Out of Gas

After orbiting Mars for 4 years, 1 month, and 3 weeks—on a mission that NASA initially hoped would last 90 days—Orbiter 1 ran out of gas on 6 August 1980. Between them, the two Viking spacecraft had provided more than 50,000 photographs, giving cartological data on 97 percent of the surface of Mars, and about 3 million weather reports. Even now, Lander 1 continues to send back daily meteorological reports and periodic photographs, and may well continue to do so until 1994.

One NASA requirement that had to be met as an element of bringing the Mars mission to an end was verification that the spacecraft transmitters were shut off, so that the Viking radio frequencies could be used again in the future without there being any chance of interference from the Viking transmitters.

By the summer of 1980, the gas supply on Orbiter 1 was running so low that it was clear the spacecraft could not operate much longer. However, by this time, in compliance with the NASA requirement, one final automatic routine had been incorporated to ensure that the transmitters would be turned off before the spacecraft went out of control. This routine made it possible for operations to continue until the gas was completely gone. It monitored the gas supply and the spacecraft attitude with respect to the sun reference. Indication of gas depletion (a gross pressure measurement) as well as loss of sun orientation (a departure of 5° from the sun line) would signal the end of the supply and the end of the mission. The routine, which also ensured that there was enough battery power to complete the operation, would start a table to shut down the transmitters. Orbiter 1 was turned off on 6 August 1980, its gas gone and its transmitters silent.

Thus the Viking orbiters, over a period of about 2 years, were made autonomous step-by-step. The results were spectacular. The spacecraft performed better, manpower and money were saved, the length of mission operations was extended for both orbiters, and more data were gathered with less effort.

The Viking orbiters were probably the first spacecraft to incorporate and depend upon this degree of autonomy, but there will be others. Autonomy in spacecraft systems will be a design goal of the future. But it is not likely that there will be another autonomous spacecraft produced out of such need, by such a remarkable crew and such a small one. And surely there will not be another in which the autonomy is incorporated while the spacecraft is circling a distant planet.

Actions of Estrogens and Progestins on Nerve Cells

Donald W. Pfaff and Bruce S. McEwen

Summary. Estrogens and progestins alter electrical and chemical features of nerve cells, particularly in hypothalamus. Temporally, these events follow nuclear receptor occupation by these steroids, although not all effects have been proved to depend on translocation of receptors to the nucleus. Narrowing studies to focus on particular medial hypothalamic cells has been useful for understanding some of the actions of these steroids in brain. The variety of morphological, chemical, and electrical effects allow for a multiplicity in the cellular functions controlled by these hormones.

In addition to responding rapidly to electrical signals from other neurons, nerve cells react more slowly and over longer periods of time to various chemical messengers arising from within the brain and from without. Among the most potent and specific of chemical signals from outside the brain are the steroid hormones, long recognized as regulators of patterns of behavior related to reproduction and defense of territory (*1*) and more recently recognized as having influences on mood and affective state (*2*).

The cellular mechanisms of steroid hormone action have gained attention in the past decade through the discovery of specific receptor-like macromolecules in the soluble fraction of target tissues which bind the hormone and carry it to the cell nuclear compartment (*3*). This has led, in turn, to incisive studies of the consequences of the actions of hormones like estradiol with respect to how new protein synthesis is induced in the uterus and its relation to cell growth, cell division, and other events (*4*). Similarly, from this model, the manner in which estradiol and progesterone interact with receptor macromolecules in the chick oviduct, trigger messenger RNA (mRNA) formation and, in turn, synthesis and secretion of specific proteins, could be studied in such detail as to approach a molecular biology of hormone action (*5*). A frequent theme in such studies is that hormone occupation of receptor sites in the cell nucleus, for more than a few minutes and often for several hours, is required for the full range of hormone effects (*6*).

The brain is no exception as far as steroids are concerned and has been found to contain receptors for all five classes of steroid hormones: estrogens, progestins, androgens, glucocorticoids, and mineralocorticoids (*7*). These receptor sites are not uniformly distributed but rather occupy specific loci within the brain. As a consequence, studies of the localization of specific steroid hormone–concentrating nerve cells are especially important in brain, where small regions are involved in various complex functions. Specialized steroid hormone autoradiographic techniques (*8*) have the advantage of detecting hormone-accumulating neurons amidst other types of cells. This technique has been used for studying estrogen and androgen receptors among vertebrate classes of fish, amphibia, reptiles, birds, and mammals (including rodents, carnivores, and a primate—the rhesus monkey) (*9*). The neuroanatomical lawfulness of sex hormone binding in the brain is considerable. All species studied have estrogen- or andro-

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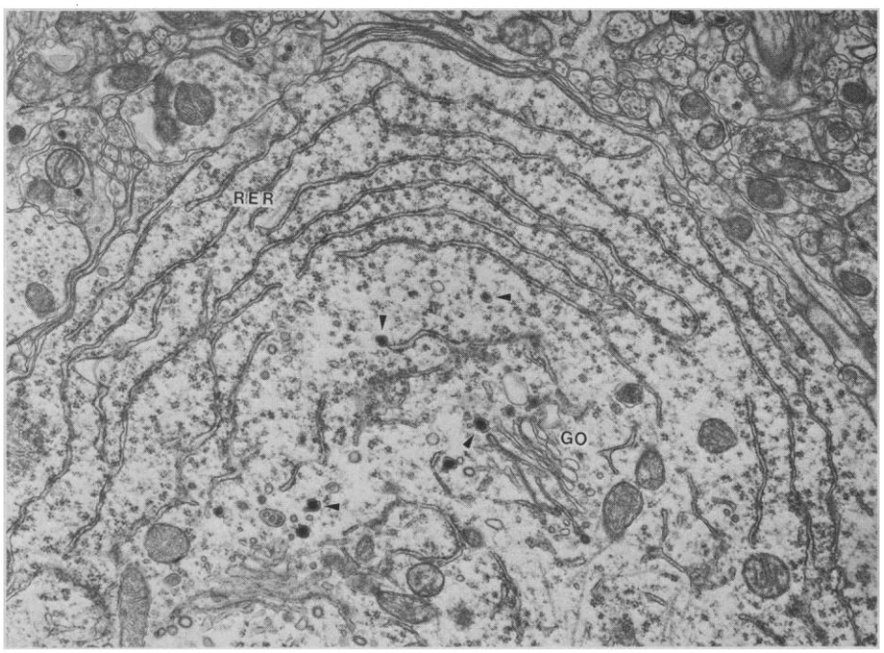
gen-concentrating nerve cells in specific locations. In all animals examined, these locations include the medial preoptic area, medial (tuberal) cell groups in the midline hypothalamus, and limbic forebrain structures such as the medial amygdala and lateral septum or their homologies. In each species, there is a marked overlapping of the locations of sex steroid binding nerve cells and the nerve cell groups controlling sex steroid dependent functions such as reproductive behavior or gonadotropin release, suggesting that hormone accumulation as detected autoradiographically reveals one step of a physiologically important control mechanism (*9, 10*). A steroid hormone not directly related to reproductive function, corticosterone, has a neuroanatomical pattern of accumulation much different from that of the sex steroids, with high neuronal labeling in the hippocampus and septum and virtually nonexistent neuronal labeling in the preoptic area and medial hypothalamus (*11*).

