affecting the Adrenal Cortex

Adrenocorticotrophin inhibitors. With the partial exception of aldosterone, the secretions of most of the hormones of the adrenal cortex are regulated by ACTH (Fig. 1). The mechanisms regulating the rate of secretion of ACTH itself, aside from the feedback system, are labile ones; they are highly sensitive to a wide variety of stimuli which can best be grouped under the term *stressful.* In general, the system seems designed to insure that an excess of adrenal corticoids will be available for any potential need. The frequency with which this system is deranged so that a harmful excess of corticoids is released is a moot point, but that this sometimes happens is certain.

It is probable that the varied stimuli, either enhancing or inhibiting, which affect ACTH secretion impinge in common on the central nervous system by either neural or vascular routes. It is generally believed that they are all funneled through the hypothalamus, but this not certain (*32*). There, it is thought, they cause a release of corticotrophin-releasing factor, which follows vascular paths to the anterior pituitary and causes ACTH secretion. It is, therefore, not surprising that the most effective inhibition of ACTH release has been achieved by (i) surgery which blocks either neural paths to the hypothalamus or vascular paths leading from it to the pituitary, or (ii) drugs which are depressants of the central nervous system. Of the latter, none has the advantage of specificity or of complete effectiveness. Nevertheless, some have served as useful laboratory tools; the term *chemical hypophysectomy* has entered the literature, although it probably suggests more than any drug has yet accomplished.

Among the drugs which can block or dampen the release of ACTH under some circumstances are the following: SKF-501 (*33, 34*), morphine (*35–37*), dibenzyline (*34, 36*), atropine (*34*), barbiturates (*38, 39*), diphenylhydantoin (*40*), meprobamate (*41*), reserpine (*42*), ether (*39*), and chlorpromazine (*43, 44*). These are, for the most part, the same drugs which can inhibit secretion of certain gonadotrophins, suggesting common pathways of action. In general, they probably act either at central sites to prevent release of the corticotrophin-releasing factor or peripherally to prevent afferent stimuli from reaching such central sites. None of them prevent ACTH secretion completely—that is, they do not produce adrenal insufficiency, but rather tend to prevent the normal extra release of ACTH following stressful stimuli (*45*). Their primary end action is on the secretion of glucocorticoids rather than of aldosterone, since the latter is only partially under the control of ACTH. The groups led by Sawyer and by Sayers (*39*) agree in the suggestion, based on various types of neurological and pharmacological evidence, that several of these drugs, such as morphine, chlorpromazine, the barbiturates, and ether, act primarily to depress the reticular activating system and thus prevent stimuli that release the corticotrophin-releasing factor from reaching the hypothalamus. Royce and Sayers (*39*) provided the direct evidence of changing blood levels of ACTH (as contrasted to indirect measures of ACTH secretion) under the influence of ether and barbiturates.

Despite certain common end results, the drugs involved differ considerably among themselves with respect to details of their actions. It should be emphasized that the majority of them, when first administered, act like stresses and may cause an initial massive outpouring of ACTH. For this reason their ACTH-suppressing activity may easily be overlooked. In the case of reserpine the initial ACTH-releasing action can itself be blocked by dibenamine (*46*). Subsequently the stimulatory action subsides and the drugs tend to block the ACTH-releasing effect of other stimuli. This has been notably demonstrated in studies on morphine and reserpine (*35, 42, 47*). The barbiturates, on the other hand, seem to depress ACTH release without a prior stimulation. The extent to which the drugs studied block the action of ACTH-releasing stimuli seems to vary with the drugs themselves, with their dosage, and perhaps with other experimental variables. Interestingly enough, Gold and his co-workers (*48*) found that chlorpromazine and some other tranquilizers, but not reserpine, will block the pituitary response to the adrenal inhibitor Metopirone (Su-4885), discussed below. Mepazine, a phenothiazine, has a predominantly stimulating action and little if any inhibitory action on ACTH secretion (*49*).

It is interesting to speculate on the practical and therapeutic consequences of this type of pharmacology. In psychic agitation, in shock or in pain, is the ACTH-inhibiting or ACTH-stimulating action of drugs conventionally prescribed one aspect of their therapeutic efficacy or an undesirable side effect? No certain answer can be given. Most of the substances involved protect against various forms of shock, but it is not known whether the adrenal-pituitary effects in such situations are coincidental or more directly related to the end results. In chronic stress a good theoretical argument could be made that a dampening of adrenal activity is advantageous. It is clear only that this long-overlooked aspect of the pharmacology of "depressant" drugs should be considered in an assessment of their total activity.

