Downloaded from pharmrev.aspetjournals.org at Thammasart University on December 8, 2012

Corticotrophin Releasing Factor
 Corticotrophin Releasing Factor
 JULIA C. BUCKINGHAM
 Neuroendocrine Unit Royal Free Hospital School of Medicine London Neuroendocrine Unit, Royal Free Hospital School of Medicine, London

MANY years ago Geoffrey W. Harris and his colleagues
ggested that the adrenocorticotrophic activity of the I. Introduction must be much that the adrenocorticotrophic activity of the suggested that the adrenocorticotrophic activity of the after anterior pituitary gland is controlled by a chemical trans-**I. Introduction**
MANY years ago Geoffrey W. Harris and his colleague
suggested that the adrenocorticotrophic activity of the
anterior pituitary gland is controlled by a chemical tran
mitter substance, later named the cort mitter substance, laterature in the substance, later named the corticotrophic activity of the anterior pituitary gland is controlled by a chemical transition mitter substance, later named the corticotrophin releasing facto MANY years ago Geoffrey W. Harris and his colleagues
suggested that the adrenocorticotrophic activity of the
anterior pituitary gland is controlled by a chemical trans-
mitter substance, later named the corticotrophin rele suggested that the adrenocorticotrophic activity of anterior pituitary gland is controlled by a chemical trimitter substance, later named the corticotrophin reling factor, liberated by neurones in the hypothala-
and convey anterior pituitary gland is controlled by a chemical transmitter substance, later named the corticotrophin releasing factor, liberated by neurones in the hypothalamus cand conveyed to the adenohypophysis via the hypothal-
 mitter substance, later named the corticotrophin releasing factor, liberated by neurones in the hypothalamus conveyed to the adenohypophysis via the hypothal-
amo-hypophysial portal vessels. This proposal naturally stimul ing factor, liberated by neurones in the hypothalamus
and conveyed to the adenohypophysis via the hypothal-
amo-hypophysial portal vessels. This proposal naturally
stimulated attempts to isolate and identify the active
sub and conveyed to the adenohypophysis via the hypothal-
amo-hypophysial portal vessels. This proposal naturally
stimulated attempts to isolate and identify the active
substance. However, while there can be no doubt that
the amo-hypophysial portal vessels. This proposal naturally
stimulated attempts to isolate and identify the active
substance. However, while there can be no doubt that
the hypothalamus contains a substance, or possibly sub-
st stimulated attempts to isolate and identify the active
substance. However, while there can be no doubt tha
the hypothalamus contains a substance, or possibly sub
stances, capable of stimulating corticotrophin (ACTH
secreti substance. However, while there can be no doubt that
the hypothalamus contains a substance, or possibly sub-
stances, capable of stimulating corticotrophin (ACTH)
secretion, its chemical identity remains a mystery. Nev-
er the hypothalamus contains a substance, or possibly substances, capable of stimulating corticotrophin (ACTH) secretion, its chemical identity remains a mystery. Nevertheless, something is known about the mechanisms that con stances, capable of stimulating corticotrophin (ACTH
secretion, its chemical identity remains a mystery. Nevertheless, something is known about the mechanism
that control its (their) secretion. In the sections that
follow, secretion, its chemical identity remains a mystery. Nevertheless, something is known about the mechanisms and that control its (their) secretion. In the sections that $\frac{cC}{d}$ follow, studies on the chemistry, physiolog reviewed. II. Evidence for the Existence of Corticotrophin
II. Evidence for the Existence of Corticotrophin
Releasing Factor

Releasing **Factor** II. Evidence for the Existence of Corticotrophin
Releasing Factor
When Harris (105) and Brooks (30) first suggested,

II. Evidence for the Existence of Corticotrophin Findmusseum Releasing Factor $\frac{105}{100}$ and Brooks (30) first suggested, steps rather tentatively, that the secretory activity of in the adenohypophysis may be control 1. EVIDENCE FOR THE EXISTENCE OF COPUCOUPODIN Releasing Factor

When Harris (105) and Brooks (30) first suggested,

perhaps rather tentatively, that the secretory activity of

the adenohypophysis may be controlled by humo transmitted stimuli from the secretory activity of
perhaps rather tentatively, that the secretory activity of
the adenohypophysis may be controlled by humorally
stransmitted stimuli from the hypothelamus little interest
wa perhaps rather tentatively, that the secretory activity of instead and the adenohypophysis may be controlled by humorally star transmitted stimuli from the hypothalamus little interest the was expressed in their hypothesis the adenohypophysis may be controlled by hum
transmitted stimuli from the hypothalamus little in
was expressed in their hypothesis. This was pro
mainly because it was thought, at that time, the
direction of blood flow in t transmitted stimuli from the hypothalamus little interest
was expressed in their hypothesis. This was probably
mainly because it was thought, at that time, that the
direction of blood flow in the hypothalamo-hypophysial
po was expressed in their hypothesis. This was probably where we mainly because it was thought, at that time, that the adirection of blood flow in the hypothalamo-hypophysial portal vessels (which form the only anatomical lin mainly because it was thought, at that time, that the direction of blood flow in the hypothalamo-hypophysial portal vessels (which form the only anatomical link between the hypothalamus and the anterior pituitary gland) wa

mus. The direction of flow in these vessels subsequently became a matter of controversy and it was not until 1949, mus. The direction of flow in these vessels subsequently
became a matter of controversy and it was not until 1949,
after the development of an elegant technique for the mus. The direction of flow in these vessels subsequently
became a matter of controversy and it was not until 1949,
after the development of an elegant technique for the
direct observation of blood flow in the portal vessel mus. The direction of flow in these vessels subsequently
became a matter of controversy and it was not until 1949,
after the development of an elegant technique for the
direct observation of blood flow in the portal vessel mus. The direction of flow in these vessels subsequently
became a matter of controversy and it was not until 1949,
after the development of an elegant technique for the
direct observation of blood flow in the portal vessel became a matter of controversy and it was not until 1949,
after the development of an elegant technique for the
direct observation of blood flow in the portal vessels of
rats, that Green and Harris (96) were able to demons after the developme
direct observation of
rats, that Green and l
conclusively that bloo
the pituitary gland.
It is now firmly of rect observation of blood flow in the portal vessels of
ts, that Green and Harris (96) were able to demonstrate
nclusively that blood passes from the hypothalamus to
e pituitary gland.
It is now firmly established that the

Downloaded from pharmrev.aspetjournals.org at Thammasart University on December 8, 2012
Downloaded from pharmrev.aspetjournals.org at Themmasart University on December 8, 2012 rats, that Green and Harris (96) were able to demonstrate
conclusively that blood passes from the hypothalamus to
the pituitary gland.
It is now firmly established that the synthesis and
release of the hormones of the aden conclusively that blood passes from the hypothalamus to
the pituitary gland.
It is now firmly established that the synthesis and
release of the hormones of the adenohypophysis are
controlled by substances released from ner It is now firmly established that the synthesis a
release of the hormones of the adenohypophysis is
controlled by substances released from nerve endings
the hypothalamus and conveyed to the anterior pituits
gland via the p controlled by substances released from nerve endings in
the hypothalamus and conveyed to the anterior pituitary
gland via the portal vessels. The evidence that demon-
strated the fundamental importance of the hypothalamus
 gland via the portal vessels. The evidence that demonstrated the fundamental importance of the hypothalamus and the hypothalamo-hypophysial portal vessels in the control of corticotrophin secretion came mainly from the hypothalamus and conveyed to the anterior pituitary
gland via the portal vessels. The evidence that demon-
strated the fundamental importance of the hypothalamus
and the hypothalamo-hypophysial portal vessels in the
c gland via the portal vessels. The evidence that demon-
strated the fundamental importance of the hypothalamus
and the hypothalamo-hypophysial portal vessels in the
control of corticotrophin secretion came mainly from
exper strated the fundamental importance of the hypothalamus
and the hypothalamo-hypophysial portal vessels in the
control of corticotrophin secretion came mainly from
experiments that involved transection of the pituitary
stalk and the hypothalamo-hypophysial portal vessels in the control of corticotrophin secretion came mainly from experiments that involved transection of the pituitary stalk, transplantation of the pituitary gland to a site remo control of cortic
experiments tha
stalk, transplant
remote from the
the hypothalamu
Ordinary trans periments that involved transection of the pituitary
alk, transplantation of the pituitary gland to a site
mote from the sella turcica, or electrical stimulation of
e hypothalamus.
Ordinary transection of the pituitary sta stalk, transplantation of the pituitary gland to a site
remote from the sella turcica, or electrical stimulation of
the hypothalamus.
Ordinary transection of the pituitary stalk is followed
first by adrenal atrophy and sub

remote from the sella turcica, or electrical stimulation of
the hypothalamus.
Ordinary transection of the pituitary stalk is followed
first by adrenal atrophy and subsequently by the recur-
rence of normal adrenocortical a the hypothalamus.

Ordinary transection of the pituitary stalk is followed

first by adrenal atrophy and subsequently by the recur-

rence of normal adrenocortical activity. Histological

studies demonstrated that, unless Ordinary transection of the pituitary stalk is followed
first by adrenal atrophy and subsequently by the recur-
rence of normal adrenocortical activity. Histological
studies demonstrated that, unless a wax paper plate was
 first by adrenal atrophy and subsequently by the recurrence of normal adrenocortical activity. Histological studies demonstrated that, unless a wax paper plate was inserted between the two cut ends, transection of the stal rence of normal adrenocortical activity. Histological
studies demonstrated that, unless a wax paper plate was
inserted between the two cut ends, transection of the
stalk was followed, almost invariably, by regeneration of
 studies demonstrated that, unless a wax paper plate was inserted between the two cut ends, transection of the stalk was followed, almost invariably, by regeneration of the portal vessels, and that the degree of regeneratio inserted betwee
stalk was follow
the portal vesse
was correlated v
activity (107).
The simple ex alk was followed, almost invariably, by regeneration of
e portal vessels, and that the degree of regeneration
as correlated with the degree of restoration of pituitary
tivity (107).
The simple experiment of removing the pi the portal vessels, and that the degree of regeneration
was correlated with the degree of restoration of pituitary
activity (107).
The simple experiment of removing the pituitary gland
from the sella turcica and transplant

was correlated with the degree of restoration of pituitary
activity (107).
The simple experiment of removing the pituitary gland
from the sella turcica and transplanting it to another site
in the body also demonstrated the in the body also demonstrated the role of the hypothal254
function. When the transplanted tissue was placed in a from
site remote from the sella turcica, for example, the an-BUCKI
function. When the transplanted tissue was placed in a
site remote from the sella turcica, for example, the an-
terior chamber of the eye, the kidney capsule, or temporal BUCK
function. When the transplanted tissue was placed in a
site remote from the sella turcica, for example, the an-
terior chamber of the eye, the kidney capsule, or temporal
lobe of the brain, partial or complete atrophy function. When the transplanted tissue was placed in a from site remote from the sella turcica, for example, the anterior chamber of the eye, the kidney capsule, or temporal lat lobe of the brain, partial or complete atrop function. When the transplanted tissue was placed in
site remote from the sella turcica, for example, the a
terior chamber of the eye, the kidney capsule, or tempor
lobe of the brain, partial or complete atrophy of tl
adre site remote from the sella turcica, for example, the
terior chamber of the eye, the kidney capsule, or temp
lobe of the brain, partial or complete atrophy of
adrenal cortices followed. When, however, the tra
planted tissue terior chamber of the eye, the kidney capsule, or temporal
lobe of the brain, partial or complete atrophy of the
adrenal cortices followed. When, however, the trans-
planted tissue was placed in the vicinity of the hypophy lobe of the brain, partial or complete atrophy of the radrenal cortices followed. When, however, the trans-
planted tissue was placed in the vicinity of the hypothal-
amus and pituitary stalk, regeneration of the hypophysi adrenal cortices foll
planted tissue was plamus and pituitary st
portal vessels occurr
was restored (108).
As early as 1936 it anted tissue was placed in the vicinity of the hypothal-
hus and pituitary stalk, regeneration of the hypophysial
rtal vessels occurred and anterior pituitary function
as restored (108).
As early as 1936 it was realised th

amus and pituitary stalk, regeneration of the hypophysial ventral vessels occurred and anterior pituitary function was restored (108).

As early as 1936 it was realised that diffuse electrical has have a spinal cord of Sta portal vessels occurred and anterior pituitary functives restored (108).
As early as 1936 it was realised that diffuse electric
stimuli applied to the head or lumbar spinal cord
rabbits (176) or rats (104) enhance adenohyp was restored (108).

As early as 1936 it was realised that diffuse electrical

stimuli applied to the head or lumbar spinal cord of

rabbits (176) or rats (104) enhance adenohypophysial

activity. In an attempt to delimit As early as 1936 it was realised that diffuse electrical heatimuli applied to the head or lumbar spinal cord of S.
rabbits (176) or rats (104) enhance adenohypophysial A.
activity. In an attempt to delimit the neural struc stimuli applied to the head or lumbar spinal cord of S
rabbits (176) or rats (104) enhance adenohypophysial
activity. In an attempt to delimit the neural structures
involved, localised electrical stimuli were applied rabbits (176) or rats (104) enhance adenohypophysial A
activity. In an attempt to delimit the neural structures
involved, localised electrical stimuli were applied directly
to regions of the hypothalamus and anterior pitui activity. In an attempt to delimit the neural structures envolved, localised electrical stimuli were applied directly the regions of the hypothalamus and anterior pituitary tigland of anaesthetised animals. Electrical stim to regions of the hypothalamus and anterior pituitary tissed
gland of anaesthetised animals. Electrical stimulation of that
the pituitary gland was ineffective but stimulation of exp
discrete areas of the hypothalamus evok gland of anaesthetised animals. Electrical stimulation of thal
the pituitary gland was ineffective but stimulation of exp
discrete areas of the hypothalamus evoked the release of extra
nterior pituitary hormones. Correspon the pituitary gland was ineffective but stimulation of discrete areas of the hypothalamus evoked the release of anterior pituitary hormones. Corresponding lesions in the hypothalamus were, however, not always effective in discrete areas of the hypothalamus evoked the release of extinent extract extent terms of the hypothalamus were, however, not always effective in dependency of the hypothalamus was performed in suggested stimulation of the anterior pituitary hormones. Corresponding lesions in hythe hypothalamus were, however, not always effective in desuppressing pituitary activity. Moreover, since the electrical stimulation of the hypothalamus was performed the hypothalamus were, however, not always effective
suppressing pituitary activity. Moreover, since the electrical stimulation of the hypothalamus was performed
anaesthetised animals, the possibility existed that to
beerv suppressing pituitary activity. Metrical stimulation of the hypothala
anaesthetised animals, the possi
observed endocrine activity was
cation induced by the anaesthesis
Harris (106) believed it import cal stimulation of the hypothalamus was performed in
aesthetised animals, the possibility existed that the
served endocrine activity was the result of a compli-
tion induced by the anaesthesia.
Harris (106) believed it imp

anaesthetised animals, the possibility existed that the observed endocrine activity was the result of a competion induced by the anaesthesia.
Harris (106) believed it important to study endocrinfunction in conscious animal observed endocrine activity was the result of a composition induced by the anaesthesia.

Harris (106) believed it important to study endocreant function in conscious animals, and, accordingly, devoped an ingenious method f cation induced by the anaesthesia.

Harris (106) believed it important to study endocrine

function in conscious animals, and, accordingly, devel-

oped an ingenious method for "remote control stimula-

tion" of the hypoth Harris (106) believed it important to study endocrine
function in conscious animals, and, accordingly, devel-
oped an ingenious method for "remote control stimula-
tion" of the hypothalamus in unanaesthetised rabbits.
With function in conscious animals, and, accordingly, developed an ingenious method for "remote control stimulation" of the hypothalamus in unanaesthetised rabbits With the aid of this technique, experiments were performed for oped an ingenious method for "remote control stimula-
tion" of the hypothalamus in unanaesthetised rabbits.
With the aid of this technique, experiments were per-
formed for relatively long periods without concomitant were
 tion" of the hypothalamus in unanaesthetised rabbi
With the aid of this technique, experiments were po
formed for relatively long periods without concomita
operative trauma. Furthermore, the experiments we
repeated many ti With the aid of this technique, experiments were performed for relatively long periods without concomitant operative trauma. Furthermore, the experiments were repeated many times in the same animal, thereby reducing the ch formed for relatively long periods without concomitan
operative trauma. Furthermore, the experiments were
repeated many times in the same animal, thereby reduce
ing the chances that variable factors, such as difference
in operative trauma. Furthermore, the experiments were
repeated many times in the same animal, thereby reduc-
ing the chances that variable factors, such as differences
in the nutritional or oestrous state of the animal, infl repeated many times in the same animal, thereby reduc-
ing the chances that variable factors, such as differences
in the nutritional or oestrous state of the animal, influ-
enced the result. The method involved a prelimina ing the chances that variable factors, such as differences laid the nutritional or oestrous state of the animal, influ-
enced the result. The method involved a preliminary the operation in which a small flat coil was inser in the nutritional or oestrous state of the animal, influ-
enced the result. The method involved a preliminary
operation in which a small flat coil was inserted between
the skull and scalp. The inner turn of the coil was
c enced the result. The method involved a preliminary the operation in which a small flat coil was inserted between the skull and scalp. The inner turn of the coil was connected to an electrode implanted in the hypothalamus operation in which a small flat coil
the skull and scalp. The inner t
connected to an electrode implanted
and the outer turn of the coil was c
electrode, the indifferent electrode.
Stimulation of the hypothalamus e skull and scalp. The inner turn of the coil was
nnected to an electrode implanted in the hypothalamus
d the outer turn of the coil was connected to a second
ectrode, the indifferent electrode.
Stimulation of the hypothal connected to an electrode implanted in the hypothalamus

and the outer turn of the coil was connected to a second

electrode, the indifferent electrode.

Stimulation of the hypothalamus was readily achieved

with the price

and the outer turn of the coil was connected to a second
electrode, the indifferent electrode.
Stimulation of the hypothalamus was readily achieved
by placing the animal's head in an electromagnetic field
and inducing a vo electrode, the indifferent electrode.
Stimulation of the hypothalamus was readily achieved
by placing the animal's head in an electromagnetic field
and inducing a voltage in the buried coil by remote
control. The experimen Stimulation of the hypothalamus was readily achieved with the policing the animal's head in an electromagnetic field thand inducing a voltage in the buried coil by remote at control. The experiments that followed demonstra by placing the animal's head in an electromagnetic field
and inducing a voltage in the buried coil by remote
control. The experiments that followed demonstrated bo
clearly that electrical stimulation of discrete areas of t and inducing a voltage in the buried coil by remote control. The experiments that followed demonstrated clearly that electrical stimulation of discrete areas of the hypothalamus increased markedly the activity of the adren control. The experiments that followed demonstrated
clearly that electrical stimulation of discrete areas of the
hypothalamus increased markedly the activity of the
adrenal cortex (98). This finding led Harris to postulate clearly that electrical stimulation of discrete areas of the hypothalamus increased markedly the activity of the adrenal cortex (98). This finding led Harris to postulat that the hypothalamus liberates a chemical transmitt hypothalamus increased markedly the activity of adrenal cortex (98). This finding led Harris to postul
that the hypothalamus liberates a chemical transmit
substance into the hypophysial portal vessels that st
ulates the ad adrenal cortex (98). This finding led Harris to postulate
that the hypothalamus liberates a chemical transmitter the
substance into the hypophysial portal vessels that stim-
in ulates the adrenocorticotrophic activity of t that the hypothalamus liberates a chemical transmitter
substance into the hypophysial portal vessels that stim-
ulates the adrenocorticotrophic activity of the adenohy-(224). pophysis. This substance was subsequently named the corticotrophin releasing factor (CRF) by Saffran et al. (224).

Slusher and Roberts (251) were the first to report the extraction of corticotrophin releasing activity fro

corticotrophin releasing factor (CRF) by Saffran et al. for fits (224).

Slusher and Roberts (251) were the first to report the lastraction of corticotrophin releasing activity from hypothalamic tissue. They isolated a lip

to regions of the hypothalamus and anterior pituitary
gland of anaesthetised animals. Electrical stimulation of
the pituitary gland was ineffective but stimulation of
experiments of Porter et al. (210). They showed that
di FRAM
from bovine posterior hypothalami that caused adrenal
ascorbic acid depletion (an indicator of increased circu-GHAM
from bovine posterior hypothalami that caused adrena
ascorbic acid depletion (an indicator of increased circu
lating ACTH) in intact but not in hypophysectomise GHAM
from bovine posterior hypothalami that caused adrenal
ascorbic acid depletion (an indicator of increased circu-
lating ACTH) in intact but not in hypophysectomised
rats. However, later work indicated that this effect from bovine posterior hypothalami that caused adrenal ascorbic acid depletion (an indicator of increased circulating ACTH) in intact but not in hypophysectomised rats. However, later work indicated that this effect was non from bovine posterior hypothalami that caused adrenal
ascorbic acid depletion (an indicator of increased circu-
lating ACTH) in intact but not in hypophysectomised
rats. However, later work indicated that this effect was
n ascorbic acid depletion (an indicator of increased circulating ACTH) in intact but not in hypophysectomised
rats. However, later work indicated that this effect was
nonspecific and that the substance was inactive in rats i lating ACTH) in intact but not in hypophysectomise
rats. However, later work indicated that this effect wa
nonspecific and that the substance was inactive in rats i
which the mobilisation of endogenous CRF was pre
vented e rats. However, later work indicated that this effect w
nonspecific and that the substance was inactive in rats
which the mobilisation of endogenous CRF was pr
vented either by hypothalamic lesions or by pretreatme
with chl nonspecific and that the substance was inactive in rats in
which the mobilisation of endogenous CRF was pre-
vented either by hypothalamic lesions or by pretreatment
with chlorpromazine, morphine, or cortisol (288). More-
 which the mobilisation of endogenous CRF was prevented either by hypothalamic lesions or by pretreatment
with chlorpromazine, morphine, or cortisol (288). More-
over, some additional doubt concerning the ability of
hypotha vented either by hypothalamic lesions or by pretreatment
with chlorpromazine, morphine, or cortisol (288). More-
over, some additional doubt concerning the ability of
hypothalamic tissue to evoke ACTH release arose when
Sa with chlorpromazine, morphine, or cortisol (288). More-
over, some additional doubt concerning the ability of
hypothalamic tissue to evoke ACTH release arose when
Saffran and Schally (223) showed that the amount of
ACTH re over, some additional doubt concerning the ability of
hypothalamic tissue to evoke ACTH release arose when
Saffran and Schally (223) showed that the amount of
ACTH released in vitro by pituitary tissue alone was
equal to t hypothalamic tissue to evoke ACTH release arose when
Saffran and Schally (223) showed that the amount of
ACTH released in vitro by pituitary tissue alone was
equal to that released by that tissue when incubated in
the pres Saffran and Schally (223) showed that the amount (ACTH released in vitro by pituitary tissue alone wiequal to that released by that tissue when incubated ithe presence of hypothalamic, neurohypophysial, or live tissue. Sub ACTH released in vitro by pituitary tissue alone was
equal to that released by that tissue when incubated in
the presence of hypothalamic, neurohypophysial, or liver
tissue. Subsequently, however, the existence of a hypo-
 equal to that released by that tissue when incubated in
the presence of hypothalamic, neurohypophysial, or liver
tissue. Subsequently, however, the existence of a hypo-
thalamic CRF was convincingly demonstrated by the
exp tissue. Subsequently, however, the existence of a hypotissue. Subsequently, however, the existence of a hypothalamic CRF was convincingly demonstrated by the experiments of Porter et al. (210). They showed that extracts of plasma from the sella turcica of stressed hypophysect thalamic CRF was convincingly demonstrated by the experiments of Porter et al. (210). They showed that extracts of plasma from the sella turcica of stressed hypophysectomised dogs caused adrenal ascorbic acid depletion in experiments of Porter et al. (210). They showed that
extracts of plasma from the sella turcica of stressed
hypophysectomised dogs caused adrenal ascorbic acid
depletion in cortisol-treated rats. No similar activity was
fou extracts of plasma from the sella turcica of stressed
hypophysectomised dogs caused adrenal ascorbic acid
depletion in cortisol-treated rats. No similar activity was
found in the carotid blood of the same dogs and it was
s hypophysectomised dogs caused adrenal ascorbic acid
depletion in cortisol-treated rats. No similar activity was
found in the carotid blood of the same dogs and it was
suggested that the corticotrophin releasing activity of depletion in cortisol-treated rats. No similar activity was
found in the carotid blood of the same dogs and it was
suggested that the corticotrophin releasing activity of the
portal blood was due to a substance acquired by found in the carotid blood of the same dogs and it was suggested that the corticotrophin releasing activity of the portal blood was due to a substance acquired by the blood on its passage through the primary capillary plex suggested that the corticotrophin releasing activity of the portal blood was due to a substance acquired by the blood on its passage through the primary capillary plexus of the hypophysial portal vessels (208, 209). Later blood on its passage through the primary capillary plexus
of the hypophysial portal vessels (208, 209). Later studies
confirmed and extended these observations (29, 218).
The ability of crude hypothalamic extracts to stimu of the hypophysial portal vessels (208, 209). Later studies
confirmed and extended these observations (29, 218).
The ability of crude hypothalamic extracts to stimulate
the secretion of adrenocorticotrophic hormone (ACTH,
 of the hypophysial portal vessels (208, 209). Later studies
confirmed and extended these observations (29, 218).
The ability of crude hypothalamic extracts to stimulate
the secretion of adrenocorticotrophic hormone (ACTH,
 confirmed and extended these observations (29, 218).