Cell fractionation studies of brain regions with hormone-accumulating cells have yielded converging and complementary results to those from autoradiography. Besides documenting high levels of cell nuclear hormone accumulation in the same nerve cell groups detected by autoradiography (*7, 12*) they have revealed cytosol receptors with affinities and other properties similar to those of receptors in classical nonneural steroid hormone target tissues (*7, 13*). Furthermore, receptor exchange assays developed for brain tissue (*14*) allow the measurement of cell nuclear hormone receptor content under various physiologically meaningful conditions and have revealed, for example, the extensive occupation of hypothalamic and limbic brain estrogen receptors resulting from circulating estradiol in proestrous females (*15*) and from testosterone aromatization in both the developing and adult male rat brain (*16*).

One of the most important uses of hormone receptor mapping in the brain is to focus attention on particular groups of nerve cells in which to search for those cellular effects of the hormones that comprise the mechanisms for their overall functional consequences.

Effects of Estradiol on Nerve Cell Electrical Activity

The first clue to the possibility that sex steroids would alter nerve cell electrical activity came from experiments showing that the discharge rates of hypothalamic neurons altered during the estrous cycle of the female rat. For example, Terasawa and Sawyer (*17*) recorded elevations in electrical activity of arcuate nucleus neurons in the hypothalamus, correlated with ovulation, while Kawakami *et al.* (*18*) found elevated discharge rates on the afternoon of the day of proestrus, a time critical for triggering of ovulatory discharge of luteinizing hormone. Microelectrode recording of single unit activity (*19, 20*) revealed high firing rates on the day of proestrus for nerve cells specifically in the ventral portion of the medial anterior hypothalamus. In these experiments, circulating hormones were probably acting directly on hypothalamic tissue, because similar microelectrode recording in animals with surgically prepared hypothalamic islands showed



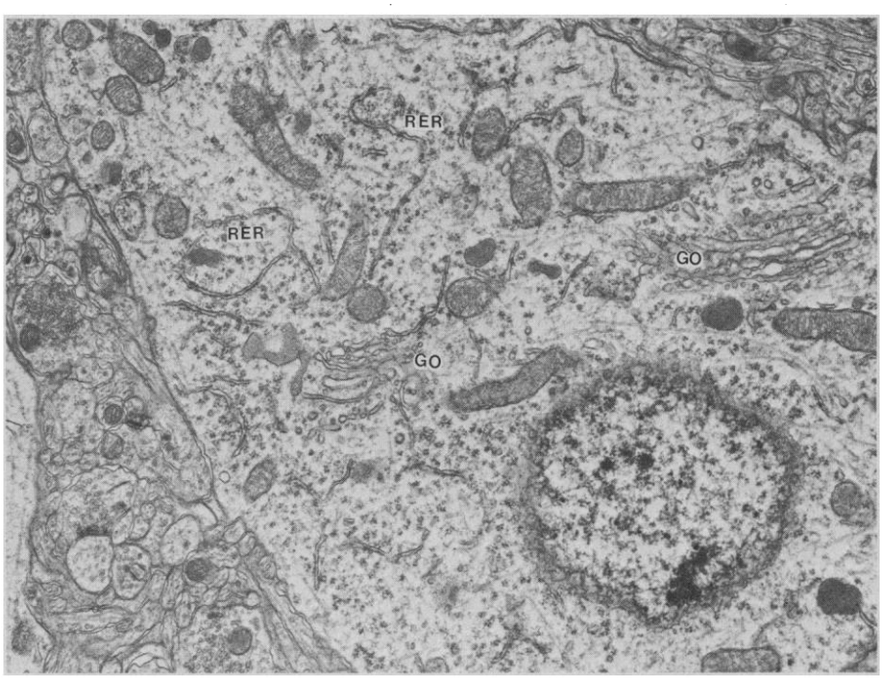


Fig. 1 (top). Electron micrograph of a nerve cell in the ventromedial hypothalamic nucleus of an estrogen-treated female rat. In this cell, large amounts of stacked rough endoplasmic reticulum (*RER*) and dense-cored vesicles (arrow heads) near the Golgi apparatus (*GO*) were seen. [Courtesy of *Cell and Tissue Research* (*43*)] Fig. 2 (bottom). Electron micrograph of a nerve cell in the ventromedial hypothalamic nucleus of a control ovariectomized female rat. In such females, less stacked rough endoplasmic reticulum and fewer dense-cored vesicles were seen than in estrogen-treated animals. Abbreviations as in Fig. 1. [Courtesy of *Cell and Tissue Research* (*43*)]

similar variations of anterior hypothalamic neuronal activity across the estrous cycle (*21*).

Since several steroid and protein hormones are varying during the periods covered by these recording experiments, a simpler situation for analyzing the specific electrical effects of estradiol is to compare ovariectomized animals with or without estrogen treatment. Under these conditions, estrogen treatment leads to increased resting discharge rates in the medial anterior hypothalamus and in basomedial hypothalamic neurons (*22*). One report showed that in spayed female cats electrical activity in the ventromedial nucleus and medial anterior hypothalamus was more responsive to peripheral stimulation after estrogen administration (*23*).

While most studies have focused on long-term actions of estrogen, with time being allowed after estrogen treatment for the metabolic preparations for changes in electrical activity to be complete, Yagi (*24*) found neurons in the medial anterior hypothalamus whose activity was briefly raised within minutes after systemic estradiol injection. Other extremely rapid changes after estradiol have now been reported after iontophoretic administration of the hormone (*25*) and after application of estradiol to cells in vitro (*26*). These findings may not be accounted for by the indirect mechanism involving the cell nucleus and genomic activation, but rather by direct membrane effects of the hormone, the exact nature of which is not clear (*27*).