Whatever may be the medical aspects of the use of such drugs, they have acquired a highly practical laboratory role in that they dampen endogenous hypothalamic-pituitary activity and thus facilitate the study of other agents which affect the release of the corticotrophin-releasing factor and of ACTH (see, for example, *43, 50*).

Direct inhibitors of the adrenal cortex. Now that some systematic effort to find them is being made, it seems that there are a variety of pharmacological ways, other than by inhibition of ACTH, in which corticoid suppression can be achieved. Such suppressants might be expected to be useful in hypertensive disease, cardiac and renal diseases, diabetes mellitus, neoplasms, and other states more definitely related to adrenal hyperfunction, such as Cush-

ing's syndrome, primary aldosteronism, and adrenogenitalism. In addition, some have proved useful diagnostic tools. Scientific attention at the moment is focused largely on three types of compounds which act on the adrenal in different ways. These are the steroidal spirolactones, the amphenone-like compounds, and compounds related to the insecticide 1, 1-dichloro-2, 2-bis (*P*-chlorophenyl) ethane (DDD). Of perhaps greater future promise is the existence of preliminary evidence that various other types of compounds may have similar activity.

Steroidal spirolactone (see Fig. 1). The original work of Kagawa *et al.* (*51*) and of Liddle (*52*), followed by that of many others, established that a group of steroidal lactones can act competitively to prevent aldosterone and other mineralocorticoids from having their typical sodium-retaining effects in the kidney and at other sites. This work has been well confirmed, and the therapeutic value of spirolactone as a diuretic and antihypertensive has been established (*53*). The gonadal steroids with previously known weak natriuretic effects act like the spirolactones (*54*). More important, perhaps, is the possibility that the discovery of the spirolactones will open the door to the discovery of other long-sought-for competitive inhibitors of adrenal and gonadal steroids. Much effort has already been expended in that direction without any notable success.

Inhibitors of steroidogenesis in the adrenal. The compound amphenone B was synthesized by Allen and Corwin (*55*) and then shown by Hertz *et al.* (*56*) to have a multiplicity of biological effects, among which was a suggested inhibition of adrenal cortical function in the rat. The other effects included progestational, antithyroid, and anesthetic actions, and in the rat a marked adrenal hypertrophy with cholesterol deposition.

It subsequently became clear that in the dog and in man amphenone interferes with the biosynthesis of all or most of the adrenal corticoids, probably by interfering with the enzymatic mechanisms responsible for the later stages of steroid synthesis (*57*). Rosenfeld and Bascom (*58*) located these inhibitions as specifically involving 11β-, 17α- and 21-hydroxylations as well as the oxidation of the 3-hydroxyl to 3-ketone. By manipulating the amphenone molecule it is possible to vary the potency and at least the quantitative pattern of its activities (*59, 60*). One can, for instance, enhance or depress the antithyroid activity, and this in itself would be of practical interest were it not that other types of antithyroid drugs of much greater potency and specificity are available.

In our laboratory a large number of compounds more or less closely related to amphenone have been studied. One of particular interest (Fig. 1) was Metopirone (Su-4885). It was first noted in dogs (*61*) that in acute experiments this compound eliminated or reduced the Porter-Silber steroids in adrenal vein blood and blocked their production by adrenal tissue of rats and guinea pigs in vitro (*59*). It seemed curious at the time, however, that when given to dogs over a long period it did not cause adrenal insufficiency and, in fact, under some conditions caused a retention of sodium, suggesting an excess of mineralocorticoid. The explanation of this paradox turned out to be, as shown independently by Liddle *et al.* (*62*) and Jenkins *et al.* (*63*), whose findings were subsequently abundantly confirmed, that in ordinary tolerated doses in intact animals or man, Su-4885 inhibits primarily 11β-hydroxylating mechanisms (Fig. 1) and hence inhibits secretion of the main natural corticoids—hydrocortisone, corticosterone, and aldosterone. If its action stopped at that point, the drug could have a wide potential usefulness in many disease states. The withdrawal of hydrocortisone from the circulation, however, removes the principal natural inhibitor of ACTH secretion. The consequent excess of ACTH acting on adrenals whose main pathways of steroidogenesis are blocked causes an outpouring of two steroids normally secreted only in very small amounts: 11-deoxyhydrocortisone (Reichstein's S) and 11-deoxycorticosterone. These are both potent salt-retaining hormones, and their presence adequately explains the observed salt retention and lack of adrenal insufficiency. The endocrine effects of Su-4885 duplicate closely those observed in a hypertensive syndrome described in man by Eberlein and Bongiovanni (*64*), due to a congenital incapacity to hydroxylate steroids at carbon-11.