The ability of crude hypothalamic extracts to stimulate

the secretion of adrenocorticotrophic hormone (ACTH,

corticotrophin) in vivo in rats with hypothalamic lesion The ability of crude hypothalamic extracts to stimulate
the secretion of adrenocorticotrophic hormone (ACTH,
corticotrophin) in vivo in rats with hypothalamic lesions
(184, 216, 293) or in animals in which the release of C the secretion of adrenocorticotrophic hormone (ACTH,
corticotrophin) in vivo in rats with hypothalamic lesions
(184, 216, 293) or in animals in which the release of CRF
was inhibited by corticosteroids (218) was subsequent corticotrophin) in vivo in rats with hypothalamic lesi
(184, 216, 293) or in animals in which the release of C
was inhibited by corticosteroids (218) was subsequen
described. Moreover, in contrast to the earlier findi
(223 (184, 216, 293) or in animals in which the release of CRF was inhibited by corticosteroids (218) was subsequently described. Moreover, in contrast to the earlier findings (223), it was convincingly demonstrated that hypot was inhibited by corticosteroids (218) was subsequently described. Moreover, in contrast to the earlier findings (223), it was convincingly demonstrated that hypothalamic extracts but not cerebral cortical extracts evoke t described. Moreover, in contrast to the earlier findings (223), it was convincingly demonstrated that hypotha-
lamic extracts but not cerebral cortical extracts evoke
the release of ACTH from pituitary tissue in vitro (100 (223), it was convidentic extracts but
the release of ACT
thus providing firm
pothalamic CRF.
 \bf{H} . if the release of ACTH from pituitary tissue in vitro (100), thus providing firm evidence for the existence of a hypothalamic CRF.
 III. Chemical Nature of Corticotrophin Releasing

Factor tissue. Subsequently, however, the existence of a hypo-
thalamic CRF was convincingly demonstrated by the experiments of Porter et al. (210). They showed that
experiments of Porter et al. (210). They showed that
the exhib

Factor

ulates the adrenocorticotrophic activity of the adenohy-
pophysis. This substance was subsequently named the
et al. (236) described the partial purification of a CRF
corticotrophin releasing factor (CRF) by Saffran et al. thalamic CRF.
 **I. Chemical Nature of Corticotrophin Releasing

Factor**

The exact location of the CRF-secreting neurons

thin the hypothalamus is not known but it is clear that III. Chemical Nature of Corticotrophin Releasing
Factor
The exact location of the CRF-secreting neurons
within the hypothalamus is not known but it is clear that
the median eminence is rich in CRF activity. Various III. Chemical Nature of Corucotrophin Releasing
Factor
The exact location of the CRF-secreting neurons
within the hypothalamus is not known but it is clear that
the median eminence is rich in CRF activity. Various
attempts Factor
The exact location of the CRF-secreting neurons
within the hypothalamus is not known but it is clear that
the median eminence is rich in CRF activity. Various
attempts have been made to isolate CRF from tissue of
bo The exact location of the CRF-secreting neuro
within the hypothalamus is not known but it is clear the
median eminence is rich in CRF activity. Vario
attempts have been made to isolate CRF from tissue
both hypothalamic and within the hypothalamus is not known but it is clear that
the median eminence is rich in CRF activity. Various
attempts have been made to isolate CRF from tissue of
both hypothalamic and neurohypophysial origin (neuro-
hyp attempts have been made to isolate CRF from tissue of
both hypothalamic and neurohypophysial origin (neuro-
hypophysial extracts possess CRF activity). It appears
that the "hormone" is a polypeptide since the CRF
activity both hypothalamic and neurohypophysial origin (neu
hypophysial extracts possess CRF activity). It appear
that the "hormone" is a polypeptide since the Cl
activity of hypothalamic extracts is readily destroyed
the proteolyt hypophysial extracts possess CRF activity). It appears
that the "hormone" is a polypeptide since the CRF
activity of hypothalamic extracts is readily destroyed by
the proteolytic enzymes, pepsin or trypsin. After prelim-
i that the "hormone" is a polypeptide since the CRF
activity of hypothalamic extracts is readily destroyed by
the proteolytic enzymes, pepsin or trypsin. After prelim-
inary purification procedures, CRF activity is present i activity of hypothalamic extracts is readily destroyed by
the proteolytic enzymes, pepsin or trypsin. After prelim-
inary purification procedures, CRF activity is present in
a plasma protein fraction of portal blood. In 19 the proteolytic enzymes, pepsin or trypsin. After prelim-
inary purification procedures, CRF activity is present in
a plasma protein fraction of portal blood. In 1958, Schally
et al. (236) described the partial purificatio inary purification procedures, CRF activity is present in a plasma protein fraction of portal blood. In 1958, Schally et al. (236) described the partial purification of a CRF from the convenient if not logical "protopituit a plasma protein fraction of portal blood. In 1958, Schally
et al. (236) described the partial purification of a CRF
from the convenient if not logical "protopituitrin" (the
posterior pituitary starting material for vasop et al. (236) described the partial purification of a CRF
from the convenient if not logical "protopituitrin" (the
posterior pituitary starting material for vasopressin iso-
lation). Two years later, two fractions with CRF from the convenient if not logical "protopituitrin" (the posterior pituitary starting material for vasopressin isolation). Two years later, two fractions with CRF activity, α -CRF and β -CRF, were isolated from the sa

PHARMACOLOGICAL REVIEWS

CORTICOTROPHIN RELEASING FACTOR 255

investigation of its structure suggested a resemblance to CORTICOTROPHIN REI

possessed pressor and antidiuretic activity. A preliminary

investigation of its structure suggested a resemblance to

flysine vasopressin (232). α -CRF, which also possessed

ACTH-like activity (231 possessed pressor and antidiuretic activity. A preliminary
investigation of its structure suggested a resemblance to
lysine vasopressin (232). α -CRF, which also possessed
ACTH-like activity (231), was described as two possessed pressor and antidiuretic activity. A preliminary
investigation of its structure suggested a resemblance to
lysine vasopressin (232). α -CRF, which also possessed
ACTH-like activity (231), was described as two investigation of its structure suggested a resemblance to fall find the vasopressin (232). α -CRF, which also possessed BACTH-like activity (231), was described as two peptides, to α_1 -CRF and α_2 -CRF, both simila ACTH-like activity (231), was described as two peptides, tone/morphine blocked the effect of vasopressin on α_1 -CRF and α_2 -CRF, both similar to but slightly larger ACTH release. Furthermore, according to Saffran an ACTH-like activity (231), was described as two peptides, to α_1 -CRF and α_2 -CRF, both similar to but slightly larger AC
than α -MSH. On the basis of these findings, it was Sa
postulated that α -CRF is merely a p α_1 -CRF and α_2 -CRF, both similar to but slightly laithen α -MSH. On the basis of these findings, it postulated that α -CRF is merely a precursor of AC (the sequence of the first 13 amino acids is identical v $\$ than α -MSH. On the basis of these findings, it was postulated that α -CRF is merely a precursor of ACT (the sequence of the first 13 amino acids is identical wit α -MSH) and that β -CRF is the neurohumoral transm postulated that α -CRF is merely a precursor of ACTH (the sequence of the first 13 amino acids is identical with α -MSH) and that β -CRF is the neurohumoral transmitter that stimulates ACTH release (234). In 1962, s (the sequence of the first 13 amino acids is identical with α -MSH) and that β -CRF is the neurohumoral transmitter that stimulates ACTH release (234). In 1962, scientists turned to hypothalamic tissue for their studi α -MSH) and that β -CRF is the neurohumoral transmitter that stimulates ACTH release (234). In 1962, scientists turned to hypothalamic tissue for their studies (101, heads). This tissue, in my opinion, provides a more ter that stimulates ACTH release (234). In 1962, scientists turned to hypothalamic tissue for their studies (101, heads). This tissue, in my opinion, provides a more rational r ("physiological") source of CRF. Hypothalami tists turned to hypothalamic tissue for their studies (101, h
235). This tissue, in my opinion, provides a more rational r
("physiological") source of CRF. Hypothalamic tissue is
yielded two fractions with CRF activity th yielded two fractions with CRF activity that possessed
chromatographic properties similar to those of the α -CRF and β -CRF obtained from the posterior pituitary
gland. However, in contrast to the β -CRF of neurohy-CRF and β -CRF obtained from the posterior pituitary CRF and β -CRF obtained from the posterior pituitary hy gland. However, in contrast to the β -CRF of neurohy-
pophysial origin, the corresponding fraction from the of
hypothalamus had considerable ACTH-like activity a gland. However, in contrast to the β -CRF of neurohy-
pophysial origin, the corresponding fraction from the
hypothalamus had considerable ACTH-like activity and
it was suggested that the fraction that resembled α -CRF hormone. pothalamus had considerable ACTH-like activity and loaw
as suggested that the fraction that resembled α -CRF pit
as probably the physiological corticotrophin releasing wit
rmone.
In an independent study by Dhariwal et a it was suggested that the fraction that resembled α -CRF pieses probably the physiological corticotrophin releasing whormone.

In an independent study by Dhariwal et al. (64), a psubstance with CRF activity was isolated

was probably the physiological corticotrophin releasing
hormone.
In an independent study by Dhariwal et al. (64), a
substance with CRF activity was isolated from ovine
hypothalami by means of gel filtration and ion exchang hormone.

In an independent study by Dhariwal et al. (64), a

substance with CRF activity was isolated from ovine

chromatography. The substance, structure unknown, was

substance of the substance of activity devoid of ACT In an independent study by Dhariwal et al. (64)
substance with CRF activity was isolated from ovi-
hypothalami by means of gel filtration and ion exchare
chromatography. The substance, structure unknown, v
believed to be a chromatography. The substance, structure unknown, was believed to be a single chemical entity devoid of ACTH-
like or pressor activity. However, the material was not
subjected to countercurrent distribution, a process that
can separate two CRF activities and thus the possibil like or pressor activity. However, the material was not
subjected to countercurrent distribution, a process that
can separate two CRF' activities and thus the possibility
of two distinct CRF's could not be excluded. Chan e subjected to countercurrent distribution, a process that
can separate two CRF activities and thus the possibility
of two distinct CRF's could not be excluded. Chan et al.
(51) demonstrated the presence of two CRF's in rat
 of two distinct CRF's could not be excluded. Chan et al. (51) demonstrated the presence of two CRF's in rat median eminence tissue, a large and a small CRF, and suggested that the activity may reside in a peptide con-
tain of two distinct CRF's could not
(51) demonstrated the presen
median eminence tissue, a larg
suggested that the activity may
taining aromatic amino acids.
For some time it was thought 1) demonstrated the presence of two CRF's in rat ninedian eminence tissue, a large and a small CRF, and seggested that the activity may reside in a peptide conting aromatic amino acids. existing aromatic amino acids. For

median eminence tissue, a large and a small CRF, and
suggested that the activity may reside in a peptide con-
taining aromatic amino acids.
For some time it was thought that vasopressin may be
chemically identical with CRF suggested that the activity may reside in a peptide containing aromatic amino acids.
For some time it was thought that vasopressin may be chemically identical with CRF (178, 181, 182) and there is circumstantial evidence t taining aromatic amino acids.
For some time it was thought that vasopressin may b
chemically identical with CRF (178, 181, 182) and ther
is circumstantial evidence to support this hypothesis. Fo
example, stress often resul For some time it was thought that vasopressin may be chemically identical with CRF (178, 181, 182) and there is circumstantial evidence to support this hypothesis. For example, stress often results in the release of both v chemically identical with CRF (178, 181, 182) and there is circumstantial evidence to support this hypothesis. For example, stress often results in the release of both vasopressin and ACTH (192). McCann and Brobeck (182) s is circumstantial evidence to support this hypothesis. For
example, stress often results in the release of both vaso-
pressin and ACTH (192). McCann and Brobeck (182)
we showed that rats with lesions in the median eminence develop diabetes insipidus and that ACTH release can
be elicited in such animals by injection of vasopressin. mo
Moreover, there was an association between the intensity
of the diabetes insipidus and the degree of inhibiti be elicited in such animals by injection of vasopressin. me
Moreover, there was an association between the intensity
of the diabetes insipidus and the degree of inhibition of
eit
pituitary adrenocorticotrophic activity in Moreover, there was an association between the int
of the diabetes insipidus and the degree of inhibit
pituitary adrenocorticotrophic activity in animal
hypothalamic-lesions (183), and the adrenal ascorb
depletion caused b of the diabetes insipidus and the degree of inhibition of
pituitary adrenocorticotrophic activity in animals with
hypothalamic lesions (183), and the adrenal ascorbic acid
depletion caused by vasopressin in hypothalamic-le pituitary adrenocorticotrophic activity in animals with
hypothalamic lesions (183), and the adrenal ascorbic acid
in
depletion caused by vasopressin in hypothalamic-le-
resioned rats was proportional to its pressor activit depletion caused by vasopressin in hypothalam
sioned rats was proportional to its pressor activity.
thermore, the immunoreactive vasopressin content thy
pothalamus, like the CRF content, was elevat
adrenalectomised rats to sioned rats was proportional to its pressor activity. Furthermore, the immunoreactive vasopressin content of the hypothalamus, like the CRF content, was elevated in adrenalectomised rats but normal in corticosteroid-treate thermore, the immunoreactive vasopressin content of the
hypothalamus, like the CRF content, was elevated in the
adrenalectomised rats but normal in corticosteroid-
treated adrenalectomised rats (66, 256). These latter life hypothalamus, like the CRF content, was elevated indicated adrenalectomised rats but normal in corticosteroid
treated adrenalectomised rats (66, 256). These latter
findings should, perhaps, be treated with some cautic
sinc adrenalectomised rats but normal in corticoste
treated adrenalectomised rats (66, 256). These l
findings should, perhaps, be treated with some cau
since the antibody to vasopressin employed may c
react with other similar p eated adrenalectomised rats (66, 256). These latter
dings should, perhaps, be treated with some caution
nce the antibody to vasopressin employed may cross-
act with other similar peptides that act as CRF.
There is also a c

possessed pressor and antidiuretic activity. A preliminary suggests that vasopressin is not the major hypothalamic
investigation of its structure suggested a resemblance to factor that triggers ACTH release. In an early pa chromatographic properties similar to those of the α - but little pressor activity in extracts of hypothalami from
CRF and β -CRF obtained from the posterior pituitary hypophysectomised rats, while McDonald et al. (18 substance with CRF activity was isolated from ovine capable of responding to stress with a rise in corticoster-
hypothalami by means of gel filtration and ion exchange one concentration (7, 294). The ability of vasopressin believed to be a single chemical entity devoid of ACTH-
licotrophic activity has been studied extensively (37, 45,
like or pressor activity. However, the material was not
subjected to countercurrent distribution, a process pressin and ACTH (192). McCann and Brobeck (182) were ineffective when injected into pentobarbitone-
showed that rats with lesions in the median eminence chlorpromazine-treated rats (45). Pressinoic acid, its
develop diabe develop diabetes insipidus and that ACTH release can
be elicited in such animals by injection of vasopressin.
Moreover, there was an association between the intensity
of the diabetes insipidus and the degree of inhibition depletion caused by vasopressin in hypothalamic-le-
sioned rats was proportional to its pressor activity. Fur-
sembled those of hypothalamic extracts (37). Similar
thermore, the immunoreactive vasopressin content of the
hy suggests that vasopressin is *not* the major hypothalamic EXASING FACTOR
suggests that vasopressin is *not* the major hypothalamic
factor that triggers ACTH release. In an early paper,
Briggs and Munson (21) demonstrated that pentobarbi-ELEASING FACTOR
suggests that vasopressin is *not* the major hypothals
factor that triggers ACTH release. In an early pe
Briggs and Munson (21) demonstrated that pentob
tone/morphine blocked the effect of vasopressin suggests that vasopressin is *not* the major hypothalamic
factor that triggers ACTH release. In an early paper,
Briggs and Munson (21) demonstrated that pentobarbi-
tone/morphine blocked the effect of vasopressin on
ACTH r suggests that vasopressin is *not* the major hypothalamic
factor that triggers ACTH release. In an early paper,
Briggs and Munson (21) demonstrated that pentobarbi-
tone/morphine blocked the effect of vasopressin on
ACTH r Briggs and Munson (21) demonstrated that pentobarbitone/morphine blocked the effect of vasopressin on tone/morphine blocked the effect of vasopressin on ACTH release. Furthermore, according to Saffran and Saffran (222), the doses used by McCann and Fruit (183) to induce ACTH secretion in hypothalamic-lesioned rats were sev ACTH release. Furthermore, according to Saffran and Saffran (222), the doses used by McCann and Fruit (183) to induce ACTH secretion in hypothalamic-lesioned rats were several thousand times greater than the dose needed to Saffran (222), the doses used by McCann and Fruit (183)
to induce ACTH secretion in hypothalamic-lesioned rats
were several thousand times greater than the dose needed
to inhibit diuresis maximally. This criticism is not n to induce ACTH secretion in hypothalamic-lesioned rats
were several thousand times greater than the dose needed
to inhibit diuresis maximally. This criticism is not nec-
essarily valid since there are no data available to were several thousand times greater than the dose needed
to inhibit diuresis maximally. This criticism is not nec-
essarily valid since there are no data available to indicate
how much systemic vasopressin is necessary in to inhibit diuresis maximally. This criticism is not necessarily valid since there are no data available to indicate
how much systemic vasopressin is necessary in the pe-
ripheral circulation to change the effective concen essarily valid since there are no data available to indicate
how much systemic vasopressin is necessary in the pe-
ripheral circulation to change the effective concentration
in the hypophysial portal vessels (94). De Wied how much systemic vasopressin is necessary in the pe-
ripheral circulation to change the effective concentration
in the hypophysial portal vessels (94) . De Wied et al.
 (293) showed that there was a great deal of CRF a ripheral circulation to change the effective concentration
in the hypophysial portal vessels (94). De Wied et al.
(293) showed that there was a great deal of CRF activity
but little pressor activity in extracts of hypothal in the hypophysial portal vessels (94). De Wied et al.
(293) showed that there was a great deal of CRF activity
but little pressor activity in extracts of hypothalami from
hypophysectomised rats, while McDonald et al. (186 but little pressor activity in extracts of hypothalami from but little pressor activity in extracts of hypothalamin
hypophysectomised rats, while McDonald et al.
found a complete lack of correlation between the re
of these two activities in response to nicotine,
loading, and water hypophysectomised rats, while McDonald et al. (186)
found a complete lack of correlation between the release
of these two activities in response to nicotine, water
loading, and water deprivation in man. Hypothalamo-
pituit found a complete lack of correlation between the release
of these two activities in response to nicotine, water
loading, and water deprivation in man. Hypothalamo-
pituitary-adrenocorticotrophic activity is reduced in rats of these two activities in response to nicotine, w
loading, and water deprivation in man. Hypothala
pituitary-adrenocorticotrophic activity is reduced in
with inherited diabetes insipidus (Brattleboro rats),
hypothalamic e loading, and water deprivation in man. Hypothalamo-
pituitary-adrenocorticotrophic activity is reduced in rats
with inherited diabetes insipidus (Brattleboro rats), but
hypothalamic extracts from such rats possess corticot pituitary-adrenocorticotrophic activity is reduced in
with inherited diabetes insipidus (Brattleboro rats),
hypothalamic extracts from such rats possess cortico
phin releasing activity (43, 89, 161) and these animal
capabl with inherited diabetes insipidus (Brattleboro rats), but
hypothalamic extracts from such rats possess corticotro-
phin releasing activity (43, 89, 161) and these animals are
capable of responding to stress with a rise in hypothalamic extracts from such rats possess cortice
phin releasing activity (43, 89, 161) and these animals
capable of responding to stress with a rise in cortico
one concentration (7, 294). The ability of vasopressin
sev phin releasing activity (43, 89, 161) and these animals are capable of responding to stress with a rise in corticoster-
one concentration (7, 294). The ability of vasopressin and
several of its analogues to stimulate pitui capable of responding to stress with a rise in corticoster-
one concentration (7, 294). The ability of vasopressin and
several of its analogues to stimulate pituitary adrenocor-
ticotrophic activity has been studied extens one concentration (7, 294). The ability of vasopressin and
several of its analogues to stimulate pituitary adrenocor-
ticotrophic activity has been studied extensively (37, 45,
92, 204). In one study (45), a sensitive and ticotrophic activity has been studied extensively (37, 45, vivo/in vitro system (290) using pentobarbitone/chlor-
promazine-treated rats were employed in parallel. Argi-
nine vasopressin and lysine vasopressin stimulate ACTH 92, 204). In one study (45), a sensitive and precise in vitro
assay technique using pituitary segments (37) and an in
vivo/in vitro system (290) using pentobarbitone/chlor-
promazine-treated rats were employed in parallel assay technique using pituitary segments (37) and an in
vivo/in vitro system (290) using pentobarbitone/chlor-
promazine-treated rats were employed in parallel. Argi-
nine vasopressin and lysine vasopressin stimulate ACTH
 vivo/in vitro system (290) using pentobarbitone/chlor-
promazine-treated rats were employed in parallel. Argi-
nine vasopressin and lysine vasopressin stimulate ACTH
secretion in both systems (45). However, the slopes of
t promazine-treated rats were employed in parallel. Arg
nine vasopressin and lysine vasopressin stimulate ACTI
secretion in both systems (45). However, the slopes of
the dose-response lines for vasopressin and hypothalami
ex nine vasopressin and lysine vasopressin stimulate ACTH
secretion in both systems (45). However, the slopes of
the dose-response lines for vasopressin and hypothalamic
extracts differed significantly, indicating that the co secretion in both systems (45). However, the slopes of
the dose-response lines for vasopressin and hypothalamic
extracts differed significantly, indicating that the corti-
cotrophin releasing principle in the hypothalamic the dose-response lines for vasopressin and hypothalextracts differed significantly, indicating that the cotrophin releasing principle in the hypothalamic exis not chemically identical with vasopressin (45) .
desglycinam extracts differed significantly, indicating that the corticotrophin releasing principle in the hypothalamic extract
is not chemically identical with vasopressin (45). The
desglycinamide derivatives of lysine and arginine-v cotrophin releasing principle in the hypothalamic ϵ is not chemically identical with vasopressin (45)
desglycinamide derivatives of lysine and arginine
pressin exhibited some activity in the in vitro syste
were ineff is not chemically identical with vasopressin (45). The
desglycinamide derivatives of lysine and arginine-vaso-
pressin exhibited some activity in the in vitro system but
were ineffective when injected into pentobarbitone-
 desglycinamide derivatives of lysine and arginine-vaso
pressin exhibited some activity in the in vitro system bu
were ineffective when injected into pentobarbitone
chlorpromazine-treated rats (45). Pressinoic acid, it
amid pressin exhibited some activity in the in vitro system bu
were ineffective when injected into pentobarbitone
chlorpromazine-treated rats (45). Pressinoic acid, it
amide, oxytocin, alanine-8-oxypressin, and the "tail frag
m were ineffective when injected into pentobarbitone-
chlorpromazine-treated rats (45). Pressinoic acid, its
amide, oxytocin, alanine-8-oxypressin, and the "tail frag-
ment" (proline-arginine-glycinamide) of arginine vaso-
 amide, oxytocin, alanine-8-oxypressin, and the "tail fragamide, oxytocin, alanine-8-oxypressin, and the "tail fragment" (proline-arginine-glycinamide) of arginine vaso-
pressin did not increase corticotrophin production in
either test system (45). Oxypressin and arginine vasotoc ment" (proline-arginine-glycinamide) of arginine vasopressin did not increase corticotrophin production i
either test system (45). Oxypressin and arginine vasotoci
exhibited very marked corticotrophin releasing activit
in pressin did not increase corticotrophin production in
either test system (45). Oxypressin and arginine vasotocin
exhibited very marked corticotrophin releasing activity
in both assays (45) and, unlike the vasopressins, the either test system (45). Oxypressin and arginine vasotocinexhibited very marked corticotrophin releasing activity
in both assays (45) and, unlike the vasopressins, the dose-
response relationships of arginine vasotocin clo exhibited very marked corticotrophin releasing activity
in both assays (45) and, unlike the vasopressins, the dose-
response relationships of arginine vasotocin closely re-
sembled those of hypothalamic extracts (37). Simi in both assays (45) and, unlike the vasopressins, the dose-
response relationships of arginine vasotocin closely re-
sembled those of hypothalamic extracts (37). Similar
findings have been reported by Gillies et al. (92) b response relationships of arginine vasotocin closely resembled those of hypothalamic extracts (37). Similar findings have been reported by Gillies et al. (92) but in their bioassay system, in which isolated pituitary cells sembled those of hypothalamic extracts (37). Simila
findings have been reported by Gillies et al. (92) but i
their bioassay system, in which isolated pituitary cell
are exposed to the putative hormone, the dose-respons
lin findings have been reported by Gillies et al. (92) be their bioassay system, in which isolated pituitary are exposed to the putative hormone, the dose-responsion fines for arginine vasotocin, like those for lysine pressin, their bioassay system, in which isolated pituitary cells
are exposed to the putative hormone, the dose-response
lines for arginine vasotocin, like those for lysine vaso-
pressin, differ significantly from those for stalk-m are exposed to the putative hormone, the dose-respondines for arginine vasotocin, like those for lysine vasepressin, differ significantly from those for stalk-medial eminence (SME) extract. These investigators have raise a lines for arginine vasotocin, like those for lysine vasopressin, differ significantly from those for stalk-median-
eminence (SME) extract. These investigators have raised
again the possibility that vasopressin within the h