An overriding characteristic of hypothalamic nerve cells is that they tend to fire slowly. Indeed, among cells near the ventromedial nucleus of the hypothalamus with axons running to the midbrain, a high portion has no resting discharge at all (*28*). Along these lines, those nerve cells in the basomedial hypothalamus whose resting discharge rates are raised by estrogen tend to be the slowest firing cells (*29*).

It is especially interesting that electrical stimulation of cells in the same region as those whose resting discharge rates are elevated by estrogen can facilitate female rat reproductive behavior (*30*). Low frequencies of stimulation are required for this effect. Conversely, electrical stimulation in the preoptic area inhibits female reproductive behavior (*30, 31*). Here systemically administered estrogen also has the opposite effect on electrical activity of single neurons: that is, decreased resting discharge rates. Lincoln (*32*) was the first to show that estradiol treatment of ovariectomized rats is followed by lower spontaneous

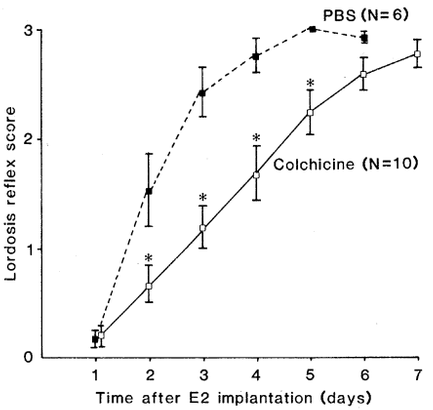


Fig. 3. Microinjection of colchicine bilaterally in the ventromedial hypothalamus 24 hours before estradiol (*E2*) treatment significantly (*) delayed lordosis reflex facilitation, compared to control microinjection of phosphate-buffered saline (means ± standard error of the mean). [Courtesy of *Brain Research* (*44*)]

activity of single units in the preoptic region as well as in the lateral septum. Moreover, probing the vaginal cervix inhibited the electrical activity of preoptic neurons in estrogen-treated animals (*33*). After long-term treatment of ovariectomized rats, fewer preoptic units with recordable spontaneous activity were found, and those that were recorded were less responsive to peripheral somatosensory stimuli (*29*).

From these studies, estrogen increases the electrical activity of nerve cells in regions that foster female reproductive behavior, which itself depends on estrogen, and decreases electrical activity of

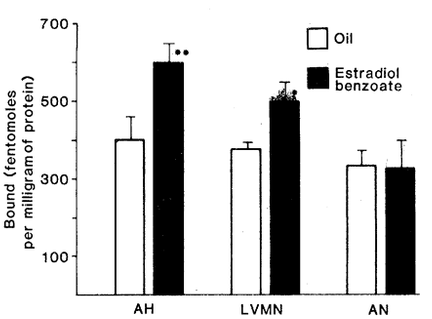


Fig. 4. Effects of estradiol benzoate treatment on the number of muscarinic receptors on medial basal hypothalamic cells. Ovariectomized rats were treated for 2 days with either sesame oil or 10 micrograms of estradiol benzoate in oil. The anterior hypothalamic (*AH*), lateral portion of the ventromedial (*LVMN*), and the arcuate nuclei (*AN*) were removed from frozen sections of rat brain according to the method of Palkovits (*67*) and homogenized in 150 microliters of phosphate buffer. Portions of the homogenate were incubated with 1 n*M* ^{3}H-labeled QNB, and specific binding was determined. $*P < .05$, $**P < .02$, Mann-Whitney *U* test. [Courtesy of *Brain Research* (*47*)]

preoptic neurons, which disrupt feminine behavior. Electrical stimulation of ventromedial hypothalamic neurons promotes the behavior (*30*). What would happen after specific blocking of sodium channels in basomedial hypothalamic neurons? Harlan *et al.* (*34*) worked with estrogen-treated rats that displayed maximal lordosis behavior, and infused local anesthetics (procaine or bupivacaine) or tetrodotoxin into the medial hypothalamus to block sodium flux across nerve cell membranes in a restricted region. In parallel experiments, electrical activity of nearby nerve cells or lordosis behavior were measured. After an intrahypothalamic infusion of procaine or bupivacaine, multi-unit electrical activity could be decreased but not abolished for periods as long as 1 hour, but lordosis behavior remained normal. In contrast, intrahypothalamic infusion of tetrodotoxin led to a complete suppression of electrical activity within 5 minutes of infusion, the suppression lasting for as long as the electrical recording site could be maintained (usually for several hours). With hypothalamic tetrodotoxin infusions, decreases in lordosis behavior began about 40 minutes after the tetrodotoxin, and the greatest effect was reached 2 to 4 hours after infusion. Thus, reproductive behavior loss follows profound and prolonged decreases in medial hypothalamic electrical activity (*34*).

Besides electrical stimulation, direct application of estradiol to the ventromedial hypothalamus suffices to facilitate feminine sexual behavior (*35*). Information regarding the presence of estrogen receptors in neurons of the ventromedial portion of the ventromedial nucleus was crucial for refined estrogen implantation experiments with nanogram amounts of ^{3}H-labeled estradiol where it was demonstrated that locally implanted hormone reaches neurons in this limited area and virtually nowhere else in the course of facilitating feminine sexual behavior in ovariectomized rats (*36*). Subsequent studies revealed that localized application of a protein synthesis inhibitor, anisomycin, to the same area reversibly inhibits the ability of systemic estradiol to promote the feminine sexual response (*37*).

The most obvious way in which hypothalamic neurons control the neural circuitry for reproductive behavior is through axons going to the dorsal midbrain (*10*). In fact, the nature of steroid hormone effects on reproductive behavior, through hypothalamic cells, explains a mechanism of sexual motivation (*38*). Despite striking parallels between the electrical effects of estrogens on hypo-

thalamic neurons and their effects on behavior, the electrical changes by themselves are not sufficient to explain everything about the behavioral effects of these hormones. Notably, increases in the electrical excitability of dorsal midbrain nerve cells after electrical stimulation of the ventromedial hypothalamus can occur without prior treatment with estrogen, whereas identical electrical stimulation of the hypothalamus requires subthreshold estrogen priming for its behavioral effects (*39*). Also, transmission of electrical changes from hypothalamus to midbrain occurs much more quickly than the behavioral effects of electrical stimulation of the ventromedial hypothalamus (*39*). Thus, another aspect of estrogen action must supplement the electrical alterations. Synthesis of new proteins in hypothalamic cells would be just the sort of time-consuming estrogen action theoretically required, and would be consonant with the main conclusions on mechanisms of steroid hormone action in many other tissues (*3–6*).