These secondary actions of Su-4885 will probably preclude or limit its use in long-term therapy. The history of the drug, however, provides another example of the fact that the practical consequences of research may be totally unforeseen when the research plan is formulated. Metopirone is finding a wide use as a tool in the differential diagnoses of pituitary-adrenal diseases. This is based on the fact that if the ACTH secretory mechanism is normal, a patient will respond to Su-4885 by excess secretion (and excretion) of 11-deoxy- steroids; the lack of such response shows a specific pituitary deficiency. In addition, if an ACTH inhibitor (for example, prednisone) is given with Su-4885, then the compensatory rise in 11-deoxy- mineralocorticoids is prevented and a sodium diuresis, useful in some conditions, is achieved (*65*).

Work now in progress in our own and other laboratories suggests that compounds with a different spectrum of effects than either amphenone or Su-4885 can be made. Such developments will be awaited with great interest.

DDD-like compounds (see Fig. 1). The insecticide DDD and related compounds have a different type of action in that they cause cytotoxic atrophy of the dog's adrenal, with a consequent reduction in steroid secretion (*66*). The adrenals of DDD-treated animals, unlike those of animals receiving the amphenones, are not responsive to ACTH as regards either growth or secretory activity. Apparently a considerable family of DDD-like substances have adrenal-inhibiting activity, and a search is being made for congeners with greater activity and less toxicity than the parent compound. None have been found that are both safe and effective for human use, but *o,p'*-DDD has rather dramatically inhibited the development of metastatic adrenal carcinoma as well as adrenal function in man (*67*).

Miscellaneous substances. Numerous other substances have been reported to cause some manifestations of adrenal inhibition. These include the strong antithyroid drug thiouracil, which causes some adrenal atrophy in rats (*68*); it is interesting to note that the adrenal inhibitor amphenone is also a thyroid inhibitor. The estrogens cause adrenal hypertrophy; this is an apparent compensatory response to their action in inhibiting a maximal corticoid synthesis, perhaps due to some interference with cholesterol metabolism (*69*). Another substance, delta-4-cholestenone, also interferes with the synthesis of cholesterol and may in that way exert its reputed inhibitory effect on corticoid secretion (*70*).

A number of recent reports suggest that a variety of substances may act as adrenal cortical suppressants: strepto-

mycin (*71*), heparin (*72*), omega-methylpantothenic acid (*73*), triazines (*74*), and acetyl strophanthidin (*75*). Schuler and Meier (*76*) proposed, on the basis of indirect evidence, that some thiosemicarbazones were adrenal inhibitors. Interestingly enough, these thiosemicarbazones also cause testicular dysfunction, particularly of the germinal epithelium. We have found in preliminary direct measurements that two of these thiosemicarbazones, Ba 9479 and Ba 11044, markedly depress adrenal function, as determined by measurements of the steroid content of adrenal vein blood.

In tissue culture an antimitotic action of hydrocortisone on HeLa cells can be blocked by pilocarpine (*77*). It will be interesting to explore the significance of such results in terms of whole organisms.

Although substances of wide therapeutic applicability are not yet at hand, the present situation, with its many opportunities for well-guided further investigations, differs greatly from that of the recent past when the existence of any pharmacological inhibitor of the adrenal cortex was questionable.

Antithyroid Drugs

Since this article is primarily concerned with current and prospective lines of investigation, only brief reference will be made to antithyroid drugs. Endocrine pharmacology has achieved, however, its greatest successes in this field; the extensive available knowledge is now recorded in textbooks, and the use of these drugs is well established in medical practice.

Thyrotrophin. In contrast to the huge number of substances which inhibit thyroid activity by some local action, there are few which are known to achieve a similar result by inhibiting the release of pituitary thyrotrophin. Thyroid hormones inhibit the release of pituitary thyrotrophin, and this is one of the main features of physiological thyroid regulation. A direct action of iodide on the secretion of pituitary thyrotrophin has often been suggested but has not yet been demonstrated (*78*). Dinitrophenol may have some effect, possibly an indirect one (*79*). Ether may inhibit the release of pituitary thyrotrophin (*80*) as well as ACTH. Reserpine certainly has a mild thyroid-inhibiting action in some circumstances, which is thought to result from inhibition of the release of pituitary thyrotrophin (*81*).