Downloaded from pharmrev.aspetjournals.org at Thammasart University on December 8, 2012

extract is abolished by incubation with "specific" arginine BUCKING

ical control of corticotrophin secretion. They showed (91)

that the corticotrophin releasing activity of rat SME

extract is abolished by incubation with "specific" arginine

vasopressin antiserum. Chromatographi ical control of corticotrophin secretion. They showed (91) p
that the corticotrophin releasing activity of rat SME of
extract is abolished by incubation with "specific" arginine was
opressin antiserum. Chromatographic sepa ical control of corticotrophin secretion. They showed (91) pit that the corticotrophin releasing activity of rat SME obextract is abolished by incubation with "specific" arginine wives
opressin antiserum. Chromatographic s that the corticotrophin releasing activity of rat SME
extract is abolished by incubation with "specific" arginine
vasopressin antiserum. Chromatographic separation of
SME extracts yielded two peaks of CRF activity. The
maj extract is abolished by incubation with "specific" arginine wasopressin antiserum. Chromatographic separation of pl
SME extracts yielded two peaks of CRF activity. The remajor peak occurred in the expected position of argi vasopressin antiserum. Chromatographic separation of pl
SME extracts yielded two peaks of CRF activity. The
major peak occurred in the expected position of arginine is
vasopressin and, in the isolated pituitary cell column SME extracts yielded two peaks of CRF activity. The remajor peak occurred in the expected position of arginine isotasopressin and, in the isolated pituitary cell column the bioassay, its dose-response relationships resembl major peak occurred in the expected position of arginine vasopressin and, in the isolated pituitary cell column
bioassay, its dose-response relationships resembled those
of vasopressin and not those of the SME extract. On vasopressin and, in the isolated pituitary cell column
bioassay, its dose-response relationships resembled those
of vasopressin and not those of the SME extract. On the
basis of these findings, Gillies et al. (92) suggeste bioassay, its dose-response relationships resembled those color vasopressin and not those of the SME extract. On the by basis of these findings, Gillies et al. (92) suggested that tan the corticotrophin releasing activity basis of these findings, Gillies et al. (92) suggested that tamine $(5-HT)$, although it was clearly active when in-
the corticotrophin releasing activity of the hypothalamus jected into hypothalamic lesioned rats or inc hypothesis is in accord with the earlier suggestion of exists that the separation of pituitary cells with enzymes
Saffran and colleagues (205) that CRF requires a syner- such as trypsin may lead to damage of the cell memthe corticotrophin releasing activity of the hypothalamus jet is due to vasopressin (or a closely related molecule) and relation that it requires a synergistic factor yet to be identified in corder to exhibit its full biol is due to vasopressin (or a closely related molecule) at that it requires a synergistic factor yet to be identified order to exhibit its full biological activity (91). The hypothesis is in accord with the earlier suggestio that it requires a synergistic factor yet to be identified in coorder to exhibit its full biological activity (91). This reproduces is in accord with the earlier suggestion of example of saffran and colleagues (205) that C order to exhibit its full biological activity (91). This rease,
hypothesis is in accord with the earlier suggestion of exis
Saffran and colleagues (205) that CRF requires a syner-
such gistic cofactor and is further suppor hypothesis is in accord with the earlier suggestion of ex
Saffran and colleagues (205) that CRF requires a syner-
gistic cofactor and is further supported by their finding br
that recombination of the two "peak fractions" Saffran and colleagues (205) that CRF requires a syngistic cofactor and is further supported by their findition that recombination of the two "peak fractions" results a complex with strong CRF-like activity and that the do gistic cofactor and is further supported by their finding branes
that recombination of the two "peak fractions" results in recept
a complex with strong CRF-like activity and that the suppor
dose-response relationships of t that recombination of the two "peak fractions" results in rece
a complex with strong CRF-like activity and that the sup
dose-response relationships of the complex closely resem-
ble those of the SME extract (89). However, a complex with strong CRF-like activity and that
dose-response relationships of the complex closely res
ble those of the SME extract (89). However, results f
experiments done in the Royal Free laboratory (44)
which the cor dose-response relationships of the complex closely reset ble those of the SME extract (89). However, results from experiments done in the Royal Free laboratory (44) which the corticotrophin releasing activity of hypoth ami ble those of the SME extract (89). However, results from only experiments done in the Royal Free laboratory (44), in which the corticotrophin releasing activity of hypothal-
ami from rats with inherited diabetes insipidus experiments done in the Royal Free laboratory (44), in which the corticotrophin releasing activity of hypothal ami from rats with inherited diabetes insipidus (Brattle boro rats) has been studied with an in vitro pituitary which the corticotrophin releasing activity of hypothal-
ami from rats with inherited diabetes insipidus (Brattle-establis
boro rats) has been studied with an in vitro pituitary
Exegment system, are not in accord with this ami from rats with inherited diabetes insipidus (Brattleboro rats) has been studied with an in vitro pituitary
segment system, are not in accord with this hypothesis.
Hypothalamic extracts from Brattleboro rats and from
no segment system, are not in accord with this hypothesis. identified. One of the major problems associated with the
Hypothalamic extracts from Brattleboro rats and from isolation of such small, relatively unstable polypeptid segment system, are not in accord with this hypothesis.
Hypothalamic extracts from Brattleboro rats and from
normal controls (Long Evans) cause dose-related in-
creases in ACTH production but both the activity and
the slo Hypothalamic extracts from Brattleboro rats and from iso
normal controls (Long Evans) cause dose-related in-
freences in ACTH production but both the activity and
do
the slope of the dose response line of the Brattleboro
 normal controls (Long Evans) cause dose-related in
creases in ACTH production but both the activity an
the slope of the dose response line of the Brattlebor
extract are significantly $(P < .001)$ less than those of th
contro creases in ACTH production but both the activity and dow
the slope of the dose response line of the Brattleboro the
extract are significantly $(P < .001)$ less than those of the ope
controls (44) . Vasopressin, in concentra the slope of the dose response line of the Brattlel
extract are significantly $(P < .001)$ less than those of
controls (44) . Vasopressin, in concentrations not s
cient to stimulate directly the secretion of ACTH
pituitary extract are significantly $(P < .001)$ less than those of the oped a controls (44) . Vasopressin, in concentrations not sufficient to stimulate directly the secretion of ACTH by worker pituitary segments in vitro, potentiat controls (44). Vasopressin, in concentrations not suffi-
cient to stimulate directly the secretion of ACTH by
pituitary segments in vitro, potentiates the corticotro-
tio
phin releasing activity of hypothalamic extracts fr cient to stimulate directly the secretion of ACTH by
pituitary segments in vitro, potentiates the corticotro-
phin releasing activity of hypothalamic extracts from
normal and diabetic rats and renders the slopes of the
dos pituitary segments in vitro, potentiates the corticotro-
phin releasing activity of hypothalamic extracts from
normal and diabetic rats and renders the slopes of the
dose-response lines of the Brattleboro extracts parallel phin releasing activity of hypothalamic extracts from the
normal and diabetic rats and renders the slopes of the res
dose-response lines of the Brattleboro extracts parallel At
with those of the controls (44). Furthermore, normal and diabetic rats and renders the slopes of the dose-response lines of the Brattleboro extracts parallel with those of the controls (44). Furthermore, in contrast to the findings of Gillies and Lowry (91), treatment dose-response lines of the Brattleboro extracts parallel
with those of the controls (44). Furthermore, in contrast
to the findings of Gillies and Lowry (91), treatment with
arginine vasopressin antiserum reduces but does n with those of the controls (44). Furthermore, in contrast
to the findings of Gillies and Lowry (91), treatment with
arginine vasopressin antiserum reduces but does not
abolish the corticotrophin releasing activity of hypot to the findings of Gillies and Lowry (91), treatment wit
arginine vasopressin antiserum reduces but does no
abolish the corticotrophin releasing activity of hypotha
lamic extracts from controls and does not affect the
from arginine vasopressin antiserum reduces but does not Seabolish the corticotrophin releasing activity of hypotha-
Iamic extracts from controls and does not affect that and
from Brattleboro rats. Moreover, the antiserum treat abolish the corticotrophin releasing activity of hypotha-
lamic extracts from controls and does not affect that
from Brattleboro rats. Moreover, the antiserum treat-
ment alters the slopes of the dose-response lines of the lamic extracts from controls and does not affect that
from Brattleboro rats. Moreover, the antiserum treat-
ment alters the slopes of the dose-response lines of the
control extract so that they are identical with those of
 from Brattleboro rats. Moreover, the antiserum treatment alters the slopes of the dose-response lines of the control extract so that they are identical with those of the Brattleboro extracts (44). These findings suggest th ment alters the slopes of the dose-response lines of the control extract so that they are identical with those of the Brattleboro extracts (44). These findings suggest that vasopressin is not the corticotrophin releasing f thalamo-pituitary-adrenocorticotrophic activity. sopressin is not the corticotrophin releasing factor but
at it acts synergistically with the hypothalamic hor-
bone and is essential for the full expression of hypo-
fralamo-pituitary-adrenocorticotrophic activity.
The exp

mone and is essential for the full expression of hypo-
thalamo-pituitary-adrenocorticotrophic activity.
The explanation for the discrepancies between these
results (44) and those of Gillies and Lowry may lie in
differences thalamo-pituitary-adrenocorticotrophic activity.
The explanation for the discrepancies between these
results (44) and those of Gillies and Lowry may lie in
differences between the methods employed to detect
corticotrophin The explanation for the discrepancies between these not
results (44) and those of Gillies and Lowry may lie in
differences between the methods employed to detect
corticotrophin releasing activity. It is well known that
new results (44) and those of Gillies and Lowry may lie in
differences between the methods employed to detect
corticotrophin releasing activity. It is well known that
new biological assay methods should be "validated" by
compa differences between the methods employed to detect
corticotrophin releasing activity. It is well known that
new biological assay methods should be "validated" by
comparison with older, well-established bioassays. Par-
alle

ical control of corticotrophin secretion. They showed (91) pituitary segments in vitro are in agreement with those
that the corticotrophin releasing activity of rat SME obtained with in vivo assay systems employing rats in pituitary segments in vitro are in agreement with those GHAM
pituitary segments in vitro are in agreement with those
obtained with in vivo assay systems employing rats in
which endogenous CRF secretion is prevented either SHAM
pituitary segments in vitro are in agreement with those
obtained with in vivo assay systems employing rats in
which endogenous CRF secretion is prevented either
pharmacologically (45) or surgically (46, 140). However, pituitary segments in vitro are in agreement with those
obtained with in vivo assay systems employing rats in
which endogenous CRF secretion is prevented either
pharmacologically (45) or surgically (46, 140). However,
rece pituitary segments in vitro are in agreement with those
obtained with in vivo assay systems employing rats in
which endogenous CRF secretion is prevented either
pharmacologically (45) or surgically (46, 140). However,
rece obtained with in vivo assay systems employing rats in
which endogenous CRF secretion is prevented either
pharmacologically (45) or surgically (46, 140). However,
recent studies suggest that the results obtained with
isolat pharmacologically (45) or surgically (46, 140). However,
recent studies suggest that the results obtained with
isolated pituitary cells are not always in accord with
those of other systems. According to M. T. Jones and
col pharmacologically (45) or surgically (46, 140). However,
recent studies suggest that the results obtained with
isolated pituitary cells are not always in accord with
those of other systems. According to M. T. Jones and
col recent studies suggest that the results obtained
isolated pituitary cells are not always in accord
those of other systems. According to M. T. Jone
colleagues (personal communication) the "CRF" sec
by isolated hypothalami i isolated pituitary cells are not always in accord with
those of other systems. According to M. T. Jones and
colleagues (personal communication) the "CRF" secreted
by isolated hypothalami in response to 5-hydroxytryp-
tamin those of other systems. According to M. T. Jones and
colleagues (personal communication) the "CRF" secreted
by isolated hypothalami in response to 5-hydroxytryp-
tamine (5-HT), although it was clearly active when in-
jecte colleagues (personal communication) the "CRF" secreted
by isolated hypothalami in response to 5-hydroxytryp-
tamine (5-HT), although it was clearly active when in-
jected into hypothalamic lesioned rats or incubated with
r by isolated hypothalami in response to 5-hydroxytryp-
tamine (5-HT), although it was clearly active when in-
jected into hypothalamic lesioned rats or incubated with
rat pituitary segments, was inactive in the pituitary ce tamine (5-HT), although it was clearly active when in-
jected into hypothalamic lesioned rats or incubated with
rat pituitary segments, was inactive in the pituitary cell
column assay described by Gillies and Lowry (90). T jected into hypothalamic lesioned rats or incubated with rat pituitary segments, was inactive in the pituitary cell column assay described by Gillies and Lowry (90). The reasons for this discrepancy are not clear. The poss rat pituitary segments, was inactive in the pituitary ce
column assay described by Gillies and Lowry (90). The
reasons for this discrepancy are not clear. The possibilit
exists that the separation of pituitary cells with e column assay described by Gillies and Lowry (90). The
reasons for this discrepancy are not clear. The possibility
exists that the separation of pituitary cells with enzymes
such as trypsin may lead to damage of the cell me exists that the separation of pituitary cells with enzymes
such as trypsin may lead to damage of the cell mem-
branes and thus alteration in the specificity of the CRF
receptor but, as yet, direct evidence is not available such as trypsin may lead to damage of the cell mem-
branes and thus alteration in the specificity of the CRF
receptor but, as yet, direct evidence is not available to
support this explanation. Nevertheless, in my opinion,
 branes and thus alteration in the specificity of the CRF
receptor but, as yet, direct evidence is not available to
support this explanation. Nevertheless, in my opinion,
these findings cast considerable doubt upon the vali receptor but, as yet, direct evidence is not available to support this explanation. Nevertheless, in my opinion, these findings cast considerable doubt upon the validity of the use of isolated cell systems for the detectio support this explanation. Nevertheless, in my opinion
these findings cast considerable doubt upon the validity
of the use of isolated cell systems for the detection of
corticotrophin releasing hormone and emphasise the im
 these findings cast cof
of the use of isolate
corticotrophin releas
portance of validatin
established systems.
The true corticotro of the use of isolated cell systems for the detection of corticotrophin releasing hormone and emphasise the importance of validating new methods against older, well-established systems.
The true corticotrophin releasing fa

mone and is essential for the full expression of hypo-
tractions to influence ACTH release in other species has
thalamo-pituitary-adrenocorticotrophic activity.
The explanation for the discrepancies between these not puri exists that the separation of pituitary cells with enzymes
such as trypsin may lead to damage of the cell mem-
branes and thus alteration in the specificity of the CRF
receptor but, as yet, direct evidence is not availabl corticotrophin releasing hormone and emphasise the im-
portance of validating new methods against older, well-
established systems.
The true corticotrophin releasing factors remain to be
identified. One of the major proble portance of validating new methods against older, well-
established systems.
The true corticotrophin releasing factors remain to be
identified. One of the major problems associated with the
isolation of such small, relativ established systems.
The true corticotrophin releasing factors remain to be
identified. One of the major problems associated with the
isolation of such small, relatively unstable polypeptides
from biological tissue is that The true corticotrophin releasing factors remain to be
identified. One of the major problems associated with the
isolation of such small, relatively unstable polypeptides
from biological tissue is that the peptides may bre identified. One of the major problems associated with the isolation of such small, relatively unstable polypeptid
from biological tissue is that the peptides may breadown or undergo other chemical transformation during
the isolation of such small, relatively unstable polypeptides
from biological tissue is that the peptides may break
down or undergo other chemical transformation during
the extraction procedures. Jones et al. (140) have develfrom biological tissue is that the peptides may break
down or undergo other chemical transformation during
the extraction procedures. Jones et al. (140) have devel-
oped a new approach to the study of the chemical nature
o down or undergo other chemical transformation durine extraction procedures. Jones et al. (140) have developed a new approach to the study of the chemical nature of CRF in the rat that may overcome this problem. The workers the extraction procedures. Jones et al. (140) have deve
oped a new approach to the study of the chemical nature
of CRF in the rat that may overcome this problem. The
workers showed that acetylcholine stimulates the secre-
 oped a new approach to the study of the chemical nature
of CRF in the rat that may overcome this problem. These
workers showed that acetylcholine stimulates the secre-
tion of "CRF" and vasopressin from isolated rat hypo-
 of CRF in the rat that may overcome this problem. These
workers showed that acetylcholine stimulates the secre-
tion of "CRF" and vasopressin from isolated rat hypo-
thalami in vitro but that 5-HT is more selective in this workers showed that acetylcholine stimulates the secretion of "CRF" and vasopressin from isolated rat hypothalami in vitro but that 5-HT is more selective in this respect and evokes the secretion of "CRF" only (140) .
At the into of "CRF" and vasopressin from isolated rat hypothelami in vitro but that 5-HT is more selective in this
respect and evokes the secretion of "CRF" only (140).
Attempts are now being made to isolate and identify th thalami in vitro but that 5-HT is more selective in this
respect and evokes the secretion of "CRF" only (140).
Attempts are now being made to isolate and identify the
CRF released into the incubation medium in response to respect and evokes the secretion of "CRF" only (140).
Attempts are now being made to isolate and identify the
CRF released into the incubation medium in response to
5-HT. Preliminary separation by chromatography on
Sephade Attempts are now being made to isolate and identify the CRF released into the incubation medium in response to 5-HT. Preliminary separation by chromatography on Sephadex G-25 demonstrated two peaks of CRF activity, fractio CRF released into the incubation medium in response to 5-HT. Preliminary separation by chromatography on Sephadex G-25 demonstrated two peaks of CRF activity, fractions A and B, with molecular weights of about 2500 and 130 5-HT. Preliminary separation by chromatography on Sephadex G-25 demonstrated two peaks of CRF activity, fractions A and B, with molecular weights of about 2500 and 1300, respectively. Both fractions evoked marked, dose-rel Sephadex G-25 demonstrated two peaks of CRF activity,
fractions A and B, with molecular weights of about 2500
and 1300, respectively. Both fractions evoked marked,
dose-related increases in pituitary ACTH release either
wh fractions A and B, with molecular weights of about 2500
and 1300, respectively. Both fractions evoked marked,
dose-related increases in pituitary ACTH release either
when injected into basal hypothalamic-lesioned rats or
 dose-related increases in pituitary ACTH release either
when injected into basal hypothalamic-lesioned rats or
when incubated with rat adenohypophysial segments in
vitro. These effects appear to be specific since neither
f dose-related increases in pituitary ACTH release eithe
when injected into basal hypothalamic-lesioned rats of
when incubated with rat adenohypophysial segments i
vitro. These effects appear to be specific since neithe
frac when injected into basal hypothalamic-lesioned rats or
when incubated with rat adenohypophysial segments in
vitro. These effects appear to be specific since neither
fraction markedly influences the release of other pitui-
 when incubated with rat adenohypophysial segments in
vitro. These effects appear to be specific since neither
fraction markedly influences the release of other pitui-
tary hormones in the rat (46, 140) but the ability of t vitro. These effects appear to be specific since neither
fraction markedly influences the release of other pitui-
tary hormones in the rat (46, 140) but the ability of the
fractions to influence ACTH release in other speci fraction markedly influences the release of other pituitary hormones in the rat (46, 140) but the ability of the fractions to influence ACTH release in other species has not been tested. The amino acid sequences of these s tary hormones in the rat (46, 140) be
fractions to influence ACTH release
not been tested. The amino acid sequent purified peptides have yet to be
identity of CRF remains an enigma.
NV. Mathoda for the Detection of not been tested. The amino acid sequences of these still

of Corticotrophin Releasing Activity

entity of CRF remains an enigma.
 W. Methods for the Detection and Quantification

of Corticotrophin Releasing Activity

Many methods have been developed for the detection

corticotrophin releasing activity. None of thes **IV. Methods for the Detection and Quantification**
of Corticotrophin Releasing Activity
Many methods have been developed for the detection
of corticotrophin releasing activity. None of these qualify tion of CRF. (A stable, potent preparation is not generally ertheless, some workers still employ relatively insensitive available.) Nevertheless, the techniques involve the de-
tection and quantification of a biologically ELEASING FACTOR
the lack of satisfactory techniques for the determination
of corticotrophin. The development of sensitive, specific, ELEASING FACTOR

the lack of satisfactory techniques for the determination

of corticotrophin. The development of sensitive, specific,

and precise bioassay methods for the estimation of cor-257
the lack of satisfactory techniques for the determination
of corticotrophin. The development of sensitive, specific,
and precise bioassay methods for the estimation of cor-
ticotrophin (2, 227) has overcome this proble the lack of satisfactory techniques for the determination
of corticotrophin. The development of sensitive, specific
and precise bioassay methods for the estimation of cor-
ticotrophin (2, 227) has overcome this problem but the lack of satisfactory techniques for the determination
of corticotrophin. The development of sensitive, specific,
and precise bioassay methods for the estimation of cor-
ticotrophin (2, 227) has overcome this problem bu of corticotrophin. The development of sensitive, specific,
and precise bioassay methods for the estimation of cor-
ticotrophin (2, 227) has overcome this problem but, nev-
ertheless, some workers still employ relatively in and precise bioassay methods for the estimation of α icotrophin $(2, 227)$ has overcome this problem but, rertheless, some workers still employ relatively insension indirect indices of ACTH secretion (e.g. adrenal corb ertheless, some workers still employ relatively insensitive
or indirect indices of ACTH secretion (e.g. adrenal as-
corbic acid depletion or adrenal corticosteroidogenesis)
that I regard as less appropriate.
Rats in which the less, some workers still employ relatively insensitive
indirect indices of ACTH secretion (e.g. adrenal as-
rbic acid depletion or adrenal corticosteroidogenesis)
at I regard as less appropriate.
Rats in which the nons