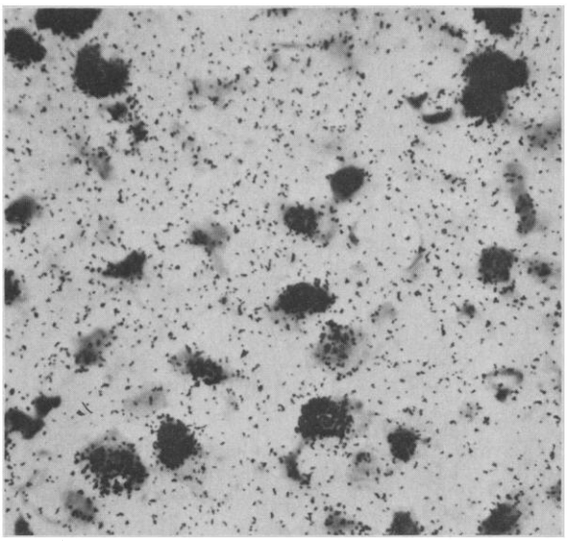


Fig. 5. Dense accumulations of silver grains in autoradiogram depict retention of ^{3}H-labeled progestin (R5020–6,7-^{3}H) by cell bodies in the hypothalamic ventromedial nucleus of an ovariectomized female rat primed with estradiol benzoate. The autoradiogram was prepared with the use of a method to prevent artifacts from translocation of labeled substances (*69*), and involved placing an unfixed 2-micrometers of frozen section onto a slide coated with Kodak NTB-3 nuclear emulsion. The autoradiogram is counterstained lightly with cresyl violet acetate (× 640). [Autoradiography was done by John Gerlach]

Estrogen Influences on Hypothalamic Protein Synthesis

The ultrastructural appearance of ventromedial hypothalamic nerve cells is consistent with this line of thought. We noticed protuberances on the nucleolus in some such neurons, and these occurred more than twice as often in cells sampled from estrogen-treated female rats than control ovariectomized animals (*40*). Since the nucleolus is the main site of ribosomal RNA synthesis (*41*), one possibility is that the electron-dense protuberances represent synthesized ribosomal RNA. Another possibility (*42*) is that they are comprised of nucleolus-associated DNA, directing RNA synthesis, presumably at an increased rate in the estrogen-treated hypothalamic cells. These questions about nucleolar changes will have to be settled by selective staining for DNA and RNA, and by treatment of thin sections with the enzymes deoxyribonuclease or ribonuclease. In the cytoplasm, also, of ventromedial hypothalamic cells estrogen treatment is followed by signs of increased rates of protein synthesis (*43*). In some ventromedial hypothalamic cells following estrogen, large amounts of rough endoplasmic reticulum were seen in stacked arrays, and dense-cored vesicles (perhaps prosecretory granules) were found near the Golgi apparatus (Fig. 1). These cells were found significantly more often than in control ovariectomized animals (Fig. 2). Here, also, as many questions are raised as answered. One conspicuous problem is that even in the ventrolateral subdivision of the ventromedial nucleus of the hypothalamus, not every nerve cell binds estrogen. If we were able to visualize estrophilic neurons as such by other morphologic criteria, the ultrastructural effects of estrogen treatment might be even larger. Further, while these electron microscopic effects in the ventromedial hypothalamus make functional sense, the question is raised as to what the effects would be in other estrogen-accumulating nerve cell groups, for example, in the medial nucleus of the amygdala, the lateral septum, or the preoptic area.

If peptides or other gene products related to neurotransmission, synthesized under the influence of estrogen in medial hypothalamic cells, are transported down the axon and important for behavior, then temporary interruption of axoplasmic transport should delay effects of the hormone on reproductive behavior. Harlan and Shivers approached this question by infusing colchicine into the medial hypothalamus of ovariectomized rats 24 hours before the beginning of estrogen treatment (*44*). Blockage of axoplasmic transport by colchicine resulted in a 2-day delay in the onset of lordosis behavior responsiveness (Fig. 3). In other experiments, infusion of colchicine into the medial hypothalamus of rats maintained on high levels of estrogen disrupted lordosis behavior. These effects were not due to an interruption of electrical activity, because Kow, recording multi-unit activity in the hypothalamus near the cannula tip, saw no effect of colchicine [see (*44*)]. These results suggest that, for the estrogen effect on lordosis behavior, axoplasmic transport

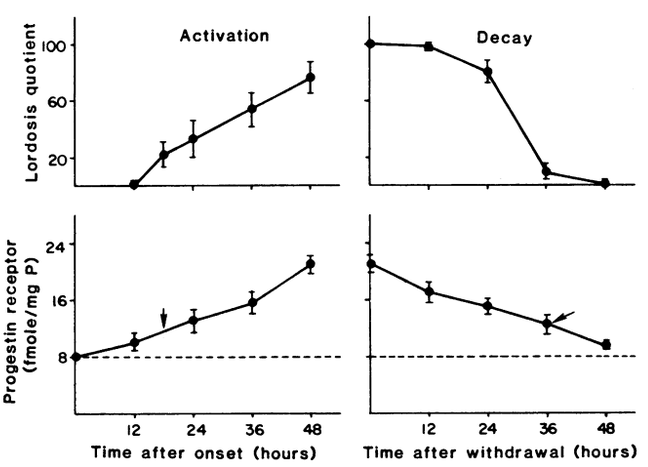


Fig. 6. Parallel changes in hypothalamic cytosol progestin binding (femtomoles of ^{3}H-labeled R5020 per milligram of protein) and reproductive behavior (lordosis quotient) after the onset (left) and withdrawal (right) of subcutaneous estradiol. Arrows show the progestin receptor levels associated with the earliest (left) and latest (right) occurrences of nonzero behavior levels. Error bars indicate the standard errors of the means. *N*'s were 6 for behavior and 5 to 7 for progestin receptor levels. [Courtesy of *Endocrinology* (*53*)]

to or away from the ventromedial hypothalamic cells of interest is required.