Direct thyroid inhibitors. Thyroid inhibition can be accomplished in various ways (*82*). One is based on the still anomalous fact that iodine, although a constituent of the thyroid secretion and hence necessary for its synthesis, can under certain circumstances act as a thyroid inhibitor (see *83*). Thiocyanate and various monovalent ions close to iodine in the Hofmeister series interfere with the mechanism by which the thyroid normally can collect and retain large quantities of iodide from the blood stream (*84*). As a result of the pioneer work of the MacKenzies (*85*) and of Astwood *et al.* (*86*), some sulfonamides and thioamides related to thiourea were shown to block thyroid hormone production, probably by blocking the iodination of tyrosine in the thyroid. From the thioamides the most useful therapeutic agents for controlling hyperthyroidism have evolved: 2-thiouracil, propylthiouracil, methimazole, iothiouracil, and so on.

Subsequently a variety of other compounds was shown to have some sort of thyroid-inhibiting influence. These include resorcinol (*87*), phenothiazenes (*88*), phenylbutazone (*89*), amphenone (*56*, *90*), 2-3-dimercaptopropanol (*91*), reserpine (*92*), and some substances of natural origin—for example *Brassica* plants (*79*). These compounds probably act in different ways. None has yet had practical application.

Stimulants and Inhibitors of the Neurohypophysis

The two known hormones of the mammalian posterior pituitary are, according to the species, either arginine- or lysine-vasopressin and oxytocin. They are now generally thought to be neurosecretions, perhaps synthesized in hypothalamic nuclei from which they traverse neurones to a discharge point from the posterior lobe. The main known function of vasopressin is to increase the permeability of nephron walls to water, thus facilitating reabsorption and inhibiting excretion of this substance.

Study of influences which either stimulate or depress the release of vasopressin has been greatly impeded by the lack of sufficiently reliable and sensitive methods of measuring this hormone in body fluids when it is present in small amounts. Generally, stimulation of the release of vasopressin is inferred if the whole pattern of response to a drug or other influence resembles the response to exogenous vasopressin. Inhibition is inferred if the response is like that in diabetes insipidus, induced either by surgical means or by water diuresis.

A large number of drugs, particularly those that produce some manifestation of toxicity, inhibit water diuresis in short-term experiments. It is common to assume that this is due to the release of vasopressin. In our experience, however, with rats as test animals, most such drugs were found to cause a shutdown not only in the excretion of water but in that of sodium and potassium as well. Under the same conditions exogenous vasopressin causes, if anything, an increase in the excretion of sodium and potassium along with water antidiuresis. Hence, such evidence provides no certain basis for implicating the neurohypophysis. It is of great interest but uncertain significance that in the absence of vasopressin the action of thiazide diuretics are reversed—that is, they cause anti-diuresis (*93*).

Diuretic drugs. A plethora of drugs, many in wide clinical use, cause water diuresis and have varying effects on the excretion of electrolytes. Ethanol is the only one of these that, on the basis of widely acceptable evidence, acts by inhibiting the secretion of vasopressin. The diuretic action of ethanol-containing beverages has been commonly observed through the ages. It was hard to convince the pharmacologists, however, that this was a specific effect of ethanol per se. Agreement that such was the case emerged from the work of Edkins and Murray (*94*), of Eggleton (95), of Strauss *et al.* (*96*), and particularly of van Dyke and Ames (*97*). The latter workers added the convincing demonstration that ethanol acted to inhibit the release of vasopressin. This interesting work has not led to therapeutic applications. While ethyl alcohol is widely self-administered, to greater or lesser advantage, for psychopharmacological purposes, it is seldom a cure for edema. In fact, the finding of Laragh *et al.* (*98*) that surgical ablation of the posterior pituitary did not prevent the formation of ascites in the dog suggests that any future discoveries of vasopressin inhibitors would not provide tools, as once we had hoped, for the treatment of diseases characterized by anasarca. In the laboratory, however, ethanol enjoys wide use as a tool for making animals suitable for the bioassay of vasopressin-like sub-

stances by blocking the release of endogenous vasopressin. A compound with similar activity but less toxicity would be still more useful.