or indirect indices of ACTH secretion (e.g. adrenal as-
corbic acid depletion or adrenal corticosteroidogenesis)
that I regard as less appropriate.
Rats in which the nonspecific release of corticotrophin
is prevented by th corbic acid depletion or adrenal corticosteroidogenesis)
that I regard as less appropriate.
Rats in which the nonspecific release of corticotrophin
is prevented by the placement of extensive lesions in the
median eminence that I regard as less appropriate.
Rats in which the nonspecific release of corticotrophin
is prevented by the placement of extensive lesions in the
median eminence have been used for many years for the
detection of CRF (2 Rats in which the nonspecific release of corticotrophin
is prevented by the placement of extensive lesions in the
median eminence have been used for many years for the
detection of CRF (289). The effectiveness of the lesio is prevented by the placement of extensive lesions in the median eminence have been used for many years for the detection of CRF (289). The effectiveness of the lesion is assessed either histologically or, more simply, by median eminence have been used for many years for the detection of CRF (289). The effectiveness of the lesion is assessed either histologically or, more simply, by subjecting the animal to a stressful stimulus and subseque detection of CRF (289). The effectiveness of the lesion is
assessed either histologically or, more simply, by sub-
jecting the animal to a stressful stimulus and subsequent
unilateral adrenalectomy to obtain a gland to pre assessed either histologically or, more simply, by subjecting the animal to a stressful stimulus and subsequent
unilateral adrenalectomy to obtain a gland to pretest.
The rate of corticosterone production in vitro by the
e jecting the animal to a stressful stimulus and subsequent
unilateral adrenalectomy to obtain a gland to pretest.
The rate of corticosterone production in vitro by the
excised gland serves as the index of ACTH release, whic unilateral adrenalectomy to obtain a gland to pretest.
The rate of corticosterone production in vitro by the
excised gland serves as the index of ACTH release, which
is small in an effectively lesioned rat. The test substa The rate of corticosterone production in vitro by the excised gland serves as the index of ACTH release, which is small in an effectively lesioned rat. The test substance is then administered i.v. to the surviving unilater excised gland serves as the index of ACTH release, whis
is small in an effectively lesioned rat. The test substant
is then administered i.v. to the surviving unilateral
adrenalectomised rat and the rate of corticosterone p is small in an effectively lesioned rat. The test substance
is then administered i.v. to the surviving unilaterally
adrenalectomised rat and the rate of corticosterone pro-
duction in vitro by the second adrenal gland is d is then administered i.v. to the surviving unilaterally adrenalectomised rat and the rate of corticosterone production in vitro by the second adrenal gland is determined. The sensitivity of the pituitary gland to CRF is lo adrenalectomised rat and the rate of corticosterone pro-
duction in vitro by the second adrenal gland is deter-
mined. The sensitivity of the pituitary gland to CRF is
lower in rats with hypothalamic lesions than in intact duction in vitro by the second adrenal gland is deter-
mined. The sensitivity of the pituitary gland to CRF is
lower in rats with hypothalamic lesions than in intact
rats but, according to de Wied (290), this problem is
re mined. The sensitivity of the pituitary gland to CRF is lower in rats with hypothalamic lesions than in intact rats but, according to de Wied (290), this problem is reduced by performing the assay within 1 to 3 days o pla lower in rats with hypothalamic lesions than in intact
rats but, according to de Wied (290), this problem is
reduced by performing the assay within 1 to 3 days of
placing the lesion. Nevertheless, the method is still rela reduced by performing the assay within 1 to 3 days of placing the lesion. Nevertheless, the method is still relaplacing the lesion. Nevertheless, the method is still relatively insensitive and lacks satisfactory precision $(\lambda = 0.3)$. Furthermore, the accurate placement of lesions requires great skill and any minute change in the lo tively insensitive and lacks satisfactory precision $(\lambda = 0.3)$. Furthermore, the accurate placement of lesions requires great skill and any minute change in the location of the electrode may reduce the effectiveness of th 0.3). Furthermore, the accurate placement of lesions requires great skill and any minute change in the location of the electrode may reduce the effectiveness of the lesion. These technical difficulties prompted a search fo quires great skill and any minute change in the locat of the electrode may reduce the effectiveness of lesion. These technical difficulties prompted a search other means of inhibiting the stress-induced secretio ACTH. Sire of the electrode may reduce the effectiveness of the
lesion. These technical difficulties prompted a search for
other means of inhibiting the stress-induced secretion of
ACTH. Sirett and Purves (247) proposed that hypophylesion. These technical difficulties prompted a search for
other means of inhibiting the stress-induced secretion of
ACTH. Sirett and Purves (247) proposed that hypophy-
sectomised rats bearing pituitary transplants in the other means of inhibiting the stress-induced secretion of
ACTH. Sirett and Purves (247) proposed that hypophy-
sectomised rats bearing pituitary transplants in the kid-
ney capsule might be suitable. In appropriately "gra ACTH. Sirett and Purves (247) proposed that hypoplectomised rats bearing pituitary transplants in the hey capsule might be suitable. In appropriately "grafterats, the i.v. injection of an acid extract of 1.0 SN caused a si sectomised rats bearing pituitary transplants in the kid-
ney capsule might be suitable. In appropriately "grafted"
rats, the i.v. injection of an acid extract of 1.0 SME
caused a significant rise in plasma corticosterone ney capsule might be suitable. In appropriately "grafted"
rats, the i.v. injection of an acid extract of 1.0 SME
caused a significant rise in plasma corticosterone concen-
tration (245-247) but higher doses failed to elici rats, the i.v. injection of an acid extract of 1.0 SME
caused a significant rise in plasma corticosterone concen-
tration (245–247) but higher doses failed to elicit an
enhanced response. This is probably because the adren caused a significant rise in plasma corticosterone concentration (245–247) but higher doses failed to elicit an enhanced response. This is probably because the adrenal glands of the "grafted" rat are atrophic and are relat tration (245–247) but higher doses failed to elicit an
enhanced response. This is probably because the adrenal
glands of the "grafted" rat are atrophic and are relatively
insensitive to ACTH. Their responsiveness is readil enhanced response. This is probably because the adrenal
glands of the "grafted" rat are atrophic and are relatively
insensitive to ACTH. Their responsiveness is readily
restored by "priming" with corticotrophin and suitabl glands of the "grafted" rat are atrophic and are relatively
insensitive to ACTH. Their responsiveness is readily
restored by "priming" with corticotrophin and suitably
"primed grafted" rats respond to SME with dose-relate insensitive to ACTH. Their responsiveness is readily
restored by "priming" with corticotrophin and suitably
"primed grafted" rats respond to SME with dose-related
increases in plasma corticosterone concentration over a
ra restored by "priming" with corticotrophin and suitably
"primed grafted" rats respond to SME with dose-related
increases in plasma corticosterone concentration over a
range of concentrations from 0.2 to 1.0 SME (248, 249). "primed grafted" rats respond to SME with dose-related
increases in plasma corticosterone concentration over a
range of concentrations from 0.2 to 1.0 SME (248, 249).
This assay is reliable and relatively precise ($\lambda = 0.$ increases in plasma corticosterone concentration over a
range of concentrations from 0.2 to 1.0 SME (248, 249).
This assay is reliable and relatively precise ($\lambda = 0.13$ to
0.17) (248, 249) but it is difficult to perform range of concentrations from 0.2 to 1.0 SME (248, 249).
This assay is reliable and relatively precise ($\lambda = 0.13$ to 0.17) (248, 249) but it is difficult to perform and requires much experience and expertise. It could be This assay

0.17) (248, 2

much exper

improved b

for ACTH.

Many in 17) (248, 249) but it is difficult to perform and require
uch experience and expertise. It could be simplified an
proved by the incorporation of a suitable direct assa
r ACTH.
Many investigators have preferred to employ ph much experience and expertise. It could be simplified and
improved by the incorporation of a suitable direct assay
for ACTH.
Many investigators have preferred to employ phar-
macological methods to prevent the stress-induc

leasing activity involve the measurement of the resulting release of ACTH. High doses of glucocorticoids are effec-
adrenocorticotrophic activity of the adenohypophysis tive in preventing ACTH discharge and thus cortico-
e improved by the incorporation of a suitable direct assa
for ACTH.
Many investigators have preferred to employ pha
macological methods to prevent the stress-induce
release of ACTH. High doses of glucocorticoids are effec
ti for ACTH.

Many investigators have preferred to employ ph

macological methods to prevent the stress-induced

release of ACTH. High doses of glucocorticoids are eff

tive in preventing ACTH discharge and thus cortic

stero Many investigators have preferred to employ phar-
macological methods to prevent the stress-induced
release of ACTH. High doses of glucocorticoids are effec-
tive in preventing ACTH discharge and thus cortico-
steroid-trea macological methods to prevent the stress-induced release of ACTH. High doses of glucocorticoids are effective in preventing ACTH discharge and thus cortico-
steroid-treated rats have been advocated as a convenient and rel release of ACTH. High doses of glucocorticoids are effective in preventing ACTH discharge and thus cortico-
steroid-treated rats have been advocated as a convenient
and reliable preparation for the detection of CRF (8, 219

as a classical biological assay method, since bioas
involves the comparison of the potency of the unkno
with that of a suitable standard preparation and, at
present time, there is no satisfactory standard prepa
tion of CRF as a classical biological assay method, since bioassay timvolves the comparison of the potency of the unknown owith that of a suitable standard preparation and, at the apresent time, there is no satisfactory standard prep involves the comparison of the potency of the unknown
with that of a suitable standard preparation and, at the
present time, there is no satisfactory standard prepara-
tion of CRF. (A stable, potent preparation is not gene present time, there is no satisfactory standard prepara-
tion of CRF. (A stable, potent preparation is not generally
available.) Nevertheless, the techniques involve the de-
tection and quantification of a biologically act tion of CRF. (A stable, potent preparation is not genera
available.) Nevertheless, the techniques involve the α
tection and quantification of a biologically active su
stance and thus, in evaluating their usefulness, th available.) Nevertheless, the techniques involve the detection and quantification of a biologically active substance and thus, in evaluating their usefulness, their precision, specificity, and sensitivity should all be con tection and quantification of a biologically active substance and thus, in evaluating their usefulness, the precision, specificity, and sensitivity should all be considered as far as is possible. Without a standard prepara stance and thus, in evaluating their usefulness, their
precision, specificity, and sensitivity should all be consid-
ered as far as is possible. Without a standard preparation
the comparability of methods for the detection precision, specificity, and sensitivity should all be considered as far as is possible. Without a standard preparation is precise the comparability of methods for the detection of corti-
cotrophin releasing activity cannot ered as far as is possible. Without a standard preparation the comparability of methods for the detection of correctrophin releasing activity cannot be determined by the index of precision can be assessed readily. In m op the comparability of methods for the detection of corticutor
cotrophin releasing activity cannot be determined but
the index of precision can be assessed readily. In my
aspinion, only those systems in which the index of p cotrophin releasing activity cannot be determined but
the index of precision can be assessed readily. In my
opinion, only those systems in which the index of preci-
sion (λ) (78) is less than 0.15 are satifactory. Sinc the index of precision can be assessed readily. In my
opinion, only those systems in which the index of preci-
sion (λ) (78) is less than 0.15 are satifactory. Since the
chemical nature of CRF is not known, the true spe opinion, only those systems in which the index of precision (λ) (78) is less than 0.15 are satifactory. Since the unchemical nature of CRF is not known, the true specificity T of methods for its detection is difficult t chemical nature of CRF is not known, the true specificity
of methods for its detection is difficult to define. A great
many substances present in the hypothalamus are known
not to affect directly the secretion of corticot chemical nature of CRF is not known, the true specificiof methods for its detection is difficult to define. A gree many substances present in the hypothalamus are know not to affect directly the secretion of corticotrophi of methods for its detection is difficult to define. A g
many substances present in the hypothalamus are know
not to affect directly the secretion of corticotrophin (
acetylcholine, noradrenaline, adrenaline, 5-HT, γ -a
 many substances present in the hypothalamus are known to affect directly the secretion of corticotrophin (e acetylcholine, noradrenaline, adrenaline, 5-HT, γ -an nobutyric acid, glycine, glutamine, histamine, enkephein, not to affect directly the secretion of corticotrophin (e.g. acetylcholine, noradrenaline, adrenaline, 5-HT, γ -aminobutyric acid, glycine, glutamine, histamine, enkephalin, endorphin, gonadotrophin releasing hormone, th acetylcholine, noradrenaline, adrenaline, 5-HT, γ -ami-
nobutyric acid, glycine, glutamine, histamine, enkepha-
lin, endorphin, gonadotrophin releasing hormone, thyro-
mirophin releasing hormone, growth hormone release nobutyric acid, glycine, glutamine, histamine, enkepha-
lin, endorphin, gonadotrophin releasing hormone, thyro-
trophin releasing hormone, growth hormone release in-
hibiting hormone) and therefore should not be active in
 lin, endorphin, gonadotrophin releasing hormone, thyrotrophin releasing hormone, growth hormone release inhibiting hormone) and therefore should not be active in an acceptably specific assay method. Similarly, without a su hibiting hormone) and therefore should not be active in
an acceptably specific assay method. Similarly, without
reasurable standard preparation, the sensitivity (the mini-
mum effective dose of CRF required) of the "assay" a suitable standard preparation, the sensitivity (the mini-
mum effective dose of CRF required) of the "assay"
methods cannot be truly assessed. Several groups have
attempted to express the sensitivity of their respective
 mum effective dose of CRF required) of the "assay" tively insensitive and lacks satisfactory precision $(\lambda =$ methods cannot be truly assessed. Several groups have 0.3). Furthermore, the accurate placement of lesions reatt mum effective dose of CRF required) of the "assay" methods cannot be truly assessed. Several groups have dattempted to express the sensitivity of their respective techniques in terms of the minimum concentration of either methods cannot be truly assessed. Several groups have 0.3
attempted to express the sensitivity of their respective qui
techniques in terms of the minimum concentration of of
either hypothalamic extract (90, 117, 206, 207, attempted to express the sensitivity of their respective q
techniques in terms of the minimum concentration of o
either hypothalamic extract $(90, 117, 206, 207, 247, 248)$ loor
lysine vasopressin $(214, 289, 290)$ requir techniques in terms of the minimum concentration of
either hypothalamic extract (90, 117, 206, 207, 247, 248)
or lysine vasopressin (214, 289, 290) required to evoke a
significant response. Neither is valid. The amount of
 either hypothalamic extract (90, 117, 206, 207, 247, 248)
or lysine vasopressin (214, 289, 290) required to evoke a
significant response. Neither is valid. The amount of
"CRF" present in an extract of one stalk median emior lysine vasopressin (214, 289, 290) required to evoke a other significant response. Neither is valid. The amount of ACTH "CRF" present in an extract of one stalk median emission mence or hypothalamus depends on the meth significant response. Neither is valid. The amount of AC

"CRF" present in an extract of one stalk median emi-

nence or hypothalamus depends on the method of ex-

traction (CRF is more readily extracted in media of low
 nence or hypothalamus depends on the method of ex-
traction (CRF is more readily extracted in media of low
pH), on the time that the organ is removed [the CRF
content of the hypothalamus varies according to a cir-
cadian p nence or hypothalamus depends on the method of ex-
traction (CRF is more readily extracted in media of low
pH), on the time that the organ is removed [the CRF ca
content of the hypothalamus varies according to a cir-
cadia traction (CRF is more readily extracted in media of low
pH), on the time that the organ is removed [the CRF cation to the hypothalamus varies according to a cir-
cadian pattern (62)], the rapidity of the dissection, and
o pH), on the time that the organ is removed [the CRF content of the hypothalamus varies according to a circadian pattern (62)], the rapidity of the dissection, and on the "stress-state" of the donor at the time of death [th content of the hypothalamus varies according to a circulation carrier (62)], the rapidity of the dissection, and enh
on the "stress-state" of the donor at the time of death glan
(the CRF activity of the hypothalamus is af cadian pattern (62)], the rapidity of the dissection, a
on the "stress-state" of the donor at the time of der
[the CRF activity of the hypothalamus is affected p
foundly by minor stressful stimuli and this is reflected
the on the "stress-state" of the donor at the time of death
[the CRF activity of the hypothalamus is affected pro-
foundly by minor stressful stimuli and this is reflected in
the potency of extracts (31, 280)]. Moreover, the r [the CRF activity of the hypothalamus is affected pro-
foundly by minor stressful stimuli and this is reflected in
the potency of extracts (31, 280)]. Moreover, the respon-
siveness of anterior pituitary tissue to vasopres foundly by minor stressful stimuli and this is reflected in
the potency of extracts (31, 280)]. Moreover, the respon-
siveness of anterior pituitary tissue to vasopressin cannot
include correlated repeatably with that to h the potency of extracts (31, 280)]. Moreover, the responsiveness of anterior pituitary tissue to vasopressin cannot
be correlated repeatably with that to hypothalamic ex-
tracts. Miahle et al. (191) showed that pituitary t siveness of anterior pituitary tissue to vasopressin cannot incube correlated repeatably with that to hypothalamic ex-
tracts. Miahle et al. (191) showed that pituitary tissue in Thi
vitro responds to hypothalamic extract be correlated repeatably with that to hypothalamic ex-
tracts. Miahle et al. (191) showed that pituitary tissue in
vitro responds to hypothalamic extract immediately after
it is removed from the donor but that it responds tracts. Miahle et al. (191) showed that pituitary tissue in
vitro responds to hypothalamic extract immediately after 0.1
it is removed from the donor but that it responds to mu
vasopressin only after a considerable preincu vitro responds to
it is removed fr
vasopressin only
riod. Similar fine
Thomas (221).
The methods is removed from the donor but that it responds to sopressin only after a considerable preincubation pe-
od. Similar findings have been reported by Sadow and
homas (221).
The methods for the detection of corticotrophin re-
 vasopressin only after a considerable preincubation pe-

riod. Similar findings have been reported by Sadow and

Thomas (221).

The methods for the detection of corticotrophin re-

leasing activity involve the measurement riod. Similar findings have been reported by Sadow and
Thomas (221).
The methods for the detection of corticotrophin releasing activity involve the measurement of the resulting
adrenocorticotrophic activity of the adenohyp Thomas (221).

The methods for the detection of corticotrophin re-

leasing activity involve the measurement of the resulting

adrenocorticotrophic activity of the adenohypophysis

either in vivo, in animals in which the The methods for the detection of colleasing activity involve the measuremen
adrenocorticotrophic activity of the a
either in vivo, in animals in which the energy of CRF has been inhibited, or in vitro.
Until recently the a

 258 BUCKINGH
sion ($\lambda = 0.22$) and sensitivity (minimum effective dose dis
= 0.2 HE (HE = extract of one hypothalamus)). Most suit
steroids that prevent the discharge of corticotrophin in SUCKINGHA
sion $(\lambda = 0.22)$ and sensitivity (minimum effective dose disa
= 0.2 HE (HE = extract of one hypothalamus)). Most subs
steroids that prevent the discharge of corticotrophin in the
response to stress also reduce sion $(\lambda = 0.22)$ and sensitivity (minimum effective dose = 0.2 HE (HE = extract of one hypothalamus)). Most steroids that prevent the discharge of corticotrophin in response to stress also reduce the capacity of the anter sion $(\lambda = 0.22)$ and sensitivity (minimum effective d
= 0.2 HE (HE = extract of one hypothalamus)). M
steroids that prevent the discharge of corticotrophin
response to stress also reduce the capacity of the ante
pituitary = 0.2 HE (HE = extract of one hypothalamus)). Most subs
steroids that prevent the discharge of corticotrophin in the
response to stress also reduce the capacity of the anterior pitu
pituitary gland to release ACTH in resp steroids that prevent the discharge of corticotrophin in the response to stress also reduce the capacity of the anterior pituitary gland to release ACTH in response to hypotha-
lamic extracts (32, 113, 280) or lysine vasop gland.

lamic extracts (32, 113, 280) or lysine vasopressin (3'
virtue of direct actions of the steroids on the piture
gland.
Many psychotropic drugs prevent the release of A(
when injected into animals pretreated with pentob
tone virtue of direct actions of the steroids on the pituitary
gland.
Many psychotropic drugs prevent the release of ACTH
when injected into animals pretreated with pentobarbi-
tone. Briggs and Munson (21) showed that treatment gland.

Many psychotropic drugs prevent the release of ACT

when injected into animals pretreated with pentobar

tone. Briggs and Munson (21) showed that treatme

with pentobarbitone and morphine inhibits the stree

induce Many psychotropic drugs prevent the release of AC
when injected into animals pretreated with pentoba
tone. Briggs and Munson (21) showed that treatm
with pentobarbitone and morphine inhibits the strinduced adrenocorticotro when injected into animals pretreated with pentobarbitone. Briggs and Munson (21) showed that treatment with pentobarbitone and morphine inhibits the stress-
induced adrenocorticotrophic activity of the adenohy-
pophysis a tone. Briggs and Munson (21) showed that treatment and with pentobarbitone and morphine inhibits the stress-
induced adrenocorticotrophic activity of the adenohy- to pophysis and this drug combination was subsequently sh
a with pentobarbitone and morphine inhibits the stress-
induced adrenocorticotrophic activity of the adenohy-
pophysis and this drug combination was subsequently sho
adapted for the assay of CRF (99). According to some wh
wo induced adrenocorticotrophic activity of the adenohy-
pophysis and this drug combination was subsequently show
adapted for the assay of CRF (99). According to some wh
workers the pentobarbitone-morphine-treated rat is very pophysis and this drug combination was subsequently subadepted for the assay of CRF (99). According to some workers the pentobarbitone-morphine-treated rat is very prensitive to CRF but Briggs and Munson (21), de Wied ret adapted for the assay of CRF (99). According to some
workers the pentobarbitone-morphine-treated rat is very
sensitive to CRF but Briggs and Munson (21), de Wied
et al. (292), and Guillemin et al. (99) found the sensitivit workers the pentobarbitone-morphine-treated rat is very
sensitive to CRF but Briggs and Munson (21), de Wied
et al. (292), and Guillemin et al. (99) found the sensitivity
of the adenohypophysis to vasopressin to be impaire sensitive to CRF but Briggs and Munson (21), de Wied
et al. (292), and Guillemin et al. (99) found the sensitivity
of the adenohypophysis to vasopressin to be impaired,
which these investigators considered to be an advanta et al. (292), and Guillemin et al. (99) found the sensitivity tand of the adenohypophysis to vasopressin to be impaired, rewhich these investigators considered to be an advantage bland an indication of specificity. Arimura of the adenohypophysis to vasopressin to be impaired, which these investigators considered to be an advantage and an indication of specificity. Arimura et al. (8) reported that the effects of this drug combination were unr which these investigators considered to be an advantage and an indication of specificity. Arimura et al. (8) reported that the effects of this drug combination were unreliable and that the method could be improved consider and an indication of specificity. Arimura et al. (8) reported that the effects of this drug combination were unreliable and that the method could be improved considerably by the incorporation of chlorpromazine. Pentobarbit ported that the effects of this drug combination wourneliable and that the method could be improved cosiderably by the incorporation of chlorpromazine. Potobarbitone-morphine-chlorpromazine-treated rats apear suitable for unreliable and that the method could be improved considerably by the incorporation of chlorpromazine. Pentobarbitone-morphine-chlorpromazine-treated rats appear suitable for the assay of CRF and respond consistently to con siderably by the incorporation of chlorpromazine. Potobarbitone-morphine-chlorpromazine-treated rats apear suitable for the assay of CRF and respond considerative to concentrations of arginine vasopressin and l pothalamic pear suitable for the assay of CRF and respond consistently to concentrations of arginine vasopressin and hypothalamic extract as low as 12.5 mU and 0.3 HE respectively (8). Other workers have found that chlorpromazine alo pear suitable for the assay of CRF and respond consist-
evently to concentrations of arginine vasopressin and hy-
pothalamic extract as low as 12.5 mU and 0.3 HE respec-
furtively (8). Other workers have found that chlorpr ently to concentrations of arginine vasopressin and hypothalamic extract as low as 12.5 mU and 0.3 HE respectively (8). Other workers have found that chlorpromazine alone inhibits the stress-induced release of ACTH in pent pothalamic extract as low as 12.5 mU and 0.3 HE respec-
tively (8). Other workers have found that chlorpromazine
indice inhibits the stress-induced release of ACTH in
sepentobarbitone-treated rats and this drug combination tively (8). Other workers have found that chlorpron
alone inhibits the stress-induced release of AC
pentobarbitone-treated rats and this drug combi
has been strongly favoured for the assay of CRF |
prominent laboratory (16 alone inhibits the stress-induced release of ACTH in sepentobarbitone-treated rats and this drug combination schases been strongly favoured for the assay of CRF by one prominent laboratory (164, 165, 290). Pentobarbitone pentobarbitone-treated rats and this drug combinatio
has been strongly favoured for the assay of CRF by on
prominent laboratory (164, 165, 290). Pentobarbitone
chlorpromazine-treated rats respond to i.v. injections c
eithe prominent laboratory (164, 165, 290). Pentobarbitone-chlorpromazine-treated rats respond to i.v. injections of either hypothalamic extracts or vasopressin with dose-related increases in the concentration of ACTH in the pla chlorpromazine-treated rats respond to i.v. injections of lave either hypothalamic extracts or vasopressin with dose-
related increases in the concentration of ACTH in the roplasma (133) and in the amount of corticosterone either hypothalamic extracts or vasopressin with develated increases in the concentration of ACTH in plasma (133) and in the amount of corticosterone pduced by the adrenal gland (164, 165, 290). The develatment does reduce related increases in the concentration of ACTH in the rouplasma (133) and in the amount of corticosterone pro-
photoed by the adrenal gland (164, 165, 290). The drug ab
treatment does reduce the sensitivity of the adenohyplasma (133) and in the amount of corticosterone pro-
duced by the adrenal gland (164, 165, 290). The drug
treatment does reduce the sensitivity of the adenohy-
pophysis to "CRF" (133) but not so markedly as the
placement duced by the adrenal gland (164, 165, 290). The drug ab
treatment does reduce the sensitivity of the adenohy-
pophysis to "CRF" (133) but not so markedly as the ba
placement of lesions in the hypothalamus. This is not po
s treatment does reduce the sensitivity of the ade
pophysis to "CRF" (133) but not so markedly s
placement of lesions in the hypothalamus. This
surprising. The secretory capacity of corticotrop
reduced by deprivation of trop pophysis to "CRF" (133) but not so markedly as the backflow. By using this technique, Hiroshige (117) replacement of lesions in the hypothalamus. This is not ported the detection of concentrations of SME extract as surpri surprising. The secretory capacity of corticotrophs is low as 0.02. Although it lacks adequate precision $(\lambda =$
reduced by deprivation of trophic stimuli. Hypothalamic- 0.27), the reported specificity and sensitivity of th reduced by deprivation of trophic stimuli. Hypothalamic-(290). the operation but the drug-treated animals are employed
within 30 minutes of the injection of chlorpromazine
(290).
Although it has been suggested that monoamine oxi-
dase inhibitors abolish the pituitary adrenocortical re

Although it has been suggested that monoamine oxiwithin 30 minutes of the injection of chlorpromazine (290).
(290).
Although it has been suggested that monoamine oxidase inhibitors abolish the pituitary adrenocortical response to stress (269), attempts to employ animals (290).