Besides axonally transported neurosecretory products of estradiol action, other neurochemicals may be regulated by this hormone in the course of facilitating feminine sexual behavior. One possible regulatory point is in the response of ventromedial hypothalamic neurons to incoming afferent nerve impulses, for which estrogen action might conceivably enhance responses to excitatory afferents or inhibit the effect of inhibitory afferents. Indeed, estradiol treatment is reported to decrease the activity of glutamic acid decarboxylase in the ventromedial nuclei of spayed rats (*45*), an effect that might conceivably reduce the efficacy of GABA (γ-aminobutyric acid) aminergic neurotransmission, which appears to be inhibitory toward lordosis responding (*46*). Conversely, estradiol treatment also appears to increase the density of muscarinic cholinergic receptor sites in the ventromedial nuclei (Fig. 4) (*47*). This effect acquires potential functional significance in light of reports (*48*) from drug infusion studies that a muscarinic cholinergic component in the rat diencephalon appears to facilitate feminine sexual responding. Much more information is required before a causal link can be established for either GABA or acetylcholine and estrogen action on the lordosis response. Although the estrogen dose and time after hormone treatment for these effects is compatible with a role in lordosis, a detailed analysis of these parameters must be carried out, as well as additional drug infusion studies into the ventromedial hypothalamus itself. Moreover, other neurotransmitters, such as serotonin (*49*), may be involved in regulating the ventromedial hypothalamic influence on feminine sexual behavior. Finally, the estrogen effects on these systems can occur in other estrogen sensitive nuclei besides the ventromedial hypothalamus (*45, 47*).

Progesterone Receptor Induction

Another inductive effect of estradiol, that of increasing the number of receptors for progesterone, occurs in the ventromedial nuclei (Fig. 5), as well as in other, but not all, estrogen-concentrating diencephalic and limbic cell groupings (*50*). This regulatory event could underlie synergisms between estradiol and progesterone which affect several endocrine and behavioral phenomena (*51*). The estrogen treatment conditions for progesterone receptor induction are similar to those used for promoting reproductive behavior (*52*). For example, the time courses of progesterone receptor induction and lordosis behavior facilitation as a function of duration of estrogen treatment are remarkably similar (Fig. 6), and the time courses of decay after estrogen withdrawal are also similar (*53*). With the type of ovariectomized animal preparation used, and the estrogen condition employed, 25 to 35 percent of maximal progesterone receptor induction was associated with nonzero behavioral performance. More detailed studies of the temporal requirements of this form of reproductive behavior for estrogen treatment (*54, 55*) also supported a strong positive correlation between lordosis behavior and cytosol progestin receptor level. Under these conditions, 24 hours or 6 hours of continuous estradiol exposure facilitated lordosis behavior and significantly elevated cytosol progestin receptors (Fig. 7). Shortening a single continuous exposure to 3 hours was not effective. Among the discontinuous schedules of treatment (Fig. 7, E to I) those adequate for facilitating the behavior were associated with elevated progestin receptor levels (*54, 55*). Protein synthesis was indeed required for progestin receptor induction as well as behavior, as indicated by the effects of anisomycin (Fig. 7, J to M) when given before one or both estrogen treatments (*56*).

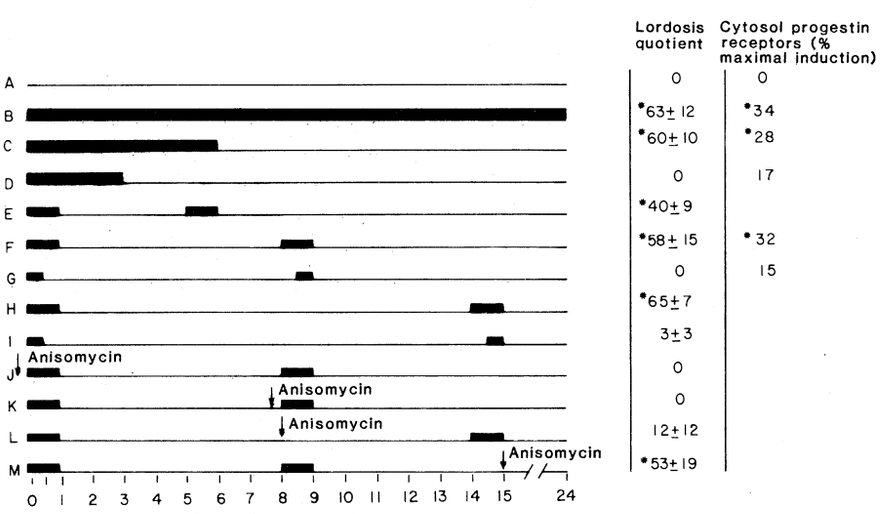


Fig. 7. Effects of subcutaneous estradiol implants (OE_2) and the protein synthesis inhibitor anisomycin on the lordosis quotient and on the hypothalamic cytosol progestin receptor levels. Progestin receptors are expressed by calculating the induction of ^{3}H-labeled R5020 retention (femtomoles per milligram of protein) as a percentage of the maximal induction (after long exposures to high estrogen doses). Effective continuous exposures to estradiol (B and C) could be mimicked by certain discontinuous exposure schedules (E, F, and H). Involvement of new protein synthesis is indicated by susceptibility to anisomycin (J, K, and L) (mean ± standard error of the mean). Statistical comparisons made by one-way analysis of variance followed by Newman-Kuels tests for individual comparisons. *N*'s were 5 to 7 for behavior and 4 to 7 for progestin receptor levels. [Courtesy of *Nature* (*54*)]

Temporal Complexities of Estradiol Action

The temporal requirements for estradiol treatment and resulting progestin receptor induction and feminine sexual behavior highlight the extremely complex nature of the hormone's action (Fig. 7). Two 1-hour periods of estradiol treatment were sufficient, provided that they were at least 4 hours apart and yet not separated by more than 14 hours. Protein synthesis inhibition before the first, before the second, and between the first and second treatments, disrupts estrogen action. Yet within 1 or 2 hours after the second estradiol treatment, protein synthesis inhibition is no longer effective. Several phases of estrogen-directed protein synthesis may be involved in actions on nerve cells, where initial estrogen exposure may sometimes set up conditions for later estrogen action (*54–56*). A possibly analogous interacting sequence of gene activation has been described for the insect steroid hormone, ecdysone, in triggering a pattern of puffs in giant polytene chromosomes of Diptera (*57*).