Drugs Affecting the Isles of Langerhans

The medical problem of diseases of the pancreas is of such magnitude that any means of pharmacological control of, or substitution for, that organ assumes great importance. The search for substitutes for insulin that could be given orally rather than by injection has been a continuing one. Several types of compounds are known to have insulin-like action, and in recent years two groups of these have found notable success in medical use, the sulfonylureas and the biguanides. The literature has been thoroughly cited in recent reviews and symposia (*99*). The discovery of the antibacterial action of sulfonamide drugs carried in its wake, as has oftentimes been the case in the history of science, some spectacular advances in entirely different fields of medicine. For one, certain sulfonamides (acetazolamide, chlorothiazide, hydrochlorothiazide, and so on) were found to be highly effective diuretic and antihypertensive agents. For another, some of the sulfonylureas were found to have an insulin-like hypoglycemic action and to be useful in the treatment of diabetes mellitus. The principal compounds involved have been tolbutamide, carbutamide, and chlorpropamide — drugs whose activities differ only in details. The main action of these drugs is to stimulate the release of pancreatic insulin. Other actions, such as an augmentation of insulin effects or direct actions on organic metabolism, are probable but ill defined.

The hypoglycemic action of some guanidines has been known for many years. It was only recently, however, that one of these, phenylethylbiguanide, found wide clinical use. Although considerable factual information exists concerning its effects, a comprehensive understanding of its mode of action is lacking. Clearly, however, it acts differently from either insulin or the sulfonamides.

Since pancreatic hyperfunction is much rarer than pancreatic deficiency, there has been less incentive to find insulin inhibitors than insulin stimulants or substitutes. Nevertheless, such drugs have an important if limited role, and therefore much enthusiasm greeted the discovery that alloxan and some related substances, when properly administered, could selectively destroy the insulin-secreting (beta) cells of the pancreas in animals (*100*). It was hoped that, among other things, alloxan might afford a practical means of control of pancreatic tumors and their metastases. These hopes were not wholly realized, but laboratory work has been greatly facilitated by the ability to produce an experimental diabetes at will with the use of alloxan. Not only is it much easier to give alloxan than to do a surgical pancreatectomy, but the selective destruction of beta-cells by alloxan, unlike surgical procedures, leaves other nonendocrine parts of the pancreas functionally intact.

Conclusions

There are a few well-established cases in which pharmacological regulation of endocrine secretion can be brought about in a highly effective and practical fashion by drugs. Prototypes exist, however, of drugs which can do the same thing less effectively for most of the other major endocrine glands, with the exception of the parathyroids. These drugs are of a great variety of types and act in many different ways. This provides a wide front from which future advances can be made, in both theoretical and applied endocrinology. It can be expected, therefore, that an endocrine pharmacology will develop comparable to the pharmacology that applies to the nervous system and to other organ systems.

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Radiocarbon Dating

The method is of increasing use to the archeologist, the geologist, the meteorologist, and the oceanographer.

W. F. Libby

Radiocarbon dating had its origin in a study of the possible effects that cosmic rays might have on the earth and on the earth's atmosphere. We were interested in testing whether any of the various effects which might be predicted could actually be found and used. Initially the problem seemed rather difficult, for ignorance of billion-electron-volt nuclear physics (cosmic-ray energies are in this range) was so abysmal at the time (and, incidentally, 14 years later is still so abysmal) that it was nearly impossible to predict with any certainty the effects of the collisions of the multi-billion-volt primary cosmic radiation with air.

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Formation of Radiocarbon

However, in 1939, just before the war, Serge Korff of New York University and others discovered that the cosmic rays produce secondary neutrons in their initial collisions with the top of the atmosphere. The neutrons were found by sending counters, designed to be sensitive to neutrons, up to high altitudes, and they were found to have an intensity which corresponded to the generation of about two neutrons per second for each square centimeter of the earth's surface.

Whereas it was extremely difficult to predict the types of nuclei that might be produced by the billion-volt primary cosmic rays, the neutrons, being secondaries, were in the million-volt energy range and, therefore, subject to laboratory tests. So at this point the question was: What will million-electron-volt neutrons do if liberated in the air? The answer to this question was already available—in fact, Korff noted in one of the papers announcing the discovery of the neutrons that the principal way in which the neutrons would disappear would be by forming radiocarbon. The reaction involved is a simple one. Oxy-