Although it has been suggested that monoamine oxidase inhibitors abolish the pituitary adrenocortical response to stress (269), attempts to employ animals treated with these drugs for the assay of CRF have not bee Although it has been suggested that monoamine ox
dase inhibitors abolish the pituitary adrenocortical r
sponse to stress (269), attempts to employ anima
treated with these drugs for the assay of CRF have no
been successfu dase inhibitors abolish the pituitary adrenocortical response to stress (269), attempts to employ animal treated with these drugs for the assay of CRF have no been successful. Schally et al. (233) showed that treat ment o sponse to stress (269), attempts to employ animals
treated with these drugs for the assay of CRF have not
been successful. Schally et al. (233) showed that treat-
ment of rats with pentobarbitone and α -ethyltryptamine
d treated with these drugs for the assay of CRF have
been successful. Schally et al. (233) showed that tre
ment of rats with pentobarbitone and α -ethyltryptan
does not prevent the stress-induced release of ACTH
reduces been successful. Schally et al. (233) showed that treatment of rats with pentobarbitone and α -ethyltryptamine does not prevent the stress-induced release of ACTH but reduces markedly the responsiveness of the adenohypop ment of rats with pentobarbitone and α -ethyltryptamine 22
does not prevent the stress-induced release of ACTH but
reduces markedly the responsiveness of the adenohy-
at pophysis to putative corticotrophin releasing fac

positivitary gland to release ACTH in response to hypotha-
inque of direct intrapituitary injection and demonstrated,
lamic extracts (32, 113, 280) or lysine vasopressin (37) by with respect to gonadotrophin secretion, a 1 has been strongly favoured for the assay of CRF by one passage of cannulae through the brain stem to the ade-
prominent laboratory (164, 165, 290). Pentobarbitone- nohypophysis may stimulate structures that can modu-
chlor disadvantage of all of the above methods is that the test
substances are administered i.v. and thus are diluted in GHAM
disadvantage of all of the above methods is that the test
substances are administered i.v. and thus are diluted in
the systemic circulation before they reach the anterior GHAM
disadvantage of all of the above methods is that the test
substances are administered i.v. and thus are diluted in
the systemic circulation before they reach the anterior
pituitary gland. Nikitovitch-Winer (199) appli disadvantage of all of the above methods is that the tes
substances are administered i.v. and thus are diluted is
the systemic circulation before they reach the anterio
pituitary gland. Nikitovitch-Winer (199) applied a te disadvantage of all of the above methods is that the tesubstances are administered i.v. and thus are diluted
the systemic circulation before they reach the anteri
pituitary gland. Nikitovitch-Winer (199) applied a tec
niqu substances are administered i.v. and thus are diluted in
the systemic circulation before they reach the anterior
pituitary gland. Nikitovitch-Winer (199) applied a tech-
nique of direct intrapituitary injection and demonst the systemic circulation before they reach the anterior pituitary gland. Nikitovitch-Winer (199) applied a technique of direct intrapituitary injection and demonstrated, with respect to gonadotrophin secretion, a 10- to 48 pituitary gland. Nikitovitch-Winer (199) applied a technique of direct intrapituitary injection and demonstrated, with respect to gonadotrophin secretion, a 10- to 48-fold increase in sensitivity to gonadotrophin releasing mique of direct intrapituitary injection and demonstrated,
with respect to gonadotrophin secretion, a 10- to 48-fold
increase in sensitivity to gonadotrophin releasing hor-
mone compared with the parallel i.v. method. Simi with respect to gonadotrophin secretion, a 10- to 48-fold
increase in sensitivity to gonadotrophin releasing hor-
mone compared with the parallel i.v. method. Similar
results were reported by Campbell et al. (48). A detail increase in sensitivity to gonadotrophin releasing hormone compared with the parallel i.v. method. Similar results were reported by Campbell et al. (48). A detailed comparison of the effects of i.v., intramedian eminence, mone compared with the parallel i.v. method. Sir
results were reported by Campbell et al. (48). A det.
comparison of the effects of i.v., intramedian emine
and intrapituitary administration of CRF to rats tre
with either p results were reported by Campbell et al. (48). A detailed
comparison of the effects of i.v., intramedian eminence,
and intrapituitary administration of CRF to rats treated
with either pentobarbitone/morphine or pentobarbicomparison of the effects of i.v., intramedian eminence,
and intrapituitary administration of CRF to rats treated
with either pentobarbitone/morphine or pentobarbi-
tone/dexamethasone was made. Dhariwal et al. (65)
showed and intrapituitary administration of CRF to rats treated
with either pentobarbitone/morphine or pentobarbi-
tone/dexamethasone was made. Dhariwal et al. (65)
showed that hypothalamic extracts that were ineffective
when giv with either pentobarbitone/morphine or pentobarbitone/dexamethasone was made. Dhariwal et al. (65) showed that hypothalamic extracts that were ineffective when given i.v. caused dose-related increases in the plasma cortico tone/dexamethasone was made. Dhariwal et al. (65
showed that hypothalamic extracts that were ineffective
when given i.v. caused dose-related increases in the
plasma corticosterone concentration when injected d
rectly into when given i.v. caused dose-related increases in the plasma corticosterone concentration when injected directly into either the median eminence or anterior pituitary gland but that the latter were more effective. The respo when given i.v. caused dose-related increases in t
plasma corticosterone concentration when injected
rectly into either the median eminence or anterior pit
tary gland but that the latter were more effective. T
responses af plasma corticosterone concentration when injected
rectly into either the median eminence or anterior pit
tary gland but that the latter were more effective. T
responses after median eminence injections were prob
bly attrib rectly into either the median eminence or anterior pitui-
tary gland but that the latter were more effective. The
responses after median eminence injections were proba-
bly attributable to the spread of material to the ade tary gland but that the latter were more effective. The responses after median eminence injections were probably attributable to the spread of material to the adeno-hypophysis since positive results were obtained only in t responses after median eminence injections were probably attributable to the spread of material to the adeno-
hypophysis since positive results were obtained only in
the limited region in which the portal vessels were most bly attributable to the spread of material to the adeno-
hypophysis since positive results were obtained only in
the limited region in which the portal vessels were most
concentrated. These findings suggested that assay
me hypophysis since positive results were obtained only if the limited region in which the portal vessels were more concentrated. These findings suggested that assemethods in which intrapituitary injections are employed are m the limited region in which the portal vessels were most concentrated. These findings suggested that assay methods in which intrapituitary injections are employed are more sensitive than the parallel i.v. techniques. Howev concentrated. These findings suggested that assay
methods in which intrapituitary injections are employed
are more sensitive than the parallel i.v. techniques. How-
ever, the stereotaxic work required for the method limits methods in which intrapituitary injections are employed
are more sensitive than the parallel i.v. techniques. How-
ever, the stereotaxic work required for the method limits
its use in the screening of large numbers of samp ever, the stereotaxic work required for the method limits
its use in the screening of large numbers of samples.
Furthermore, according to Hiroshige and Itoh (118), the
injection technique employed by Dhariwal et al. has
se ever, the stereotaxic work required for the method limits
its use in the screening of large numbers of samples.
Furthermore, according to Hiroshige and Itoh (118), the
injection technique employed by Dhariwal et al. has
se its use in the screening of large numbers of samples.
Furthermore, according to Hiroshige and Itoh (118), the
injection technique employed by Dhariwal et al. has
serious shortcomings. Firstly, it is difficult to inject int Furthermore, according to Hiroshige and Itoh (118), the injection technique employed by Dhariwal et al. has
serious shortcomings. Firstly, it is difficult to inject into
some areas of the pituitary gland, and secondly, the injection technique employed by Dhariwal et al. h
serious shortcomings. Firstly, it is difficult to inject in
some areas of the pituitary gland, and secondly, tl
passage of cannulae through the brain stem to the ad
nohypop serious shortcomings. Firstly, it is difficult to inject into some areas of the pituitary gland, and secondly, the passage of cannulae through the brain stem to the adenohypophysis may stimulate structures that can modulat some areas of the pituitary gland, and secondly, the passage of cannulae through the brain stem to the ade-nohypophysis may stimulate structures that can modulate ACTH secretion or may allow the spread of injected substanc passage of cannulae through the brain stem to the ade
nohypophysis may stimulate structures that can modu
late ACTH secretion or may allow the spread of injecte
substances up the cannula back to such structures. Hi
roshige nohypophysis may stimulate structures that can modulate ACTH secretion or may allow the spread of injected substances up the cannula back to such structures. Hiroshige and colleagues (117–119) have adopted a parapharyngeal late ACTH secretion or may allow the spread of injecte
substances up the cannula back to such structures. Hi
roshige and colleagues (117–119) have adopted a para
pharyngeal approach to the adenohypophysis that en
ables the substances up the cannula back to such structures. Hiroshige and colleagues (117–119) have adopted a para-
pharyngeal approach to the adenohypophysis that en-
ables the gland to be reached without the risk of dam-
aging br roshige and colleagues (117–119) have adopted a para-
pharyngeal approach to the adenohypophysis that en-
ables the gland to be reached without the risk of dam-
aging brain structures or contaminating the tissue with
backf pharyngeal approach to the adenohypophysis that enables the gland to be reached without the risk of damaging brain structures or contaminating the tissue with backflow. By using this technique, Hiroshige (117) reported th ables the gland to be reached without the risk of dam-
aging brain structures or contaminating the tissue with
backflow. By using this technique, Hiroshige (117) re-
ported the detection of concentrations of SME extract a backflow. By using this technique, Hiroshige (117) reported the detection of concentrations of SME extract as low as 0.02. Although it lacks adequate precision ($\lambda = 0.27$), the reported specificity and sensitivity of thi low as 0.02. Although it lacks adequate precision ($\lambda =$

The loss of pituitary sensitivity and the possibility of 0.27), the reported specificity and sensitivity of this method recommend its repetition and use by other investigators of CRF.
The loss of pituitary sensitivity and the possibility of incomplete blockade of the hypothalamo method recommend its repetition and use by other in-
vestigators of CRF.
The loss of pituitary sensitivity and the possibility of
incomplete blockade of the hypothalamo-pituitary tract
together with the technical difficult vestigators of CRF.
The loss of pituitary sensitivity and the possibility of
incomplete blockade of the hypothalamo-pituitary tract
together with the technical difficulties associated with in
vivo methods stimulated worker The loss of pituitary sensitivity and the possibility of
incomplete blockade of the hypothalamo-pituitary tract
together with the technical difficulties associated with in
vivo methods stimulated workers to develop in vitr incomplete blockade of the hypothalamo-pituitary tract
together with the technical difficulties associated with in
vivo methods stimulated workers to develop in vitro
systems for the assessment of corticotrophin releasing
 together with the technical difficulties associated with in
vivo methods stimulated workers to develop in vitro
systems for the assessment of corticotrophin releasing
activity. Initially, hemisected pituitary glands, remov vivo methods stimulated workers to develop in vitro
systems for the assessment of corticotrophin releasing
activity. Initially, hemisected pituitary glands, removed
from rats often weighing as much as 200 g (52, 100, 204,
 systems for the assessment of corticotrophin releasing
activity. Initially, hemisected pituitary glands, removed
from rats often weighing as much as $200 g$ (52, 100, 204,
 $223, 224$) were employed. The problems of poor di activity. Initially, hemisected pituitary glands, removed
from rats often weighing as much as 200 g $(52, 100, 204, 223, 224)$ were employed. The problems of poor diffusion
of substances into the gland and the possibili from rats often weighing as much as 200 g $(52, 100, 204, 223, 224)$ were employed. The problems of poor diffusion of substances into the gland and the possibility of necrosis at the centre of the tissue coupled with th of substances into the gland and the possibility of necrosis
at the centre of the tissue coupled with the use of indirect
or insensitive methods for the determination of ACTH
made the early in vitro methods insensitive and

PHARMACOLOGICAL REVIEWS

aspet

CORTICOTROPHIN RELEASING FACTOR 259

stead of hemisected) pituitary glands removed from small CORTICOTROPHIN R
cise. The dangers of poor diffusion and necrosis have
been substantially reduced by the use of quartered (in-
stead of hemisected) pituitary glands removed from small
rats (75 g) (37). Various attempts hav cise. The dangers of poor diffusion and necrosis have the
been substantially reduced by the use of quartered (in-
stead of hemisected) pituitary glands removed from small biot
rats (75 g) (37). Various attempts have been m cise. The dangers of poor diffusion and necrosis have
been substantially reduced by the use of quartered (in-
stead of hemisected) pituitary glands removed from small
rats (75 g) (37). Various attempts have been made to
in been substantially reduced by the use of quartered (in-
stead of hemisected) pituitary glands removed from small bioass.
rats (75 g) (37). Various attempts have been made to betwee
increase the sensitivity of pituitary seg stead of hemisected) pituitary glands removed from small bioass
rats (75 g) (37). Various attempts have been made to betwe
increase the sensitivity of pituitary segments to "CRF". meth
Seiden and Brodish (238) reported tha rats (75 g) (37) . Various attempts have been made to bincrease the sensitivity of pituitary segments to "CRF". m
Seiden and Brodish (238) reported that lowering the pH sand increasing the osmolarity of the incubat increase the sensitivity of pituitary segments to "CRF". moved that lowering the pH
Seiden and Brodish (238) reported that lowering the pH
and increasing the osmolarity of the incubation medium
rawere helpful. Other groups and increasing the osmolarity of the incubation medium
were helpful. Other groups have found that the capacity
of adenohypophysial tissue to secrete ACTH in vitro is
enhanced either by using glands removed from rats ad-
re and increasing the osmolarity of the incubation medium rather than with unreliability of the bioassay. Moreover, were helpful. Other groups have found that the capacity the statement by Gaddum, "when biological methods of were helpful. Other groups have found that the capacity
of adenohypophysial tissue to secrete ACTH in vitro is
enhanced either by using glands removed from rats ad-
renalectomised some days previously (31, 46) or, more
sim of adenohypophysial tissue to secrete ACTH in vitro-
enhanced either by using glands removed from rats
renalectomised some days previously (31, 46) or, m
simply, by "priming" the segments in vitro with eit
"CRF" (46) or ly enhanced either by using glands removed from rats ad-
renalectomised some days previously (31, 46) or, more a
simply, by "priming" the segments in vitro with either b
"CRF" (46) or lysine vasopressin (37). These modifica-
 renalectomised some days previously $(31, 46)$ or, more agr
simply, by "priming" the segments in vitro with either bio
"CRF" (46) or lysine vasopressin (37) . These modifica-
metions, coupled with the use of a sensitiv simply, by "priming" the segments in vitro with either bisident (Mark Terminimum effective dose *m* overticotrophin (2) has resulted in the development of a highly sensitive (minimum effective dose = 0.02 HE) and reprecis "CRF" (46) or lysine vasopressin (37). These modifica-
tions, coupled with the use of a sensitive bioassay for well
corticotrophin (2) has resulted in the development of a
highly sensitive (minimum effective dose = 0.02 (37).

highly sensitive (minimum effective dose = 0.02 HE) and precise (λ = 0.06) method for the measurement of CRI (37).

The most "sensitive" assays described so far are those in which suspensions of isolated pituitary ce precise $(\lambda = 0.06)$ method for the measurement of CRF t

(37).

The most "sensitive" assays described so far are those in

in which suspensions of isolated pituitary cells are chal-

lenged with "CRF". The first such meth (37). The most "sensitive" assays described so far are those
in which suspensions of isolated pituitary cells are chal-
lenged with "CRF". The first such method was described
by Portanova and Sayers (206, 207). These work The most "sensitive" assays described so far are those ing
in which suspensions of isolated pituitary cells are chal-
lenged with "CRF". The first such method was described exp
by Portanova and Sayers (206, 207). These wor in which suspensions of isolated pituitary cells are chalconged with "CRF". The first such method was described exply Portanova and Sayers (206, 207). These workers as AC sayed the ACTH secreted by their pituitary cells wi by Portanova and Sayers (206, 207). These workers assayed the ACTH secreted by their pituitary cells with the sensitive adrenal cell method and reported that they could detect amounts of hypothalamic extract as small as 0. by Portanova and Sayers (206, 207). These workers assayed the ACTH secreted by their pituitary cells with the sensitive adrenal cell method and reported that they could detect amounts of hypothalamic extract as small as 0. sayed the ACTH secreted by their pituitary cells with
the sensitive adrenal cell method and reported that they
could detect amounts of hypothalamic extract as small
as 0.005 HE. Several modifications of their technique
hav the sensitive adrenal cell method and reported that the could detect amounts of hypothalamic extract as sm
as 0.005 HE. Several modifications of their techniq
have subsequently been described. Takebe et al. (26
showed that could detect amounts of hypothalamic extract as small ing
as 0.005 HE. Several modifications of their technique in
have subsequently been described. Takebe et al. (264) she
showed that dispersed, pooled, rat adenohypophysi as 0.005 HE. Several modifications of their technique
have subsequently been described. Takebe et al. (264)
showed that dispersed, pooled, rat adenohypophysial
cells cultured for several days could be used for the assay
of have subsequently been described. Takebe et al. (264) slabowed that dispersed, pooled, rat adenohypophysial uncells cultured for several days could be used for the assay word CRF. They demonstrated a positive relationship showed that dispersed, pooled, rat adenohypophysial
cells cultured for several days could be used for the assay
of CRF. They demonstrated a positive relationship be-
tween the amount of ACTH released by the cultured
cells cells cultured for several days could be used for the assay with
of CRF. They demonstrated a positive relationship be-
tween the amount of ACTH released by the cultured the
cells and the logarithm of the dose of hypothala of CRF. They demonstrated a positive relationship be-
tween the amount of ACTH released by the cultured the
cells and the logarithm of the dose of hypothalamic chextract over a range of concentrations from 0.0125 to 1.25 tween the amount of ACTH released by the cultured
cells and the logarithm of the dose of hypothalamic
extract over a range of concentrations from 0.0125 to 1.25
HE. This system is reasonably precise $(\lambda = 0.15)$ and the
sa cells and the logarithm of the dose of hypothalamic cextract over a range of concentrations from 0.0125 to 1.25 a
HE. This system is reasonably precise $(\lambda = 0.15)$ and the cases cultured cells can be satisfactorily used i extract over a range of concentrations from 0.0125 to 1.25 HE. This system is reasonably precise ($\lambda = 0.15$) and the same cultured cells can be satisfactorily used in repetitive assays performed on the same or differ HE. This system is reasonably precise $(\lambda = 0.15)$ and the corries correctly correctly used in repetitive cassays performed on the same or different days, thus lare providing a relatively economical and simple technique pr same cultured cells can be satisfactorily used in repetitive
assays performed on the same or different days, thus
providing a relatively economical and simple technique
for assessing corticotrophin releasing activity. Gill assays performed on the same or different days, thus
providing a relatively economical and simple technique
for assessing corticotrophin releasing activity. Gillies and
Lowry (90) have developed a system in which columns o providing a relatively economical and simple technique providing a relatively economical and simple technique of for assessing corticotrophin releasing activity. Gillies and encomplement is also the substances. In this sys for assessing corticotrophin releasing activity. Gillies and
Lowry (90) have developed a system in which columns of
isolated rat adenohypophysial cells suspended in Biogel
are perfused with test substances. In this system, Lowry (90) have developed a system in which columnisolated rat adenohypophysial cells suspended in Bionare perfused with test substances. In this system, froxygenated media or samples are continually pass through the cells isolated rat adenohypophysial cells suspended in Biogel
are perfused with test substances. In this system, fresh
oxygenated media or samples are continually passed
through the cells and thus neither the secreta-
gogue nor are perfused with test substances. In this system, fresh oxygenated media or samples are continually passed through the cells and thus neither the secreta-gogue nor metabolic waste products are allowed to accumulate in the oxygenated media or samples are continually passed
through the cells and thus neither the secreta-
gogue nor metabolic waste products are allowed to ac-
cumulate in the media bathing the cells. This method,
like that of Ta through the cells and thus neither the secreta-
gogue nor metabolic waste products are allowed to ac-
cumulate in the media bathing the cells. This method, do
like that of Takebe et al. (264), has the advantage that st
man gogue nor metabolic waste products are allowed to accumulate in the media bathing the cells. This method, dos
like that of Takebe et al. (264), has the advantage that stin
many samples may be processed on the same cells wi cumulate in the media bathing the cells. This method, like that of Takebe et al. (264), has the advantage that many samples may be processed on the same cells with no apparent change in the sensitivity of the cells to trop like that of Takebe et al. (264), has the advantage that many samples may be processed on the same cells with no apparent change in the sensitivity of the cells to trophic stimuli. This is in complete contrast to the findi many samples may be processed on the same cells with
no apparent change in the sensitivity of the cells to
botrophic stimuli. This is in complete contrast to the find-
things with pituitary fragments, which respond to repe no apparent change in the sensitivity of the cells to
trophic stimuli. This is in complete contrast to the find-
ings with pituitary fragments, which respond to repetitive
dosing with hypothalamic extracts or vasopressin w trophic stimuli. This is in complete contrast to the find-
ings with pituitary fragments, which respond to repetitive
dosing with hypothalamic extracts or vasopressin with
significantly elevated increments in ACTH secretio ings with pituitary fragments, which respond to repetit dosing with hypothalamic extracts or vasopressin v
significantly elevated increments in ACTH secretion
46). It is surprising, with the availability of sensit
accurate dosing with hypothalamic extracts or vasopressin with trop
significantly elevated increments in ACTH secretion (37, the
46). It is surprising, with the availability of sensitive, mu
accurate, specific, and precise bioassay significantly elevated increments in ACTH secretion (37, 46). It is surprising, with the availability of sensitive, accurate, specific, and precise bioassays for the determination of ACTH, that Gillies and Lowry (90) chose 46). It is surprising, with the availability of sensitive, mus. For example, the peak of the circadian excursion in accurate, specific, and precise bioassays for the determi-
nation of ACTH, that Gillies and Lowry (90) ch

cise. The dangers of poor diffusion and necrosis have their statement that the results obtained with the im-
been substantially reduced by the use of quartered (in-
stead of hemisected) pituitary glands removed from small ELEASING FACTOR
their statement that the results obtained with the im-
munoassay are "more reliable" than those achieved with ELEASING FACTOR
their statement that the results obtained with the im-
munoassay are "more reliable" than those achieved with
bioassay techniques. It is true that marked discrepancies ELEASING FACTOR
their statement that the results obtained with the im-
munoassay are "more reliable" than those achieved with
bioassay techniques. It is true that marked discrepancies
between the results obtained with immu their statement that the results obtained with the im-
munoassay are "more reliable" than those achieved with
bioassay techniques. It is true that marked discrepancies
between the results obtained with immuno- and bioassay their statement that the results obtained with the im-
munoassay are "more reliable" than those achieved with
bioassay techniques. It is true that marked discrepancies
between the results obtained with immuno- and bioassay between the results obtained with immuno- and bioassay
methods have been reported, but they are probably as-
sociated with the lack of specificity of the immunoassay bioassay techniques. It is true that marked discrepancies
between the results obtained with immuno- and bioassay
methods have been reported, but they are probably as-
sociated with the lack of specificity of the immunoassa between the results obtained with immuno- and bioassay
methods have been reported, but they are probably as-
sociated with the lack of specificity of the immunoassay
rather than with unreliability of the bioassay. Moreover methods have been reported, but they are probable sociated with the lack of specificity of the immuno rather than with unreliability of the bioassay. More the statement by Gaddum, "when biological me and chemical methods f sociated with the lack of specificity of the immunoassay
rather than with unreliability of the bioassay. Moreover,
the statement by Gaddum, "when biological methods
and chemical methods for the assay of a pharmacologi-
cal rather than with unreliability of the bioassay. Moreover,
the statement by Gaddum, "when biological methods
and chemical methods for the assay of a pharmacologi-
cally active substance disagree so widely that the dis-
agre and chemical methods for the assay of a pharmacologically active substance disagree so widely that the disagreement cannot be due to the error of the tests, the biological method is, by definition, right and the chemical m and chemical methods for the assay of a pharmacologically active substance disagree so widely that the disagreement cannot be due to the error of the tests, the biological method is, by definition, right and the chemical m cally active substance disage
agreement cannot be due to
biological method is, by defini
method is wrong" (47) could
well as to chemical methods.
It has sometimes been su reement cannot be due to the error of the tests, the
plogical method is, by definition, right and the chemical
ethod is wrong" (47) could apply to immunoassays as
ell as to chemical methods.
It has sometimes been suggested

corticotrophin (2) has resulted in the development of a
highly sensitive (minimum effective dose = 0.02 HE) and
precise (λ = 0.06) method for the measurement of CRF
(37).
The most "sensitive" assays described so far biological method is, by definition, right and the chemical
method is wrong" (47) could apply to immunoassays as
well as to chemical methods.
It has sometimes been suggested that the pituitary
receptors in vitro may lack s method is wrong" (47) could apply to immunoassays as
well as to chemical methods.
It has sometimes been suggested that the pituitary
receptors in vitro may lack specificity for CRF and thus
that in vitro systems may not be well as to chemical methods.
It has sometimes been suggested that the pituits
receptors in vitro may lack specificity for CRF and th
that in vitro systems may not be suitable for the detecti
and quantification of physiolog It has sometimes been suggested that the pituitary
receptors in vitro may lack specificity for CRF and thus
that in vitro systems may not be suitable for the detection
and quantification of physiological corticotrophin rel receptors in vitro may lack specificity for CRF and thus
that in vitro systems may not be suitable for the detection
and quantification of physiological corticotrophin releas-
ing factors. Since there is no standard prepar that in vitro systems may not be suitable for the detection
and quantification of physiological corticotrophin releas-
ing factors. Since there is no standard preparation of
corticotrophin releasing factor it is possible a and quantification of physiological corticotrophin releasing factors. Since there is no standard preparation of corticotrophin releasing factor it is possible at present to express CRF activity only in terms of the amount ing factors. Since there is no standard preparation of corticotrophin releasing factor it is possible at present to express CRF activity only in terms of the amount of ACTH produced by the anterior pituitary gland. It is e corticotrophin releasing factor it is possible at present express CRF activity only in terms of the amount ACTH produced by the anterior pituitary gland. It essential, therefore, that any method for the detection CRF shoul express CRF activity only in terms of the amount of ACTH produced by the anterior pituitary gland. It is essential, therefore, that any method for the detection of CRF should be validated as far as is possible by comparing ACTH produced by the anterior pituitary gland. It is
essential, therefore, that any method for the detection of
CRF should be validated as far as is possible by compar-
ing the activity of the same samples on other, prefer essential, therefore, that any method for the detection of CRF should be validated as far as is possible by comparing the activity of the same samples on other, preferably in vivo, methods. Comparative studies (45, 46, 140 CRF should be validated as far as is possible by comparing the activity of the same samples on other, preferably in vivo, methods. Comparative studies $(45, 46, 140)$ have shown a good correlation between the results obta ing the activity of the same samples on other, preferal
in vivo, methods. Comparative studies (45, 46, 140) ha
shown a good correlation between the results obtain
using pituitary fragments in vitro and those achiev
with in in vivo, methods. Comparative studies $(45, 46, 140)$ have
shown a good correlation between the results obtained
using pituitary fragments in vitro and those achieved
with in vivo systems, employing rats in which the endo shown a good correlation between the results obtained
using pituitary fragments in vitro and those achieved
with in vivo systems, employing rats in which the endog-
enous release of CRF was prevented either by lesions in
t using pituitary fragments in vitro and those achieved
with in vivo systems, employing rats in which the endog-
enous release of CRF was prevented either by lesions in
the hypothalamus or treatment with pentobarbitone and
c with in vivo systems, employing rats in which the endog-
enous release of CRF was prevented either by lesions in
the hypothalamus or treatment with pentobarbitone and
chlorpromazine. However, there are doubts (M. T. Jones
 enous release of CRF was prevented either by lesions in
the hypothalamus or treatment with pentobarbitone and
chlorpromazine. However, there are doubts (M. T. Jones
and colleagues, personal communication) concerning the
co the hypothalamus or treatment with pentobarbitone and chlorpromazine. However, there are doubts (M. T. Jones and colleagues, personal communication) concerning the correlation of the results obtained with isolated pituitar chlorpromazine. However, there are doubts (M. T. Jones
and colleagues, personal communication) concerning the
correlation of the results obtained with isolated pituitary
cells (90) and those achieved employing either hypot and colleagues, personal communication) concerning the
correlation of the results obtained with isolated pituitary
cells (90) and those achieved employing either hypotha-
lamic lesioned rats or pituitary segments in vitro. correlation of the results obtained with isolated pituitary
cells (90) and those achieved employing either hypotha-
lamic lesioned rats or pituitary segments in vitro. This
problem requires a great deal of further investig cells (90) and those achieved employing either hypothermic lesioned rats or pituitary segments in vitro. The problem requires a great deal of further investigation a emphasises the need to evaluate new bioassay methody com lamic lesioned rats o
problem requires a greemphasises the need
by comparing them v
ably in vivo systems. From From Secretion of Corticotrophin
phasises the need to evaluate new bioassay method
comparing them with older, well-established, prefe.
y in vivo systems.
V. Control of the Secretion of Corticotrophin
Releasing Factor n with older, well-es
ns.
the Secretion of Co
Releasing Factor
Selve (239, 240) disc

ly in vivo systems.