Progesterone Action on Sexual Behavior

In contrast to those of estradiol, the temporal aspects of initial progesterone action on female sexual behavior in rats seem simpler. For one thing, it occurs more rapidly with onset latencies of 30 to

60 minutes after intravenous hormone administration (*58, 59*). In spite of its speed, progesterone facilitation is blocked by protein synthesis inhibition (*60*). In fact, administration of anisomycin after progesterone facilitation has begun produces a progressive inhibition of the behavioral response over the next hour or so, implying that proteins dependent on progesterone action may turn over rapidly (*60*). Progesterone facilitation is particularly important for the "proceptive" (*60, 61*) aspect of feminine sexual behavior, and this aspect of progesterone action can be selectively eliminated by anisomycin treatment even when high levels of receptivity occur without progesterone treatment because of high levels of estrogen priming (*60*).

Progesterone action on feminine sexual behavior is strongly linked to the ventromedial hypothalamic nuclei. First, low doses of progesterone, diluted in cholesterol, are effective in promoting feminine sexual behavior when implanted in the ventromedial hypothalamus and nowhere else (*62*). Second, estrogen-inducible progestin receptors are found in the ventrolateral portion of the ventromedial nuclei, where estrogen-concentrating cells are also located (Fig. 5) (*50, 52*). Third, anisomycin application to the ventromedial hypothalamus blocks reversibly the facilitative effects of systemic progesterone in estrogen-primed female rats (*37*). Finally, in estrogen-primed, castrated male rats, which fail to respond to progesterone with respect to feminine sexual behavior (*52, 63*), progesterone receptor levels are markedly deficient in the ventromedial nuclei and yet are normal in the nearby arcuate nuclei of the hypothalamus (*64*).

Nevertheless, progesterone action in the ventromedial nuclei has not been linked to a biosynthetic event in the ventromedial nucleus which may be associated with behavior. The nature of rapidly turning over proteins induced by progesterone remains a mystery. Another unusual aspect of progesterone action concerns the mechanism by which it brings about its inhibitory influences on sexual behavior (*51*). Two mechanisms are now under consideration. First is the possibility that decreased progestin receptor levels resulting from an initial bolus of progesterone may be responsible for reduced or refractory responding to subsequent progesterone administration (*65*). Second is the possibility that progesterone may induce other proteins with a longer latency and greater half-life which have an inhibitory behavioral effect not evident until after the first, facilitative phase is past (*66*).

Prospects

Studies of receptors for steroid sex hormones in the hypothalamus and limbic forebrain have set the stage for detailed examination of estrogen and progestin actions on nerve cells. Ultrastructural analyses of hormone effects will approach these questions on a discrete cell-by-cell basis, while chemical fractionation of dissected hypothalamic tissue may identify newly synthesized hormone inducible peptides and proteins. Localized measurements of specific gene products such as enzymes and neurotransmitter receptors, with the use of microdissection (*67*) and quantitative autoradiographic (*68*) procedures, may reveal the nature of others of the hormone induced proteins that are relevant for altered neurotransmission and altered behavior. Of interest for the interactions between electrical and chemical hormone effects are tissue-slice preparations, in which electrophysiological recordings can be carried out with better physical control of the extracellular environment than is possible in vivo. Directing these studies under the simplest functional conditions offers the possibility of clear hypotheses about cellular mechanisms which can be applied, in turn, to questions of current interest such as sex differences in hormone action on the brain.

References and Notes

1. F. A. Beach, *Hormones and Behavior* (Hoeber, New York, 1948); W. C. Young, *Sex and Internal Secretions* (Williams & Wilkins, Baltimore, 1961); O. Floody and D. W. Pfaff, *Assn. Res. Nerv. Mental Dis. Res. Publ.* **52**, 149 (1974).
2. G. M. Brown, *Hosp. Pract.* **10**, 71 (1975); E. K. Klaiber, D. M. Braverman, W. Vogel, Y. Kobayashi, *Arch. Gen. Psychiatry* **36**, 550 (1979); R. T. Rubin, J. M. Reinisch, R. F. Haskett, *Science* **211**, 1318 (1981).
3. E. V. Jensen and H. J. Jacobson, *Rec. Prog. Horm. Res.* **18**, 387 (1962); R. J. B. King and W. I. P. Mainwaring, *Steroid-Cell Interactions* (University Park Press, Baltimore, 1974); B. S. Katzenellenbogen, *Annu. Rev. Physiol.* **42**, 17 (1980).
4. A. B. De Angelo and J. Gorski, *Proc. Natl. Acad. Sci. U.S.A.* **66**, 693 (1970); F. Stormshak, R. Leake, N. Wertz, J. Gorski, *Endocrinology* **99**, 1501 (1976); J. H. Clark and E. J. Peck, Jr., *Female Sex Steroids: Receptors and Function* (Springer-Verlag, Berlin, 1979).
5. J. P. Stein, S. L. C. Woo, A. Dugaiczyk, S. Tsai, A. R. Means, B. W. O'Malley, in *Gene Regulation by Steroid Hormones*, A. K. Roy and J. H. Clark, Eds. (Springer-Verlag, New York, 1980).
6. J. N. Anderson, E. J. Peck, J. H. Clark, *Endocrinology* **96**, 160 (1975); N. C. Lan and B. S. Katzenellenbogen, *ibid.* **98**, 220 (1976).
7. B. S. McEwen, P. G. Davis, B. Parsons, D. W. Pfaff, *Annu. Rev. Neurosci.* **2**, 65 (1979).
8. J. I. Morrell and D. W. Pfaff, in *Neuroendocrinology of Reproduction*, N. T. Adler, Ed. (Plenum, New York, 1981), p. 519.
9. J. I. Morrell and D. W. Pfaff, *Am. Zool.* **18**, 447 (1978); Y. S. Kim, W. E. Stumpf, M. Sar, M. C. Martinez-Vargas, *ibid.*, p. 425; M. Halpern, J. I. Morrell, D. W. Pfaff, *Gen. Comp. Endocrinol.* **46**, 211 (1982); D. W. Pfaff, J. Gerlach, B. S. McEwen, M. Ferin, P. Carmel, E. Zimmerman, *J. Comp. Neurol.* **170**, 279 (1976); J. Gerlach *et al.*, *Brain Res.* **103**, 603 (1976).
10. D. W. Pfaff, *Estrogens and Brain Function: Neural Analysis of a Hormone-Controlled Mammalian Reproductive Behavior* (Springer-Verlag, New York, 1980).
11. B. S. McEwen, J. M. Weiss, L. Schwartz, *Nature (London)* **220**, 911 (1968); *Brain Res.* **16**, 227 (1969); *ibid.* **17**, 471 (1970).
12. B. S. McEwen, in *Subcellular Mechanisms in Reproductive Neuroendocrinology*, F. Naftolin, K. J. Ryan, J. Davies, Eds. (Elsevier, Amsterdam, 1976), pp. 277–304.
13. J. Kato, *J. Steroid Biochem.* **6**, 979 (1975); *ibid.* **11**, 845 (1979); T. O. Fox, *Proc. Natl. Acad. Sci. U.S.A.* **72**, 4303 (1975).
14. J. N. Anderson, J. H. Clark, E. J. Peck, Jr., *Biochem. J.* **126**, 561 (1972); E. J. Roy and B. S. McEwen, *Steroids* **30**, 657 (1977); K. L. Kelner, A. L. Miller, E. J. Peck, Jr., *J. Receptor Res.* **1**, 215 (1980); J. D. Blaustein and H. H. Feder, *Endocrinology* **106**, 1061 (1980).
15. M. Y. McGinnis, L. C. Krey, N. J. MacLusky, B. S. McEwen, *Neuroendocrinology* **33**, 158 (1981).
16. I. Lieberburg, L. C. Krey, B. S. McEwen, *Brain Res.* **178**, 207 (1979); L. C. Krey, F. Kamel, B. S. McEwen, *ibid.* **193**, 277 (1980).
17. E. Terasawa and C. H. Sawyer, *Endocrinology* **85**, 143 (1969).
18. M. Kawakami, E. Terasawa, T. Ibuki, *Neuroendocrinology* **6**, 30 (1970).
19. R. G. Dyer, C. J. Pritchett, B. A. Cross, *J. Endocrinol.* **53**, 151 (1972).
20. R. L. Moss and O. T. Law, *Brain Res.* **30**, 435 (1971).
21. B. A. Cross and R. G. Dyer, in *Steroid Hormones and Brain Function, UCLA Forum in Medical Sciences, 15th*, C. H. Sawyer and R. A. Gorski, Eds. (Univ. of California Press, Los Angeles, 1971), pp. 95–102.
22. M. Kawakami, E. Terasawa, T. Ibuki, M. Manaka, *ibid.*, pp. 79–93; B. A. Cross and R. G. Dyer, *J. Physiol. (London)* **222**, 25p (1972).
23. M. Alcaraz, C. Guzman-Flores, M. Salas, C. Beyer, *Brain Res.* **15**, 439 (1969).
24. K. Yagi, *ibid.* **53**, 343 (1973).
25. M. J. Kelly, R. L. Moss, C. A. Dudley, C. P. Fawcett, *Exp. Brain Res.* **30**, 43 (1977).
26. B. Dufy, J.-D. Vincent, H. Fleury, P. Du Pasquier, D. Gourdji, A. Tixier-Vidal, *Science* **204**, 509 (1979); T. J. Teyler, R. M. Vardaris, D. Lewis, A. B. Rawitch, *ibid.* **209**, 1017 (1980).
27. B. S. McEwen, A. Biegon, T. Rainbow, C. Paden, L. Snyder, V. De Groff, in *Steroid Hormone Regulation of the Brain*, K. Fuxe, J.-A. Gustafsson, L. Wetterberg, Eds. (Pergamon, Oxford, 1981), pp. 15–29.
28. Y. Sakuma and D. W. Pfaff, *Exp. Brain Res.* **46**, 292 (1982).
29. J. Bueno and D. W. Pfaff, *Brain Res.* **101**, 67 (1976).
30. D. W. Pfaff and Y. Sakuma. *J. Physiol. (London)* **288**, 189 (1979).
31. C. W. Malsbury, D. W. Pfaff, A. M. Malsbury, *Brain Res.* **181**, 267 (1980).
32. D. W. Lincoln, *J. Endocrinol.* **37**, 177 (1967).
33. _____ and B. A. Cross, *ibid.*, p. 191.
34. R. Harlan, B. D. Shivers, L.-M. Kow, D. W. Pfaff, *Soc. Neurosci. Abstr.* **7**, 615 (1981); *Brain Res.*, in press.
35. R. D. Lisk, *Am. J. Physiol.* **203**, 493 (1962); G. Dörner, F. Döcke, S. Moustafa, *J. Reprod. Fertil.* **17**, 583 (1968); R. Barfield and J. Chen, *Endocrinology* **101**, 1716 (1977); B. Rubin and R. Barfield, *ibid.* **106**, 504 (1980).
36. P. G. Davis, B. McEwen, D. W. Pfaff, *Endocrinology* **104**, 898 (1979).
37. T. C. Rainbow, M. Y. McGinnis, P. G. David, B. S. McEwen, *Brain Res.* **233**, 417 (1982).
38. D. W. Pfaff, Ed., *The Physiological Mechanisms of Motivation* (Springer-Verlag, New York, 1982).
39. Y. Sakuma and D. W. Pfaff, *J. Neurophysiol.* **44**, 1012 (1980).
40. R. S. Cohen and D. W. Pfaff, *Soc. Neurosci. Abstr.* **8**, 531 (1982).
41. H. Busch and K. Smetana, *The Nucleolus* (Academic Press, New York, 1970).
42. S. Fakan and E. Puvion, *Int. Rev. Cytol.* **65**, 255 (1980); G. Goessens and A. Lepoint, *Biol. Cellulaire* **35**, 211 (1979).
43. R. Cohen and D. W. Pfaff, *Cell Tissue Res.* **217**, 451 (1981).
44. R. E. Harlan, B. D. Shivers, L.-M. Kow, D. W. Pfaff, *Brain Res.* **238**, 153 (1982).
45. C. J. Wallis and W. G. Luttge, *J. Neurochem.* **34**, 609 (1980).
46. S. Schwartz-Giblin, P. Femano, D. W. Pfaff, unpublished observations.
47. T. C. Rainbow, V. De Groff, V. N. Luine, B. S. McEwen, *Brain Res.* **198**, 239 (1980).
48. L. G. Clemens and G. P. Dohanich, *Pharmacol. Biochem. Behav.* **13**, 89 (1980); L. G. Clemens, R. R. Humphrys, G. P. Dohanich, *ibid.*, p. 81; G. P. Dohanich and L. G. Clemens, *Horm. Behav.* **15**, 157 (1981).