V. Control of the Secretion of Corticotrophin

Releasing Factor

Many years ago, Selye (239, 240) discovered that toxic

ses of drugs and other noxious treatments (stressful V. Control of the Secretion of Corticotrophin
Releasing Factor
Many years ago, Selye (239, 240) discovered that toxic
doses of drugs and other noxious treatments (stressful
stimuli) produced hypertrophy of the adrenal cort v. Control of the secretion of Corticotrophin
Releasing Factor
Many years ago, Selye (239, 240) discovered that toxic
doses of drugs and other noxious treatments (stressful
stimuli) produced hypertrophy of the adrenal cor interesting **Factor**
Many years ago, Selye (239, 240) discovered that toxic
doses of drugs and other noxious treatments (stressful
stimuli) produced hypertrophy of the adrenal cortex in
intact but not in hypophysectomised Many years ago, Selye (239, 240) discovered that toxic
doses of drugs and other noxious treatments (stressful
stimuli) produced hypertrophy of the adrenal cortex in
intact but not in hypophysectomised rats. This effect
obv doses of drugs and other noxious treatments (stressful
stimuli) produced hypertrophy of the adrenal cortex in
intact but not in hypophysectomised rats. This effect
obviously was mediated by ACTH. Enormous interest in
the m stimuli) produced hypertrophy of the adrenal cortex in
intact but not in hypophysectomised rats. This effect
obviously was mediated by ACTH. Enormous interest in
the mechanisms that control the secretion of ACTH was
stimul intact but not in hypophysectomised rats. This effect
obviously was mediated by ACTH. Enormous interest in
the mechanisms that control the secretion of ACTH was
stimulated. It is now known that the adrenocortico-
trophic a obviously was mediated by ACTH. Enormous intere
the mechanisms that control the secretion of ACTH
stimulated. It is now known that the adrenocor
trophic activity of the pituitary gland is correlated
the corticotrophin rele the mechanisms that control the secretion of ACTH was
stimulated. It is now known that the adrenocortico-
trophic activity of the pituitary gland is correlated with
the corticotrophin releasing activity of the hypothala-
m stimulated. It is now known that the adrenocorticotrophic activity of the pituitary gland is correlated with the corticotrophin releasing activity of the hypothala-
mus. For example, the peak of the circadian excursion in trophic activity of the pituitary gland is correlated with
the corticotrophin releasing activity of the hypothala-
mus. For example, the peak of the circadian excursion in
adrenocortical activity in the rat is accompanied the corticotrophin releasing activity of the hypothala-
mus. For example, the peak of the circadian excursion in
adrenocortical activity in the rat is accompanied by a rise
in the CRF content of the hypothalamus (62, 117, 263, 270). Elevated levels of CRF in the hypothalamus

Downloaded from pharmrev.aspetjournals.org at Thammasart University on December 8, 2012

260

of procestrous (121) before the preovulatory surge of superintiary-adrenocorticotrophic activity (33). Exposure of a BUCKING
of procestrous (121) before the preovulatory surge of st
pituitary-adrenocorticotrophic activity (33). Exposure of a
rats to ether vapour causes a rapid fall and subsequent in BUCE
of procestrous (121) before the preovulatory surge of
pituitary-adrenocorticotrophic activity (33). Exposure of
rats to ether vapour causes a rapid fall and subsequent
rise in hypothalamic CRF content together with an of procestrous (121) before the preovulatory surge of pituitary-adrenocorticotrophic activity (33). Exposure of rats to ether vapour causes a rapid fall and subsequent rise in hypothalamic CRF content together with an in-c of procestrous (121) before the preovulatory surge of subpituitary-adrenocorticotrophic activity (33). Exposure of adress rats to ether vapour causes a rapid fall and subsequent ime rise in hypothalamic CRF content togethe pituitary-adrenocorticotrophic activity (33). Exposure of adm
rats to ether vapour causes a rapid fall and subsequent ime
rise in hypothalamic CRF content together with an in-
crease in the ACTH content of the adenohypophy rats to ether vapour causes a rapid fall and subsequent
rise in hypothalamic CRF content together with an in-
crease in the ACTH content of the adenohypophysis and
the plasma (31, 120, 280). These changes are followed by
a rise in hypothalamic CRF content together with an crease in the ACTH content of the adenohypophysis the plasma (31, 120, 280). These changes are followed a rise in the plasma concentration of corticosterone (1). Moreover, crease in the ACTH content of the adenohypophysis
the plasma (31, 120, 280). These changes are followe
a rise in the plasma concentration of corticosterone
1). Moreover, the stress-induced changes in hypo
lamic CRF content the plasma $(31, 120, 280)$. These changes are followed by be
a rise in the plasma concentration of corticosterone (fig. of
1). Moreover, the stress-induced changes in hypotha-sta
lamic CRF content, like those in pituitar a rise in the plasma concentration of corticoster 1). Moreover, the stress-induced changes in lamic CRF content, like those in pituitary adrectorophic activity, are exaggerated by adrenalect reduced by corticosteroid treat A Moreover, the stress-induced changes in hypotheric CRF content, like those in pituitary adrenocol trophic activity, are exaggerated by adrenalectomy a duced by corticosteroid treatment (31, 280). A great deal of attentio

lamic CRF content, like those in pituitary adrenocorticotrophic activity, are exaggerated by adrenalectomy and reduced by corticosteroid treatment (31, 280).
A great deal of attention has focussed on the mechanisms that co cotrophic activity, are exaggerated by adrenalectomy and
reduced by corticosteroid treatment (31, 280).
A great deal of attention has focussed on the mecha-
nisms that control the secretion of CRF. It appears that
the prod reduced by corticosteroid treatment (31, 280).
A great deal of attention has focussed on the mechanisms that control the secretion of CRF. It appears that
the production of this hypothalamic hormone involves
the integratio A great deal of attention has focussed on the mechanisms that control the secretion of CRF. It appears that the production of this hypothalamic hormone involves the integration and differentiation of a torrent of afferent the production of this hypothalamic hormone involves
the integration and differentiation of a torrent of afferent
impulses, which may be either excitatory or inhibitory,
from several regions of the brain. Studies involving the production of this hypothalamic hormone involves T
the integration and differentiation of a torrent of afferent
impulses, which may be either excitatory or inhibitory, tr
from several regions of the brain. Studies invo the integration and differentiation of a torrent of afferent rat
impulses, which may be either excitatory or inhibitory, tran
from several regions of the brain. Studies involving elec-
trical stimulation or lesions of spec impulses, which may be either excitatory or inhibitory,
from several regions of the brain. Studies involving elec-
trical stimulation or lesions of specific areas of the brain
suggest that the amygdala (155, 156, 179, 213, from several regions of the brain. Studies involving electrical stimulation or lesions of specific areas of the brain cross of suggest that the amygdala $(155, 156, 179, 213, 250)$ and as hippocampus $(69, 147, 155-157)$ trical stimulation or lesions of specific areas of the brain consuggest that the amygdala (155, 156, 179, 213, 250) and a hippocampus (69, 147, 155–157) are of fundamental importance in this respect but other brain areas, hippocampus (69, 147, 155–157) are of fundamental im-
portance in this respect but other brain areas, notably
the thalamus, basal septal area, and rostral midbrain
reticular formation, may also be involved. There have
been portance in this respect but other brain areas, notably
the thalamus, basal septal area, and rostral midbrain
reticular formation, may also be involved. There have
been many attempts to characterize the neurones that
influ the thalamus, basal septal area, and rostral midbrain
reticular formation, may also be involved. There have
been many attempts to characterize the neurones that
influence the activity of the hypothalamic corticotrophin
rel reticular formation, may also be involved. There have wheen many attempts to characterize the neurones that vinfluence the activity of the hypothalamic corticotrophin his releasing hormone cells. Most of these studies have been many attempts to characterize the neurones that valuat
influence the activity of the hypothalamic corticotrophin hypoti
releasing hormone cells. Most of these studies have in-
volved conventional in vivo techniques in releasing hormone cells. Most of these studies have in-
volved in the regulation of CRF secretion. The
that influence the activity of the central nervous system possibility that a central cholinergic nervous pathway
are im

A

C

E **0** 0

 $\overline{2}$

3

E I I-**0**

1300

1000

700

400 $\mathbf 0$

Ii I- . **0-**

a)-

hippocampus $(69, 147, 155-157)$ are of fundamental im-
portance in this respect but other brain areas, notably
tion in vivo must be questioned but, nevertheless, this
the thalamus, basal septal area, and rostral midbrain substances that readily cross the blood-brain barrier, are
administered peripherally. The results from such exper-GHAM
substances that readily cross the blood-brain barrier, a
administered peripherally. The results from such exper-
iments are sometimes hard to interpret. The doses of t GHAM
substances that readily cross the blood-brain barrier, are
administered peripherally. The results from such exper-
iments are sometimes hard to interpret. The doses of the
implanted drugs are frequently very high and substances that readily cross the blood-brain barrier, and administered peripherally. The results from such experiments are sometimes hard to interpret. The doses of the implanted drugs are frequently very high and the pos substances that readily cross the blood-brain barrier, are
administered peripherally. The results from such exper-
iments are sometimes hard to interpret. The doses of the
implanted drugs are frequently very high and the p administered peripherally. The results from such experiments are sometimes hard to interpret. The doses of the implanted drugs are frequently very high and the possibility that the drugs diffuse to other brain areas cannot implanted drugs are frequently very high and the polity that the drugs diffuse to other brain areas car
be disregarded. Moreover, the drugs administered
often rather nonspecific. For example, reserpine, a *i*
stance widely bility that the drugs diffuse to other brain areas cannot
be disregarded. Moreover, the drugs administered are
often rather nonspecific. For example, reserpine, a sub-
stance widely used in experimental neuroendocrinology, be disregarded. Moreover, the drugs administered and often rather nonspecific. For example, reserpine, a substance widely used in experimental neuroendocrinology not only depletes the brain of noradrenaline but also ϵ 5often rather nonspecific. For example, reserpine, a substance widely used in experimental neuroendocrinology,
not only depletes the brain of noradrenaline but also of
5-HT and dopamine. Noradrenaline biosynthesis is effecstance widely used in experimental neuroendocrinology,
not only depletes the brain of noradrenaline but also of
5-HT and dopamine. Noradrenaline biosynthesis is effec-
tively inhibited by 6-hydroxydopamine but the animals
 not only depletes the brain of noradrenaline but also of 5-HT and dopamine. Noradrenaline biosynthesis is effectively inhibited by 6-hydroxydopamine but the animals thus treated show signs of nervousness and aggression tha 5-HT and dopamine. Noradrenaline biosynthesis is effec-
tively inhibited by 6-hydroxydopamine but the animals
thus treated show signs of nervousness and aggression
that in themselves may influence the secretion of CRF.
The tively inhibited by 6-hydroxydopamine but the animals
thus treated show signs of nervousness and aggression
that in themselves may influence the secretion of CRF.
The development of an in vitro method in which whole
rat hy thus treated show signs of nervousness and aggression
that in themselves may influence the secretion of CRF.
The development of an in vitro method in which whole
rat hypothalami are incubated in the presence of neuro-
tran that in themselves may influence the secretion of CRF.
The development of an in vitro method in which whole
rat hypothalami are incubated in the presence of neuro-
transmitter substances has provided a new approach to
the The development of an in vitro method in which whole
rat hypothalami are incubated in the presence of neuro-
transmitter substances has provided a new approach to
the study of the neural mechanisms controlling the se-
cret rat hypothalami are incubated in the presence of neuro-
transmitter substances has provided a new approach to
the study of the neural mechanisms controlling the se-
cretion of CRF and has overcome many of the problems
asso transmitter substances has provided a new approach to
the study of the neural mechanisms controlling the se
cretion of CRF and has overcome many of the problems
associated with in vivo work. Of course, the validity of
resu the study of the neural mechanisms controlling the secretion of CRF and has overcome many of the problems associated with in vivo work. Of course, the validity of results translated from in vitro experiments to the situati cretion of CRF and has overcome many of the problems
associated with in vivo work. Of course, the validity of
results translated from in vitro experiments to the situ-
ation in vivo must be questioned but, nevertheless, th results translated from in vitro experiments to the situresults translated from in vitro experiments to the situation in vivo must be questioned but, nevertheless, this system, in which a whole hypothalamus is challenged with putative neurotransmitter substances, has provided v *hypothalamus* that influence CRF production. stem, in which a whole hypothalamus is challenged
th putative neurotransmitter substances, has provided
luable information concerning the receptors in the
pothalamus that influence CRF production.
It appears that several n with putative neurotransmitter substances, has provided
valuable information concerning the receptors in the
hypothalamus that influence CRF production.
It appears that several neurotransmitter substances
are involved in t

valuable information concerning the receptors in the hypothalamus that influence CRF production.
It appears that several neurotransmitter substances
are involved in the regulation of CRF secretion. The
possibility that a c hypothalamus that influence CRF production.
It appears that several neurotransmitter substances
are involved in the regulation of CRF secretion. The
possibility that a central cholinergic nervous pathway
controls the relea

190

B

!

E
 60 ^c
 0
 0

D

z. 40 a) **C** 0 $\frac{1}{2}$ 20 $\frac{1}{2}$ 'I, 0**U**

0**0**

ACTH (m-u./anterior)

pituitary gland)

23

23

26

26

of $\frac{a}{b}$
 $\frac{a}{c}$
 $\frac{a}{d}$
 $\frac{a}{d}$
 $\frac{a}{b}$
 $\frac{a}{d}$
 $\frac{a}{d}$
 $\frac{a}{b}$
 $\frac{a}{d}$
 $\frac{a}{d}$
 $\frac{a}{b}$
 $\frac{a}{d}$

CORTICOTROPHIN
droczi et al. (70), who showed that implantation of car-
bachol into various regions of the central nervous system **CORTICOTROPHIN RELEASI**
droczi et al. (70), who showed that implantation of car-
bachol into various regions of the central nervous system
stimulates pituitary-adrenocorticotrophic activity. A CORTICOTROPHIN RELEASIN
droczi et al. (70), who showed that implantation of car-
bachol into various regions of the central nervous system
stimulates pituitary-adrenocorticotrophic activity. A
considerable amount of evide droczi et al. (70), who showed that implantation of car-
bachol into various regions of the central nervous system
stimulates pituitary-adrenocorticotrophic activity. A
considerable amount of evidence now supports the hy-
 droczi et al. (70), who showed that implantation of carbachol into various regions of the central nervous system
stimulates pituitary-adrenocorticotrophic activity. A
considerable amount of evidence now supports the hy-
po bachol into various regions of the central nervous system
stimulates pituitary-adrenocorticotrophic activity. A
considerable amount of evidence now supports the hy-
pothesis of Endroczi et al. For example, implantation of stimulates pituitary-adrenocorticotrophic activity. A considerable amount of evidence now supports the hypothesis of Endroczi et al. For example, implantation of atropine into the anterior hypothalamus reduces the adrenoc considerable amount of evidence now supports the
pothesis of Endroczi et al. For example, implantatio
atropine into the anterior hypothalamus reduces
adrenocortical response to stress (110, 112, 145)
carbachol increases th pothesis of Endroczi et al. For example, implantation of atropine into the anterior hypothalamus reduces the adrenocortical response to stress (110, 112, 145) and carbachol increases the plasma corticosterone concentration atropine into the anterior hypothalamus reduces the
adrenocortical response to stress $(110, 112, 145)$ and
carbachol increases the plasma corticosterone concentra-
tion when infused into the lateral ventricles of the rat adrenocortical response to stress (110, 112, 145) and
carbachol increases the plasma corticosterone concentra-
tion when infused into the lateral ventricles of the rat
(1). Furthermore, picomolar concentrations of acetylc carbachol increases the plasma corticosterone concentration when infused into the lateral ventricles of the rat (1). Furthermore, picomolar concentrations of acetylcholine evoke both the synthesis and release of CRF by iso tion when infused into the lateral ventricles of the rat (1). Furthermore, picomolar concentrations of acetylcholine evoke both the synthesis and release of CRF by betisolated rat hypothalami in vitro (20, 39, 114). It is (1). Furthermore, picomolar concentrations of acetylcholine evoke both the synthesis and release of CRF by isolated rat hypothalami in vitro (20, 39, 114). It is not clear from the results of experiments in vivo whether t line evoke both the synthesis and release of CRF by isolated rat hypothalami in vitro $(20, 39, 114)$. It is not clear from the results of experiments in vivo whether the actions of acetylcholine are mediated by stimulati isolated rat hypothalami in vitro (20, 39, 114). It is n
clear from the results of experiments in vivo whether t
actions of acetylcholine are mediated by stimulation
nicotinic or muscarinic cholinoceptors since pilocarpi
(clear from the results of experiments in vivo whether the
actions of acetylcholine are mediated by stimulation of
micotinic or muscarinic cholinoceptors since pilocarpine
(259, 260) and nicotine (260) have been shown to st actions of acetylcholine are mediated by stimulation of σ incotinic or muscarinic cholinoceptors since pilocarpine (259, 260) and nicotine (260) have been shown to stimu-
late pituitary-adrenocorticotrophic activity. T micotinic or muscarinic cholinoceptors since pilocarpine (259, 260) and nicotine (260) have been shown to stimulate pituitary-adrenocorticotrophic activity. The actions of acetylcholine on CRF secretion in vitro are mimick (259, 260) and nicotine (260) have been shown to stimulate pituitary-adrenocorticotrophic activity. The actions of acetylcholine on CRF secretion in vitro are mimicked by bethanechol and nicotine but the maximum response late pituitary-adrenocorticotrophic activity. The actions portocorrelation of acetylcholine on CRF secretion in vitro are mimicked subsethanechol and nicotine but the maximum response reto either of these cholinomimetic ag of acetylcholine on CRF secretion in vitro are mimicked
by bethanechol and nicotine but the maximum response
to either of these cholinomimetic agents is significantly
less than to acetylcholine (fig. 2). Furthermore, these by bethanechol and nicotine but the maximum response
to either of these cholinomimetic agents is significantly
less than to acetylcholine (fig. 2). Furthermore, these
actions of bethanechol and nicotine are inhibited by th to either of these cholinomimetic agents is significantly access than to acetylcholine (fig. 2). Furthermore, these nections of bethanechol and nicotine are inhibited by their by respective specific antagonists, atropine a respective specific antagonists, atropine and pempidine,
while those of acetylcholine are reduced by each of these
drugs but completely abolished only when the two drugs
are given together (41). These data suggest that the while those of acetylcholine are reduced by each of these drugs but completely abolished only when the two drugare given together (41). These data suggest that the actions of acetylcholine are effected by the stimulation o noceptors. of a mixed population of nicotinic and muscarinic choli-

of a mixed population of nicotinic and muscarinic choli-
noceptors.
The role of 5-HT in the control of CRF secretion is
these well understood. It appears that distinct 5-hydroxy-
tryptaminergic systems within the brain may noceptors.

The role of 5-HT in the control of CRF secreties well understood. It appears that distinct 5-hypotaminergic systems within the brain may be in the stimulation and inhibition of hypothalam tary-adrenocorticotrop The role of 5-HT in the control of CRF secretion is
less well understood. It appears that distinct 5-hydroxy-
tryptaminergic systems within the brain may be involved
in the stimulation and inhibition of hypothalamo-pitui-
 less well understood. It appears that distinct 5-hydroxy-
tryptaminergic systems within the brain may be involved
in the stimulation and inhibition of hypothalamo-pitui-
tary-adrenocorticotrophic activity. Studies in vivo tryptaminergic systems within the brain may be involved
in the stimulation and inhibition of hypothalamo-pitui-
tary-adrenocorticotrophic activity. Studies in vivo that
involve implantation of 5-HT either into the lateral in the stimulation and inhibition of hypothalamo-pitui-
tary-adrenocorticotrophic activity. Studies in vivo that
involve implantation of 5-HT either into the lateral ven-
tricles or into various regions of the hypothalamus tary-adrenocorticotrophic activity. Studies in vivo that Minvolve implantation of 5-HT either into the lateral ven-
tricles or into various regions of the hypothalamus sug-
tory gest that the indoleamine has no effect on t involve implantation of 5-HT either into the lateral ven-
tricles or into various regions of the hypothalamus sug-
gest that the indoleamine has no effect on the basal
secretion of CRF but inhibits its release in response tricles or into various regions of the hypothalamus sug-
gest that the indoleamine has no effect on the basal B
secretion of CRF but inhibits its release in response to th
stressful stimuli (267, 276, 277). Several other f secretion of CRF but inhibits its release in response to stressful stimuli (267, 276, 277). Several other findings support this idea (242, 282). The possibility that a 5-hydroxytryptaminergic system may stimulate the pro-
 secretion of CRF but inhibits its release in response to the stressful stimuli (267, 276, 277). Several other findings rat support this idea (242, 282). The possibility that a 5-this hydroxytryptaminergic system may stimu stressful stimuli (267, 276, 277). Several other findings rapport this idea (242, 282). The possibility that a 5-
hydroxytryptaminergic system may stimulate the pro-
duction of CRF was first suggested by Krieger and Rizzo support this idea (242, 282). The possibility that a 5-
hydroxytryptaminergic system may stimulate the pro-
duction of CRF was first suggested by Krieger and Rizzo
(162). They proposed that the circadian excursion of 17-
h hydroxytryptaminergic system may stimulate the pro-
duction of CRF was first suggested by Krieger and Rizzo (17
(162). They proposed that the circadian excursion of 17- red
hydroxycorticosteroids is controlled to some exte duction of CRF was first suggested by Krieger and Rizzo (162). They proposed that the circadian excursion of 17-
hydroxycorticosteroids is controlled to some extent by 5-
HT. More recent studies indicate that the amine may (162). They proposed that the circadian excursion of 17-
hydroxycorticosteroids is controlled to some extent by 5-
 \overline{HT} . More recent studies indicate that the amine may effect
also play a positive role in the regulati hydroxycorticosteroids is controlled to some extent by 5-
HT. More recent studies indicate that the amine may
elso play a positive role in the regulation of stress-induced (4
adrenocortical function. Results from experimen HT. More recent studies indicate that the amine may
also play a positive role in the regulation of stress-induced
adrenocortical function. Results from experiments in vivo
and in vitro substantiate these observations. Infu also play a positive role in the regulation of stress-induced (4)
adrenocortical function. Results from experiments in vivo
and in vitro substantiate these observations. Infusion of see
5-hydroxytryptophan, a precursor of adrenocortical function. Results from experiments in v
and in vitro substantiate these observations. Infusion
5-hydroxytryptophan, a precursor of 5-HT, into the r
sus monkey (50) or man (136) significantly elevates to
plas 5-hydroxytryptophan, a precursor of 5-HT, into the rhesus monkey (50) or man (136) significantly elevates the plasma cortisol, while cyproheptadine (a rather nonspecific drug that inhibits the actions of 5-HT, acetylcholin sus monkey (50) or man (136) significantly elevates the sus monkey (50) or man (136) significantly elevates the plasma cortisol, while cyproheptadine (a rather nonspecific drug that inhibits the actions of 5-HT, acetylcholine, and histamine) reduces the plasma cortisol concentr plasma cortisol, while cyproheptadine (a rather nonspectific drug that inhibits the actions of 5-HT, acetylcholine, ter and histamine) reduces the plasma cortisol concentration Sir both in normal subjects and in patients cific drug that inhibits the actions of 5-HT, acetylcholine, tend histamine) reduces the plasma cortisol concentration Sinther in both in normal subjects and in patients with Cushing's versynthesis of 5-HT stimulate both and histamine) reduces the plasma cortisol concentration
both in normal subjects and in patients with Cushing's
syndrome of "hypothalamic origin" (53, 63, 160). Very
small doses of 5-HT stimulate both the synthesis and
rel

FIG. 2. Effects of acetylcholine $(8 \tcdot 10^{-11}$ FIG. 2. Effects of acetylcholine (O. equals the mean of five determinations. Standard errors are omitted since in every case they were within \pm 10% of the mean.
(Reprinted with permission from J. C. Buckingham and J. R. be thanechol (∇ — ∇) on hypothalamic CRF release and content in witro. Each point is the mean of five determinations. Standard errors are omitted since in every case they were within \pm 10% of the mean. (Reprinted vitro. Each point is the mean of five determinations. Standard error control. Each point is the mean of five determinations. Standard error are omitted since in every case they were within \pm 10% of the mean (Reprinted w

actions of bethanechol and nicotine are inhibited by their by hexamethonium. These findings have not been con-
respective specific antagonists, atropine and pempidine, firmed in the Royal Free laboratory. The production of respective specific antagonists, atropine and pempidine, firmed in the Royal Free laboratory. The production of while those of acetylcholine are reduced by each of these CRF in vitro in response to 5-HT was not influenced actions of acetylcholine are effected by the stimulation sufficient to inhibit maximally the actions of acetylcho-
of a mixed population of nicotinic and muscarinic choli-
noceptors.
two laboratories is not clear but it is are omitted since in every case they were whilm 1 10% of the mean.
(Reprinted with permission from J. C. Buckingham and J. R. Hodges,
J. Physiol. (London), 290:421-431, 1979.).
Moreover, its effects are completely inhibite J. Physiol. (London), 290:421-431, 1979.).