49. B. J. Meyerson, *Acta Physiol. Scand.* **63** (Suppl. 241), 1 (1964); F. P. Zemlan, I. L. Ward, W. R. Crowley, D. L. Margules, *Science* **179**, 1010 (1973); M. M. Foreman and R. L. Moss, *Horm. Behav.* **10**, 97 (1978); V. N. Luine and C. M. Paden, *Neuroendocrinology* **34**, 245 (1982); V. N. Luine and C. T. Fischette, *ibid.*, p. 237.
50. M. Warembourg, *Mol. Cell. Endocrinol.* **12**, 67 (1978); *Neurosci. Lett.* **9**, 329 (1978).
51. W. C. Young, *Sex and Internal Secretions* (Williams & Wilkins, Baltimore, 1961); H. H. Feder and B. L. Marrone, *Ann. N.Y. Acad. Sci.* **186**, 331 (1977).
52. B. S. McEwen *et al.*, in *Progesterone and Progestins*, C. W. Bardin, P. Mauvais-Jarvis, E. Milgrom, Eds. (Raven, New York, in press).
53. B. Parsons, N. J. MacLusky, L. Krey, D. W. Pfaff, B. S. McEwen, *Endocrinology* **107**, 774 (1980).
54. B. Parsons, T. C. Rainbow, D. W. Pfaff, B. S. McEwen, *Nature (London)* **292**, 58 (1981).
55. B. Parsons, B. S. McEwen, D. W. Pfaff, *Endocrinology* **110**, 613 (1982).
56. B. Parsons, T. Rainbow, D. W. Pfaff, B. S. McEwen, *ibid.*, p. 620.
57. U. Clever, *Science* **146**, 794 (1964); M. Ashburner, *Dev. Biol.* **39**, 141 (1974); ——— and H. D. Berendes, in *The Genetics and Biology of Drosophila*, M. Ashburner and T. R. F. Wright, Eds. (Academic Press, New York, 1978), pp. 315–395.
58. B. J. Meyerson, *Horm. Behav.* **3**, 1 (1972); C. Kubli-Grafias and R. E. Whalen, *ibid.* **9**, 380 (1977).
59. M. Y. McGinnis, B. Parsons, T. C. Rainbow, L. C. Krey, B. S. McEwen, *Brain Res.* **218**, 365 (1981).
60. T. C. Rainbow, P. G. Davis, B. S. McEwen, *ibid.* **194**, 548 (1980).
61. B. J. Tennent, E. R. Smith, J. M. Davidson, *Horm. Behav.* **14**, 65 (1980).
62. B. S. Rubin and R. J. Barfield, *Abstracts of the Eastern Conference on Reproductive Behavior*, New Orleans, 1979; *Endocrinology*, in press; B. S. Rubin, thesis, Rutgers University (1981).
63. J. M. Davidson and S. Levine, *J. Endocrinol.* **44**, 129 (1969); L. G. Clemens, J. Shryne, R. A. Gorski, *Physiol. Behav.* **5**, 673 (1970); R. E. Whalen, W. G. Luttge, B. B. Gorzalka, *Horm. Behav.* **2**, 83 (1971).
64. T. C. Rainbow, B. Parsons, B. S. McEwen, *Nature (London)* **300**, 648 (1982).
65. J. D. Blaustein and H. H. Feder, *Brain Res.* **177**, 489 (1979); also see J. D. Blaustein and H. H. Feder in (*14*).
66. B. Parsons and B. S. McEwen, *J. Neurosci.* **1**, 527 (1981).
67. M. Palkovits, *Brain Res.* **59**, 449 (1973).
68. T. C. Rainbow, A. Biegon, W. V. Bleisch, *Life Sci.*, **30**, 1769 (1982).
69. J. L. Gerlach and B. S. McEwen, *Science* **175**, 1133 (1972).
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Industrial Innovation Policy: Lessons from American History

Richard R. Nelson and Richard N. Langlois

Government involvement in the research and development (R & D) process has a long history in this country. As is too often the case, this rich experience has seldom been consulted in policy debates over government programs to stimulate industrial innovation.

Summary. The historical interrelations of government support of R & D and technical change in seven major American industries point to three types of policy that have been successful in the past: (i) government R & D support for technologies in which the government has a strong and direct procurement interest; (ii) decentralized systems of government-supported research in the "generic" area between the basic and the applied; and (iii) a decentralized system of clientele-oriented support for applied R & D. A fourth type of policy, under which the government attempts to "pick winners" in commercial applied R & D, has been a clear-cut failure.

This article is an attempt to identify some of the lessons of past federal R & D policy. It summarizes the conclusions of a study, recently completed at the Center for Science and Technology Policy at New York University, of how such policies have shaped technological change in seven major American industries—semiconductors, computers, aircraft, pharmaceuticals, agriculture, residential construction, and automobiles (*1*). What makes this study unique is its explicitly comparative, cross-industry focus: it was predicated on the hypothesis—amply supported in the resulting case studies—that the kinds of government programs that have shown themselves feasible and effective vary greatly among industrial sectors, depending upon the nature of the governmental involvement and the nature of competition in the industry.

The selection of industries for study was made with an eye toward obtaining a sample with a broad spectrum of characteristics: industries with fragmented as well as with concentrated structures and industries subject to much government intervention and to relatively little. The design of the study was also informed by a desire to attract recognized scholars knowledgeable about the technology in each industry; the prior interests and areas of expertise of these scholars were therefore a factor in the selection of industries. The study was then carried out as a cooperative research effort (*2*).

The Unraveling Consensus

In treating the questions of innovation policy as warranting detailed empirical exploration, we were acknowledging, reluctantly, that the general theoretical analyses and statistical observations of economists provide only limited and incomplete guidance for policy. We are not alone in this perception; the most significant aspect of the recent economic literature on innovation is its progressive inconclusiveness about the appropriate role for government.

It was not always that way. Economic research a decade or more ago had settled on two closely related sets of propositions about industrial innovation. The first of these was that technological change is an important source of productivity growth and, simultaneously, that R & D expenditure is a principal determinant of technological advance. The implication drawn from this was that R & D spending is a kind of "control variable" through which one would affect macroeconomic productivity.

The second set of arguments derived from theoretical rather than statistical work. Economists during the 1950's and '60's developed models in which private firms possessed an inherent tendency to

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