Moreover, its effects are completely inhibited by appropriate doses of methysergide or cyproheptadine, which

suggests that the indoleamine is acting at specific 5-HT

receptors Moreover, its effects are completely inhibited by appropriate doses of methysergide or cyproheptadine, which suggests that the indoleamine is acting at specific 5-HT receptors (41). Jones et al. (141) proposed that these a Moreover, its effects are completely inhibited by apprepriate doses of methysergide or cyproheptadine, whicsuggests that the indoleamine is acting at specific 5-HT receptors (41). Jones et al. (141) proposed that thes acti priate doses of methysergide or cyproheptadine, which
suggests that the indoleamine is acting at specific 5-HT
receptors (41). Jones et al. (141) proposed that these
actions of 5-HT may be mediated by a cholinergic inter-
 suggests that the indoleamine is acting at specific 5-HT
receptors (41). Jones et al. (141) proposed that these
actions of 5-HT may be mediated by a cholinergic inter-
neurone since, in their system, its effects were aboli receptors (41). Jones et al. (141) proposed that these
actions of 5-HT may be mediated by a cholinergic inter-
neurone since, in their system, its effects were abolished
by hexamethonium. These findings have not been con-
 actions of 5-HT may be mediated by a cholinergic inter-
neurone since, in their system, its effects were abolished
by hexamethonium. These findings have not been con-
firmed in the Royal Free laboratory. The production of
 firmed in the Royal Free laboratory. The production of by hexamethonium. These findings have not been confirmed in the Royal Free laboratory. The production of CRF in vitro in response to 5-HT was not influenced by the addition of either pempidine, hexamethonium, or atropine t firmed in the Royal Free laboratory. The production CRF in vitro in response to 5-HT was not influenced the addition of either pempidine, hexamethonium atropine to the incubation medium in concentrations of acetylchine (41 CRF in vitro in response to 5-HT was not influenced by
the addition of either pempidine, hexamethonium, or
atropine to the incubation medium in concentrations
sufficient to inhibit maximally the actions of acetylcho-
line the addition of either pempidine, hexamethonium, or
atropine to the incubation medium in concentrations
sufficient to inhibit maximally the actions of acetylcho-
line (41). The reason for this discrepancy between the
two l atropine to the incubation medium in concentrations
sufficient to inhibit maximally the actions of acetylcho-
line (41). The reason for this discrepancy between the
two laboratories is not clear but it is worth mentioning
 sufficient to inhibit maximally the actions of acetylcholine (41). The reason for this discrepancy between the two laboratories is not clear but it is worth mentioning that the concentrations of hexamethonium employed by J line (41). The reason for this discrepancy between the two laboratories is not clear but it is worth mentioning that the concentrations of hexamethonium employed by Jones et al. (141) were found by the Royal Free group to (41). at the concentrations of hexamethonium employed by
nes et al. (141) were found by the Royal Free group to
sufficiently high to exert variable nonspecific effects
1).
Neurones that secrete γ -aminobutyric acid (GABA)
d c

be sufficiently high to exert variable nonspecific effects (41).

Neurones that secrete γ -aminobutyric acid (GABA)

and catecholamines are believed to exert a tonic inhibi-

tory influence over the hypothalamic secreti be sufficiently high to exert variable nonspecific effects (41).

Neurones that secrete γ -aminobutyric acid (GABA)

and catecholamines are believed to exert a tonic inhibi-

tory influence over the hypothalamic secreti (41).

Neurones that secrete γ -aminobutyric acid (GABA

and catecholamines are believed to exert a tonic inhit

tory influence over the hypothalamic secretion of CR.

Both the basal and stress-induced activity of the h Neurones that secrete γ -aminobutyric acid (GABA)
and catecholamines are believed to exert a tonic inhibi-
tory influence over the hypothalamic secretion of CRF.
Both the basal and stress-induced activity of the hypo-
t and catecholamines are believed to exert a tonic inhibitory influence over the hypothalamic secretion of CRF.
Both the basal and stress-induced activity of the hypothalamo-pituitary-adrenocortical (HPA) complex in the rat tory influence over the hypothalamic secretion of CRF.
Both the basal and stress-induced activity of the hypothalamo-pituitary-adrenocortical (HPA) complex in the
rat were reduced when GABA was implanted into the
third ven Both the basal and stress-induced activity of the hypo-
thalamo-pituitary-adrenocortical (HPA) complex in the
rat were reduced when GABA was implanted into the
third ventricle and enhanced by the injection of the
GABA-rece thalamo-pituitary-adrenocortical (HPA) complex in the
rat were reduced when GABA was implanted into the
third ventricle and enhanced by the injection of the
GABA-receptor antagonists, picrotoxin and bicuculline
(174). Furt rat were reduced when GABA was implanted into the
third ventricle and enhanced by the injection of the
GABA-receptor antagonists, picrotoxin and bicuculline
(174). Furthermore, very small doses of GABA markedly
reduced bot third ventricle and enhanced by the injection of the GABA-receptor antagonists, picrotoxin and bicuculline (174). Furthermore, very small doses of GABA markedly reduced both acetylcholine- and 5-HT-stimulated CRF productio GABA-receptor antagonists, picrotoxin and bicuculline (174). Furthermore, very small doses of GABA markedly reduced both acetylcholine- and 5-HT-stimulated CRF production by isolated rat hypothalami in vitro and its effect (41). duced both acetylcholine- and 5-HT-stimulated CRF
oduction by isolated rat hypothalami in vitro and its
fects were inhibited by picrotoxin (141) and bicuculline
1).
The role of the catecholamines in the control of the
cret

production by isolated rat hypothalami in vitro and its
effects were inhibited by picrotoxin (141) and bicuculline
(41).
The role of the catecholamines in the control of the
secretion of CRF has been extensively studied by effects were inhibited by picrotoxin (141) and bicuculli
(41).
The role of the catecholamines in the control of t
secretion of CRF has been extensively studied by Gano
and colleagues. The catecholamine precursor, L-dih
dro (41).
The role of the catecholamines in the control of
secretion of CRF has been extensively studied by Gan
and colleagues. The catecholamine precursor, L-di
droxyphenylalanine (L-DOPA), inhibited the 17-hydro
ycorticoster The role of the catecholamines in the control of
secretion of CRF has been extensively studied by Ganand
colleagues. The catecholamine precursor, L-di
droxyphenylalanine (L-DOPA), inhibited the 17-hydr
ycorticosteroid resp secretion of CRF has been extensively studied by Ganong
and colleagues. The catecholamine precursor, L-dihy-
droxyphenylalanine (L-DOPA), inhibited the 17-hydrox-
ycorticosteroid response to stress in dogs when adminis-
te and colleagues. The catecholamine precursor, L-dihydroxyphenylalanine (L-DOPA), inhibited the 17-hydroxycorticosteroid response to stress in dogs when adminitered either i.v. (271) or into the third ventricle (272 Similar droxyphenylalanine (L-DOPA), inhibited the 17-hydrox-
ycorticosteroid response to stress in dogs when adminis-
tered either i.v. (271) or into the third ventricle (272).
Similar inhibitory effects were also evident after ycorticosteroid response to stress in dogs when administered either i.v. (271) or into the third ventricle (272).
Similar inhibitory effects were also evident after intra-
ventricular implantation of L-noradrenaline, dopa tered either i.v. (271) or into the third ventricle (2'
Similar inhibitory effects were also evident after int
ventricular implantation of L-noradrenaline, dopamin
 α -ethyltryptamine, or tyramine (272), while inhibition Similar inhibitory effects were also evident after intra-
ventricular implantation of L-noradrenaline, dopamine,
 α -ethyltryptamine, or tyramine (272), while inhibition of
catecholamine biosynthesis by administration of

Downloaded from pharmrev.aspetjournals.org at Thammasart University on December 8, 2012

EXECTED 262
tions of corticosterone (230) and ACTH (228). On the ter-
basis of these and other (1, 3, 79, 82, 111, 266) findings, it BUCKING
tions of corticosterone (230) and ACTH (228). On the
basis of these and other (1, 3, 79, 82, 111, 266) findings, it
was proposed that both noradrenergic and dopaminergic BUCKII
tions of corticosterone (230) and ACTH (228). On the
basis of these and other (1, 3, 79, 82, 111, 266) findings, it
was proposed that both noradrenergic and dopaminergic
mechanisms are involved in the secretion of C tions of corticosterone (230) and ACTH (228) . On the basis of these and other $(1, 3, 79, 82, 111, 266)$ findings, it was proposed that both noradrenergic and dopaminergic mechanisms are involved in the secretion of C tions of corticosterone (230) and ACTH (228) . On the to
basis of these and other $(1, 3, 79, 82, 111, 266)$ findings, it the
was proposed that both noradrenergic and dopaminergic mechanisms are involved in the secreti basis of these and other $(1, 3, 79, 82, 111, 266)$ findings, it
was proposed that both noradrenergic and dopaminergic
mechanisms are involved in the secretion of CRF, but
more recent evidence indicates that only the form was proposed that both noradrenergic and dopaminergi
mechanisms are involved in the secretion of CRF, bu
more recent evidence indicates that only the former is c
any functional significance. Apomorphine, implante
into the more recent evidence indicates that only the former is of
any functional significance. Apomorphine, implanted
into the third ventricle, did not influence pituitary adre-
nocortical activity. Inhibition of dopamine- β -hyd any functional significance. Apomorphine, implanted any functional significance. Apomorphine, implare into the third ventricle, did not influence pituitary a nocortical activity. Inhibition of dopamine- β -hydroxy with bis(1-methylhexahydro-1,4,-diazepinyl-4-thio bonyl) d into the third ventricle, did not influence pituitary adre
nocortical activity. Inhibition of dopamine- β -hydroxylas
with bis(1-methylhexahydro-1,4,-diazepinyl-4-thioca
bonyl) disulphide decreased the hypothalamic norad mocortical activity. Inhibition of dopamine- β -hydroxylas
with bis(1-methylhexahydro-1,4,-diazepinyl-4-thioca
bonyl) disulphide decreased the hypothalamic noradre
aline content and increased ACTH secretion, while trea
m with bis(1-methylhexahydro-1,4,-diazepinyl-4-thiocar-
bonyl) disulphide decreased the hypothalamic noradren-
aline content and increased ACTH secretion, while treat-
ment with dihydroxyphenylserine (which causes a selec-
 bonyl) disulphide decreased the hypothalamic noradre
aline content and increased ACTH secretion, while tree
ment with dihydroxyphenylserine (which causes a sele
tive decrease in hypothalamic dopamine) overcame the
rise in aline content and increased ACTH secretion, while treatment with dihydroxyphenylserine (which causes a selective decrease in hypothalamic dopamine) overcame the unrise in ACTH secretion induced by α -methylparatyrosine ment with dihydroxyphenylserine (which causes a selective decrease in hypothalamic dopamine) overcame the unders rise in ACTH secretion induced by α -methylparatyrosine in the (81). Moreover, noradrenaline inhibited bot tive decrease in hypothalamic dopamine) overcame t
rise in ACTH secretion induced by α -methylparatyrosi
(81). Moreover, noradrenaline inhibited both basal a
acetylcholine- or 5-HT-stimulated CRF secretion fro
the rat h rise in ACTH secretion induced by α -methylparatyrosine in (81). Moreover, noradrenaline inhibited both basal and ed
acetylcholine- or 5-HT-stimulated CRF secretion from ad
the rat hypothalamus in vitro but dopamine was (81). Moreover, noradrenaline inhibited both basal and
acetylcholine- or 5-HT-stimulated CRF secretion from
the rat hypothalamus in vitro but dopamine was ineffec-
tive in this respect (39, 141). Despite some reports to t acetylcholine- or 5-HT-stimulated CRF secretion from
the rat hypothalamus in vitro but dopamine was ineffec-
tive in this respect (39, 141). Despite some reports to the
contrary, it is now generally agreed that the inhibi the rat hypothalamus in vitro but dopamine was in
tive in this respect (39, 141). Despite some reports t
contrary, it is now generally agreed that the inhib
influence of noradrenaline is mediated by stimulati
 α -adrenoc tive in this respect (39, 141). Despite some reports to the contrary, it is now generally agreed that the inhibitor influence of noradrenaline is mediated by stimulation α -adrenoceptors. Ganong (80) showed that intrave contrary, it is now generally agreed that the inhibitory
influence of noradrenaline is mediated by stimulation of
 α -adrenoceptors. Ganong (80) showed that intraventric-
ular injection of phenoxybenzamine (an α -adren influence of noradrenaline is mediated by stimulation of α -adrenoceptors. Ganong (80) showed that intraventric-
ular injection of phenoxybenzamine (an α -adrenoceptor
antagonist) prevented the L-DOPA-induced suppress α -adrenoceptors. Ganong (80) showed that intraventric-
ular injection of phenoxybenzamine (an α -adrenoceptor
antagonist) prevented the L-DOPA-induced suppression
of the stress response while Eisenberg (68) reported ular injection of phenoxybenzamine (an α -adrenoceptor street antagonist) prevented the L-DOPA-induced suppression but of the stress response while Eisenberg (68) reported that iolo phentolamine (another α -adrenocept antagonist) prevented the L-DOPA-induced suppression
of the stress response while Eisenberg (68) reported that
phentolamine (another α -adrenoceptor antagonist) aug-
mented the pituitary-adrenocortical response to stres phentolamine (another α -adrenoceptor antagonist) aug-
mented the pituitary-adrenocortical response to stress in
ist normal rats but that the β -adrenoceptor antagonist, pro-
pranolol, was ineffective in this respect. mented the pituitary-adrenocortical response to stress in
normal rats but that the β -adrenoceptor antagonist, pro-
pranolol, was ineffective in this respect. Others have
shown that the basal secretion of corticosteroid normal rats but that the β -adrenoceptor antagonist, pro-
pranolol, was ineffective in this respect. Others have
shown that the basal secretion of corticosteroids is also
elevated by treatment with α -adrenoceptor ant pranolol, was ineffective in this respect. Others have
shown that the basal secretion of corticosteroids is also
elevated by treatment with α -adrenoceptor antagonists
(229). Furthermore, the inhibitory effect of noradr and the based secretion of corticosteroids is also of
elevated by treatment with α -adrenoceptor antagonists
(229). Furthermore, the inhibitory effect of noradrenaline his
on CRF secretion in vitro was mimicked by adren (229). Furthermore, the inhibitory effect of noradrenaline
on CRF secretion in vitro was mimicked by adrenaline
and the α -adrenoceptor agonists, methoxamine and
phenylephrine, but not by the β -adrenoceptor agonist,
 (229). Furthermore, the inhibitory effect of noradrenaline
on CRF secretion in vitro was mimicked by adrenaline
and the α -adrenoceptor agonists, methoxamine and
phenylephrine, but not by the β -adrenoceptor agonist,
 on CRF secretion in vitro was mimicked by adrenaline
and the α -adrenoceptor agonists, methoxamine and
phenylephrine, but not by the β -adrenoceptor agonist,
isoprenaline, and it was antagonised by phentolamine
but no 141). Ensylephrine, but not by the β -adrenoceptor agonis
oprenaline, and it was antagonised by phentolamint
it not by atenolol (a β -adrenoceptor antagonist) (4)
1).
In summary, it appears that central cholinergic nerv-
is

isoprenaline, and it was antagonised by phentolamir
but not by atenolol (a β -adrenoceptor antagonist) (4
141).
In summary, it appears that central cholinergic ner-
ous pathways stimulate and that GABA-ergic and adre
ne but not by atenolol (a β -adrenoceptor antagonist) (41, be

141). (1

In summary, it appears that central cholinergic nerv-

ous pathways stimulate and that GABA-ergic and adre-

of nergic pathways inhibit the productio 141). (12
In summary, it appears that central cholinergic nerv-
ous pathways stimulate and that GABA-ergic and adre-
of the production of CRF. Both wide
stimulatory and inhibitory roles have been ascribed to
neurones that In summary, it appears that central cholinergic nerv-
ous pathways stimulate and that GABA-ergic and adre-
nergic pathways inhibit the production of CRF. Both
stimulatory and inhibitory roles have been ascribed to
neurones ous pathways stimulate and that GABA-ergic and adre
nergic pathways inhibit the production of CRF. Both
stimulatory and inhibitory roles have been ascribed to
neurones that secrete 5-HT and much further work is
necessary t rgic pathways inhibit the production of CRF. Both
mulatory and inhibitory roles have been ascribed to
urones that secrete 5-HT and much further work is
cessary to elucidate their true physiological function.
It is generall neurones that secrete 5-HT and much further work is
necessary to elucidate their true physiological function.
It is generally agreed that both corticotrophin (195,
283) and corticosterone (cortisol in appropriate species)

neurones that secrete 5-HT and much further work is in
necessary to elucidate their true physiological function. D
It is generally agreed that both corticotrophin (195,
c283) and corticosterone (cortisol in appropriate spe necessary to elucidate their true physiological function. D
It is generally agreed that both corticotrophin (195,
283) and corticosterone (cortisol in appropriate species) stare capable of influencing the functional activi It is generally agreed that both corticotrophin (195, c
283) and corticosterone (cortisol in appropriate species) s
are capable of influencing the functional activity of the v
HPA system by negative feedback mechanisms. Li 283) and corticosterone (cortisol in appropriate species)
are capable of influencing the functional activity of the
HPA system by negative feedback mechanisms. Little is
known about the inhibitory actions of ACTH, but thos are capable of influencing the functional activity of the very short (less than 5 minutes). This observation was
HPA system by negative feedback mechanisms. Little is confirmed by Jones et al. (137), who found the system t HPA system by negative feedback mechanisms. Little
known about the inhibitory actions of ACTH, but the
of the corticosteroids have been examined extensive
Nevertheless, the precise site and mode of action of
steroids and t known about the inhibitory actions of ACTH, but those of the corticosteroids have been examined extensivel.
Nevertheless, the precise site and mode of action of the steroids and their physiological importance as "neuromodu of the corticosteroids have been examined extensively.
Nevertheless, the precise site and mode of action of the
steroids and their physiological importance as "neuro-
modulators" have been the subject of controversy. Stud-Nevertheless, the precise site and mode of action of the
steroids and their physiological importance as "neuro-
modulators" have been the subject of controversy. Stud-
ies in adrenalectomised, adrenal-enucleated, and intac steroids and their physiological importance as "neuro-
modulators" have been the subject of controversy. Stud-
ies in adrenalectomised, adrenal-enucleated, and intact
animals with and without corticosterone treatment under modulators" have been the subject of controversy. Stud-
ies in adrenalectomised, adrenal-enucleated, and intact
animals with and without corticosterone treatment under
nonstress conditions have demonstrated a distinct in-
 ies in adrenalectomised, adrenal-enucleated, and interainmals with and without corticosterone treatment unconstress conditions have demonstrated a distinct verse relationship between the pituitary and plas ACTH concentrati

terone in the blood (34, 35, 53, 77, 130, 180). Although majority of observations indicate that the marked EHAM
terone in the blood $(34, 35, 53, 77, 130, 180)$. Although
there are some reports to the contrary $(115, 296)$, the
majority of observations indicate that the marked
changes in the basal secretion of ACTH that these terone in the blood (34, 35, 53, 77, 130, 180). Although
there are some reports to the contrary (115, 296), the
majority of observations indicate that the marked
changes in the basal secretion of ACTH that these ex-
perime terone in the blood $(34, 35, 53, 77, 130, 180)$. Although
there are some reports to the contrary $(115, 296)$, the
majority of observations indicate that the marked
changes in the basal secretion of ACTH that these ex-
p there are some reports to the contrary (115, 296), the majority of observations indicate that the marked changes in the basal secretion of ACTH that these experimental procedures cause are accompanied by small differences majority of observations indicate that the marked
changes in the basal secretion of ACTH that these ex-
perimental procedures cause are accompanied by small
differences in hypothalamic CRF content (32, 38, 249,
281), which changes in the basal secretion of ACTH that these
perimental procedures cause are accompanied by su
differences in hypothalamic CRF content (32, 38,
281), which suggests that the blood corticosteroids
important in the cont perimental procedures cause are accompanied by small
differences in hypothalamic CRF content (32, 38, 24
281), which suggests that the blood corticosteroids a
important in the control of the activity of the hypotha
amo-hyp tions. 1), which suggests that the blood corticosteroids are
portant in the control of the activity of the hypothal-
no-hypophysial complex under basal nonstress condi-
ns.
The role of the blood corticosteroids in the control of

of the stress response while Eisenberg (68) reported that iological doses of corticosterone (31) (fig. 3). However,
phentolamine (another α -adrenoceptor antagonist) aug-
mented the pituitary-adrenocortical response to important in the control of the activity of the hypothal-
amo-hypophysial complex under basal nonstress condi-
tions.
The role of the blood corticosteroids in the control of
the stress-induced secretion of corticotrophin i amo-hypophysial complex under basal nonstress condi-
tions.
The role of the blood corticosteroids in the control of
the stress-induced secretion of corticotrophin is less well
understood. There can be no doubt that chronic tions.
The role of the blood corticosteroids in the control
the stress-induced secretion of corticotrophin is less we
understood. There can be no doubt that chronic chang
in the level of circulating corticosteroids influen The role of the blood corticosteroids in the control of
the stress-induced secretion of corticotrophin is less well
understood. There can be no doubt that chronic changes
in the level of circulating corticosteroids influen the stress-induced secretion of corticotrophin is less well understood. There can be no doubt that chronic changes
in the level of circulating corticosteroids influence mark-
edly the HPA response to stress. The stress-ind understood. There can be no doubt that chronic changes
in the level of circulating corticosteroids influence mark-
edly the HPA response to stress. The stress-induced
adrenocorticotrophic activity of the adenohypophysis is in the level of circulating corticosteroids influence markedly the HPA response to stress. The stress-induced adrenocorticotrophic activity of the adenohypophysis is elevated in adrenalectomised rats (13, 35, 123, 130, 132 adrenocorticotrophic activity of the adenohypophysis is
elevated in adrenalectomised rats (13, 35, 123, 130, 132)
and is inhibited in intact animals that have received
prolonged treatment with corticosteroids (36, 122, 124 adrenocorticotrophic activity of the adenohypophysis is

elevated in adrenalectomised rats (13, 35, 123, 130, 132)

and is inhibited in intact animals that have received

prolonged treatment with corticosteroids (36, 122, elevated in adrenalectomised rats $(13, 35, 123, 130, 132)$
and is inhibited in intact animals that have received
prolonged treatment with corticosteroids $(36, 122, 124,$
226). Moreover, the rapid fall and subsequent ris and is inhibited in intact animals that have received
prolonged treatment with corticosteroids (36, 122, 124,
226). Moreover, the rapid fall and subsequent rise in
hypothalamic CRF content that occurs in response to
stress prolonged treatment with corticosteroids (36, 122, 12
226). Moreover, the rapid fall and subsequent rise is
hypothalamic CRF content that occurs in response t
stressful stimuli is exaggerated in adrenalectomised ra
but nor 226). Moreover, the rapid fall and subsequent rise in hypothalamic CRF content that occurs in response to stressful stimuli is exaggerated in adrenalectomised rats but normal in adrenalectomised rats maintained on physiolo hypothalamic CRF content that occurs in response
stressful stimuli is exaggerated in adrenalectomised r
but normal in adrenalectomised rats maintained on ph
iological doses of corticosterone (31) (fig. 3). Howev
the result stressful stimuli is exaggerated in adrenalectomibut normal in adrenalectomised rats maintained cological doses of corticosterone (31) (fig. 3). Here results of experiments that involve the acute istration of steroids sugg but normal in adrenalectomised rats maintained on phiological doses of corticosterone (31) (fig. 3). Howeve the results of experiments that involve the acute admistration of steroids suggest that the hypothalamo-pitary-adr iological doses of corticosterone (31) (fig. 3). However,
the results of experiments that involve the acute admin-
istration of steroids suggest that the hypothalamo-pitui-
tary-adrenocorticotrophic response to stress is i tary-adrenocorticotrophic response to stress is indepenistration of steroids suggest that the hypothalamo-pitui-
tary-adrenocorticotrophic response to stress is indepen-
dent of the blood corticosteroid concentration at the time
of stress. Smelik (253) found no direct correlat tary-adrenocorticotrophic response to stress is indepedent of the blood corticosteroid concentration at the tin
of stress. Smelik (253) found no direct correlation b
tween the plasma corticosterone concentration and i
hibi dent of the blood corticosteroid concentration at the time
of stress. Smelik (253) found no direct correlation be-
tween the plasma corticosterone concentration and in-
hibition of stress-induced pituitary-adrenocortical a of stress. Smelik (253) found no direct correlation be-
tween the plasma corticosterone concentration and in-
hibition of stress-induced pituitary-adrenocortical activ-
ity in rats given single large doses of the steroid, tween the plasma corticosterone concentration and in-
hibition of stress-induced pituitary-adrenocortical activ-
ity in rats given single large doses of the steroid, either
i.p. or s.c.; inhibition of ACTH release occurred hibition of stress-induced pituitary-adrenocortical activity in rats given single large doses of the steroid, either i.p. or s.c.; inhibition of ACTH release occurred only some time after the blood corticosterone concentra ity in rats given single large doses of the steroid, either
i.p. or s.c.; inhibition of ACTH release occurred only
some time after the blood corticosterone concentration
had returned to the resting level. This observation i.p. or s.c.; inhibition of ACTH release occurred only
some time after the blood corticosterone concentration
had returned to the resting level. This observation has
been confirmed by using both direct (34) and indirect some time after the blood corticosterone concentration
had returned to the resting level. This observation has
been confirmed by using both direct (34) and indirect
(127) indices of ACTH secretion and the concept of a
"del had returned to the resting level. This observation has
been confirmed by using both direct (34) and indirect
 (127) indices of ACTH secretion and the concept of a
"delayed" feedback mechanism that controls the release been confirmed
(127) indices of
"delayed" feedba
of corticotrophin
widely accepted.
Recently a "ra edly the HPA response to stress. The stress-induced HPA responses $\frac{1}{2}$ also been finded in adrenalectomised rats (13, 35, 123, 130, 132) and is inhibited in intact animals that have received $\frac{1}{2}$ and is inhibite

"delayed" feedback mechanism that controls the release
of corticotrophin in response to stressful stimuli is now
widely accepted.
Recently a "rapid" feedback mechanism has also been
implicated in the control of stress-indu of corticotrophin in response to stressful stimuli is now
widely accepted.
Recently a "rapid" feedback mechanism has also been
implicated in the control of stress-induced HPA activity.
Dallman and Yates (61) demonstrated t widely accepted.

Recently a "rapid" feedback mechanism has also been

implicated in the control of stress-induced HPA activity.

Dallman and Yates (61) demonstrated that infusion of

corticosterone inhibited ACTH secreti Recently a "rapid" feedback mechanism has also been
implicated in the control of stress-induced HPA activity.
Dallman and Yates (61) demonstrated that infusion of
corticosterone inhibited ACTH secretion in response to
stre implicated in the control of stress-induced HPA activity.
Dallman and Yates (61) demonstrated that infusion of
corticosterone inhibited ACTH secretion in response to
stress but that the duration of action of the steroid wa Dallman and Yates (61) demonstrated that infusion of
corticosterone inhibited ACTH secretion in response to
stress but that the duration of action of the steroid was
very short (less than 5 minutes). This observation was
c corticosterone inhibited ACTH secretion in response to
stress but that the duration of action of the steroid was
very short (less than 5 minutes). This observation was
confirmed by Jones et al. (137), who found the system stress but that the duration of action of the steroid was
very short (less than 5 minutes). This observation was
confirmed by Jones et al. (137), who found the system to
be sensitive to the rate of increase of the concentr very short (less than 5 minutes). This observation was confirmed by Jones et al. (137), who found the system to be sensitive to the rate of increase of the concentration of corticosterone in the plasma and to be saturated confirmed by Jones et al. (137), who found the system to
be sensitive to the rate of increase of the concentration
of corticosterone in the plasma and to be saturated at
concentrations above the "physiological range". Seve be sensitive to the rate of increase of the concentration
of corticosterone in the plasma and to be saturated at
concentrations above the "physiological range". Several
authors have disputed the physiological significance of corticosterone in the plasma and to be saturated at concentrations above the "physiological range". Several authors have disputed the physiological significance of these results. Only indirect indices of ACTH secretion concentrations above the "physiological range". Several
authors have disputed the physiological significance of
these results. Only indirect indices of ACTH secretion
were employed and the rate of infusion of corticosteron authors have disputed the physiological significance of these results. Only indirect indices of ACTH secretion were employed and the rate of infusion of corticosterone was very high. Furthermore, the experiments were perfo were employed and the rate of infusion of corticosterone was very high. Furthermore, the experiments were performed under pentobarbitone anaesthesia and the possibility that this influenced the activity of the HPA system could not be excluded. In subsequent experiments

PHARMACOLOGICAL REVIEWS

treated, adrenalectomised, and corticosterone-treated rats before and after stress. \Box before stress; \Box , 1 minute after stress; \Box , 2 minutes after and after stress. \Box , before stress; \Box , 1 minute after stres FIG. 3. Hypothalamo-pituitary adrenocorticotrophic activity in untreated, adrenalectomised, and corticosterone-treated rats before and after stress. \Box , before stress: \Box , 1 minute after stress: \Box , 2 minutes after ingham, all the strees, **Q**, before strees; **N**, 1 minute after strees; letress: Esch column is the mean of five determination with its standard error. (Reprinted with permission ingham, *J. Physiol. (London)*, 286: 331-34 stress. Each column is the mean of five determinations and is shown
with its standard error. (Reprinted with permission from J. C. Buck-
ingham, J. Physiol. (London), 286: 331-342, 1979.)
performed on conscious rats, Jones

with its standard error. (Reprinted with permission from J. C. Buck-
ingham, J. Physiol. (London), 286: 331-342, 1979.)
performed on conscious rats, Jones and Tiptaft (143)
found that the adrenocortical response to stress ingham, J. Physiol. (London), 286: 331-342, 1979.)
performed on conscious rats, Jones and Tiptaft (found that the adrenocortical response to stress
impaired 10 minutes after a s.c. injection of corticos
one. In this study performed on conscious rats, Jones and Tiptaft (14 found that the adrenocortical response to stress wimpaired 10 minutes after a s.c. injection of corticost one. In this study no estimations of the plasma concentration of performed on conscious rats, Jones and Tiptaft (143
found that the adrenocortical response to stress we
impaired 10 minutes after a s.c. injection of corticoster
one. In this study no estimations of the plasma concer
trati impaired 10 minutes after a s.c. injection of corticoster-
one. In this study no estimations of the plasma concen-
well documented and the possibility that other brain
tration of the injected steroid were made; furthermor impaired 10 minutes after a s.c. injection of corticoster-
pussions. In this study no estimations of the plasma concen-
tration of the injected steroid were made; furthermore, are
the investigators did not discuss their p one. In this study no estimations of the plasma concentration of the injected steroid were made; furthermed the investigators did not discuss their previous suggest (137) that the rapid feedback mechanism is sensitive the tration of the injected steroid were made; furthermore, areas
the investigators did not discuss their previous suggestion $(19, 127)$
(137) that the rapid feedback mechanism is sensitive to It
the rate of rise of the plas the investigators did not discuss their previous suggestion (19,
(137) that the rapid feedback mechanism is sensitive to It
the rate of rise of the plasma concentration of corticos-
of terone. Other papers, based on indire (137) that the rapid feedback mechanism is sensitive to It
the rate of rise of the plasma concentration of corticos-
terone. Other papers, based on indirect indices of ACTH und
secretion, have provided additional evidence the rate of rise of the plasma concentration of corticos-
terone. Other papers, based on indirect indices of ACTH use
cretion, have provided additional evidence that is in o
accord with the existence of a rapid feedback me terone. Other papers, based on indirect indices of ACTH secretion, have provided additional evidence that is in accord with the existence of a rapid feedback mechanism (58, 144) but the concept of its being "rate-sensitive 172). cord with the existence of a rapid feedback mechanism

3, 144) but the concept of its being "rate-sensitive" was

t discussed further in more recent papers (139, 142,

2).

Corticosteroids are believed to exert their inhib

(58, 144) but the concept of its being "rate-sensitive" was
not discussed further in more recent papers (139, 142, and
172). effects on HPA activity by acting on specific receptors in mu
the adenohypophysis (6, 37, 75, 76 not discussed further in more recent papers (139, 142, are

172). ef

Corticosteroids are believed to exert their inhibitory

effects on HPA activity by acting on specific receptors in

the adenohypophysis (6, 37, 75, 76, 172).

Corticosteroids are believed to exert their inhibitory

effects on HPA activity by acting on specific receptors in

the adenohypophysis $(6, 37, 75, 76, 142, 172, 220)$, the

hypothalamus $(31, 39, 72, 142, 172, 26$

directly on the adenohypophysis to inhibit the release
but not the synthesis of ACTH induced by CRF (37, 38).
Experiments in vitro indicate that corticosterone may LEASING FACTOR
centres higher in the brain (59, 60, 71, 149, 154, 187, 297).
Evidence for inhibition at the pituitary level has been LEASING FACTOR 263

centres higher in the brain $(59, 60, 71, 149, 154, 187, 297)$.

Evidence for inhibition at the pituitary level has been

obtained from studies both in vivo $(6, 220)$ and in vitro 263

centres higher in the brain (59, 60, 71, 149, 154, 187, 297).

Evidence for inhibition at the pituitary level has been

obtained from studies both in vivo (6, 220) and in vitro

(37, 38, 75, 76, 196). It appears that centres higher in the brain (59, 60, 71, 149, 154, 187, 297).
Evidence for inhibition at the pituitary level has been
obtained from studies both in vivo (6, 220) and in vitro
(37, 38, 75, 76, 196). It appears that corticos centres higher in the brain $(59, 60, 71, 149, 154, 187, 297)$.
Evidence for inhibition at the pituitary level has been
obtained from studies both in vivo $(6, 220)$ and in vitro
 $(37, 38, 75, 76, 196)$. It appears that c Evidence for inhibition at the pituitary level has been
obtained from studies both in vivo (6, 220) and in vitro
(37, 38, 75, 76, 196). It appears that corticosteroids act
directly on the adenohypophysis to inhibit the rel obtained from studies both in vivo (6, 220) and in vitro
(37, 38, 75, 76, 196). It appears that corticosteroids act
directly on the adenohypophysis to inhibit the release
but not the synthesis of ACTH induced by CRF (37, 3 (37, 38, 75, 76, 196). It appears that corticosteroids act
directly on the adenohypophysis to inhibit the release
but not the synthesis of ACTH induced by CRF (37, 38).
Experiments in vitro indicate that corticosterone ma directly on the adenohypophysis to inhibit the release
but not the synthesis of ACTH induced by CRF (37, 38).
Experiments in vitro indicate that corticosterone may
also inhibit CRF-stimulated ACTH biosynthesis but only
aft also inhibit CRF-stimulated ACTH biosynthesis but only after prolonged contact of the steroid with the tissue (31).
The existence of corticosteroid receptors in the hypo-Experiments in vitro indicate that corticosterone may
also inhibit CRF-stimulated ACTH biosynthesis but only
after prolonged contact of the steroid with the tissue (31).
The existence of corticosteroid receptors in the hyp also inhibit CRF-stimulated ACTH biosynthesis but of after prolonged contact of the steroid with the tissue (The existence of corticosteroid receptors in the hypothalamus is well documented. Corticosteroids inhibit renocor after prolonged contact of the steroid with the tissue (31).
The existence of corticosteroid receptors in the hypo-
thalamus is well documented. Corticosteroids inhibit ad-
renocortical activity when implanted into the hyp thalamus is well documented. Corticosteroids inhibit ad-
renocortical activity when implanted into the hypothal-
amus (72, 264). They also inhibit the secretion of CRF
by isolated rat hypothalami in vitro in concentrations thalamus is well documented. Corticosteroids inhibit ad-
renocortical activity when implanted into the hypothal-
amus (72, 264). They also inhibit the secretion of CRF
by isolated rat hypothalami in vitro in concentrations renocortical activity when implanted into the hypothal-
amus (72, 264). They also inhibit the secretion of CRF
by isolated rat hypothalami in vitro in concentrations
considerably lower than those needed to influence the
ad amus (72, 264). They also inhibit the secretion of CRF
by isolated rat hypothalami in vitro in concentrations
considerably lower than those needed to influence the
adrenocorticotrophic activity of the anterior pituitary
gl considerably lower than those needed to influence the adrenocorticotrophic activity of the anterior pituitary gland in vitro (31, 39, 172). Experiments in vivo have considerably lower than those needed to influence the
adrenocorticotrophic activity of the anterior pituitary
gland in vitro (31, 39, 172). Experiments in vivo have
yielded similar results (281). Corticosteroid treatment
r adrenocorticotrophic activity of the anterior pituitary
gland in vitro (31, 39, 172). Experiments in vivo have
yielded similar results (281). Corticosteroid treatment
reduces the hypothalamic CRF content (38, 73), de-
pres gland in vitro (31, 39, 172). Experiments in vivo have
yielded similar results (281). Corticosteroid treatment
reduces the hypothalamic CRF content (38, 73), de-
presses hypothalamic unit activity (217), and prevents
the r reduces the hypothalamic CRF content (38, 73), de-
presses hypothalamic unit activity (217), and prevents
the release of CRF from already increased stores in the
median eminence of adrenalectomised rats (86). These
finding presses hypothalamic unit activity (217), and prevents presses hypothalamic unit activity (217), and prevents
the release of CRF from already increased stores in the
median eminence of adrenalectomised rats (86). These
findings may be the result of direct actions of the stero the release of CRF from already increased stores in the
median eminence of adrenalectomised rats (86). These
findings may be the result of direct actions of the steroid
on the hypothalamus and to actions on higher centres on the hypothalamus and to actions on higher centres in
the brain since in these experiments corticosterone was
administered either orally or systemically. A substantial findings may be the result of direct actions of the steroid
on the hypothalamus and to actions on higher centres in
the brain since in these experiments corticosterone was
administered either orally or systemically. A subs on the hypothalamus and to actions on higher centres in
the brain since in these experiments corticosterone was
administered either orally or systemically. A substantial
amount of evidence indicates that corticosteroids ex the brain since in these experiments corticosterone was
administered either orally or systemically. A substantial
amount of evidence indicates that corticosteroids exert
feedback effects at extrahypothalamic sites in the c administered either orally or systemically. A substantial

amount of evidence indicates that corticosteroids exert

feedback effects at extrahypothalamic sites in the central

nervous system (19, 59, 60, 71, 149, 154, 187 amount of evidence indicates that corticosteroids exert
feedback effects at extrahypothalamic sites in the central
nervous system (19, 59, 60, 71, 149, 154, 187, 190, 297).
For several reasons some of this work is difficul feedback effects at extrahypothalamic sites in the central
nervous system (19, 59, 60, 71, 149, 154, 187, 190, 297).
For several reasons some of this work is difficult to
interpret. Firstly, the concentration of the steroi nervous system (19, 59, 60, 71, 149, 154, 187, 190, 297).
For several reasons some of this work is difficult to
interpret. Firstly, the concentration of the steroid used
in implantation studies may be unphysiologically hig For several reasons some of this work is difficult to interpret. Firstly, the concentration of the steroid used in implantation studies may be unphysiologically high. Secondly, the steroid may diffuse away from the site of interpret. Firstly, the concentration of the steroid used
in implantation studies may be unphysiologically high.
Secondly, the steroid may diffuse away from the site of
injection. Thirdly, the selective uptake of corticost in implantation studies may be unphysiologically high.
Secondly, the steroid may diffuse away from the site of
injection. Thirdly, the selective uptake of corticosteroids
by brain structures after peripheral injection does Secondly, the steroid may diffuse away from the site of injection. Thirdly, the selective uptake of corticosteroids by brain structures after peripheral injection does not demonstrate the existence of specific receptors bu injection. Thirdly, the selective uptake of corticosteroids
by brain structures after peripheral injection does not
demonstrate the existence of specific receptors but
merely reflects the tissue's capacity to bind the ster by brain structures after peripheral injection does not
demonstrate the existence of specific receptors but
merely reflects the tissue's capacity to bind the steroid.
The presence of receptors can only be postulated when
 demonstrate the existence of specific receptors
merely reflects the tissue's capacity to bind the ster
The presence of receptors can only be postulated w
the binding is associated with the specific change
HPA activity or o merely reflects the tissue's capacity to bind the steroid.
The presence of receptors can only be postulated when
the binding is associated with the specific changes in
HPA activity or other specific steroid action. Neverth The presence of receptors can only be postulated when
the binding is associated with the specific changes in
HPA activity or other specific steroid action. Neverthe-
less, the importance of the amygdala and the hippocam-
p the binding is associated with the specific changes in
HPA activity or other specific steroid action. Neverthe-
less, the importance of the amygdala and the hippocam-
pus (153, 154) as sites of corticosteroid feedback has HPA activity or other specific steroid action. Nevertheless, the importance of the amygdala and the hippocampus (153, 154) as sites of corticosteroid feedback has been well documented and the possibility that other brain a It is 153, 154) as sites of corticosteroid feedback has been
ell documented and the possibility that other brain
eas may also be involved should not be disregarded
9, 154, 190).
It is hard to evaluate the relative importan

(19, 154, 190). well documented and the possibility that other brain
areas may also be involved should not be disregarded
(19, 154, 190).
It is hard to evaluate the relative importance of each
of the "feedback sites" in the control of HPA areas may also be involved should not be disregarded

(19, 154, 190).

It is hard to evaluate the relative importance of each

of the "feedback sites" in the control of HPA activity

under normal physiological conditions. (19, 154, 190).
It is hard to evaluate the relative importance of each
of the "feedback sites" in the control of HPA activity
under normal physiological conditions. Experiments in
our laboratory (37) demonstrated that str It is hard to evaluate the relative importance of each
of the "feedback sites" in the control of HPA activity
under normal physiological conditions. Experiments in
our laboratory (37) demonstrated that stress-induced
adren of the "feedback sites" in the control of HPA activity
under normal physiological conditions. Experiments in
our laboratory (37) demonstrated that stress-induced
adrenocorticotrophic activity is always paralleled by con-
c under normal physiological conditions. Experiments in
our laboratory (37) demonstrated that stress-induced
adrenocorticotrophic activity is always paralleled by con-
comitant changes in hypothalamic CRF content (fig. 3)
an our laboratory (37) demonstrated that stress-induced
adrenocorticotrophic activity is always paralleled by con-
comitant changes in hypothalamic CRF content (fig. 3)
and it seems reasonable to infer that the regulatory
eff adrenocorticotrophic activity is always paralleled by concomitant changes in hypothalamic CRF content (fig. 3) and it seems reasonable to infer that the regulatory effects of corticosteroids on the stress-induced secretion comitant changes in hypothalamic CRF content (fig. 3)
and it seems reasonable to infer that the regulatory
effects of corticosteroids on the stress-induced secretion
of ACTH are exerted predominantly at the hypothala-
mus and it seems reasonable to infer that the regulator effects of corticosteroids on the stress-induced secretic of ACTH are exerted predominantly at the hypothal mus or on centres higher in the brain. The pituitar receptors mus or on centres higher in the brain. The pituitary
receptors may be involved in the control of ACTH secre-
tion under nonstress conditions. Several groups (31, 38,

REV

PHARMACOLOGI

aspet

264
115, 249, 296) have shown that the adrenocorticotroph
activity of the adenohypophysis is influenced more read BUC
264
115, 249, 296) have shown that the adrenocorticotrophi
activity of the adenohypophysis is influenced more read-
ily by changes in the level of circulating corticosteroid BUCK
115, 249, 296) have shown that the adrenocorticotrophic
activity of the adenohypophysis is influenced more read-
ily by changes in the level of circulating corticosteroids
than is the CRF content of the hypothalamus. 115, 249, 296) have shown that the adrenocorticotrophic activity of the adenohypophysis is influenced more readily by changes in the level of circulating corticosteroids than is the CRF content of the hypothalamus. However 115, 249, 296) have shown that the adrenocorticotrophic
activity of the adenohypophysis is influenced more read-
ily by changes in the level of circulating corticosteroids
than is the CRF content of the hypothalamus. Howev activity of the adenohypophysis is influenced more read-
ily by changes in the level of circulating corticosteroids eff
than is the CRF content of the hypothalamus. However, be
the absolute hormone content of a tissue does the absolute hormone content of a tissue does not necessarily reflect its secretory capacity $(123, 132)$ and the abilities, in vitro, of hypothalami and anterior pituitary segments to secrete CRF $(31, 115)$ and ACTH $(3$ abilities, in vitro, of hypothalami and anterior pituitary hyperaldosteronism.

segments to secrete CRF (31, 115) and ACTH (31), The possibility that the sex steroids influence the respectively, are exaggerated by adrenale segments to secrete CRF $(31, 115)$ and ACTH (31) , respectively, are exaggerated by adrenalectomy and reduced by corticosteroid treatment, possibly as a result of direct effects on the tissue itself or to actions on neu respectively, are exaggerated by adrenalectomy and reduced by corticosteroid treatment, possibly as a result of direct effects on the tissue itself or to actions on neurones that control its activity. Both in vivo and in v duced by corticosteroid treatment, possibly as a result of eredirect effects on the tissue itself or to actions on neurones this that control its activity. Both in vivo and in vitro studies po have suggested that the hypot direct effects on the tissue itself or to actions on neurones the that control its activity. Both in vivo and in vitro studies phave suggested that the hypothalamus is more sensitive to the inhibitory effects of corticoste that control its activity. Both in vivo and in vitro studies phave suggested that the hypothalamus is more sensitive tito the inhibitory effects of corticosterone than is the feanterior pituitary gland (31, 172, 281). If t have suggested that the hypothalamus is more sensitive tive
to the inhibitory effects of corticosterone than is the fec
anterior pituitary gland (31, 172, 281). If this is the case and
the receptors in the adenohypophysis to the inhibitory effects of corticosterone than is the fecanterior pituitary gland (31, 172, 281). If this is the case an the receptors in the adenohypophysis and perhaps those over in centres higher in the brain would be anterior pituitary gland (31, 172, 281). If this is the case are the receptors in the adenohypophysis and perhaps those our in centres higher in the brain would be stimulated only rewhen relatively severe suppression of HP the receptors in the adenohypophysis and perhaps those order in centres higher in the brain would be stimulated only rever when relatively severe suppression of HPA activity is einvalued. Teleologically this hypothesis is in centres higher in the brain would be stimulated only rer
when relatively severe suppression of HPA activity is eit
required. Teleologically this hypothesis is appealing since
the hypothalamus is the beginning of the fin when relatively severe suppression of HPA activity is eith
required. Teleologically this hypothesis is appealing since gree
the hypothalamus is the beginning of the final common trog
pathway leading to ACTH secretion. Much the hypothalamus is the beginning of the final common
pathway leading to ACTH secretion. Much further work
on this aspect of HPA physiology will be necessary to
test this hypothesis.
The possibility that steroid hormones o

pathway leading to ACTH secretion. Much further work hon this aspect of HPA physiology will be necessary to a test this hypothesis. The possibility that steroid hormones other than the a glucocorticoids, corticosterone and on this aspect of HPA physiology will be necessary to add
test this hypothesis. Complements of the HPA system has the and
glucocorticoids, corticosterone and cortisol, are capable pre
of influencing the activity of the HPA test this hypothesis.
The possibility that steroid hormones other than the
glucocorticoids, corticosterone and cortisol, are capable
of influencing the activity of the HPA system has been
suggested and the actions of other The possibility that steroid hormones other than the
glucocorticoids, corticosterone and cortisol, are capable
present of influencing the activity of the HPA system has been
suggested and the actions of other adrenocortica glucocorticoids, corticosterone and cortisol, are capable poor influencing the activity of the HPA system has been to suggested and the actions of other adrenocortical hormones have been investigated. Progesterone appears of influencing the activity of the HPA system has been teron
suggested and the actions of other adrenocortical hor-
mones have been investigated. Progesterone appears to (121)
be inactive. However, the delayed inhibitory e suggested and the actions of other adrenocortic mones have been investigated. Progesterone apple inactive. However, the delayed inhibitory effection of are mimicked by 11-deoxycortisol, 11-deoxycorticone, 11β -hydroxypr mones have been investigated. Progesterone appo
be inactive. However, the delayed inhibitory effecorticosterone on the stress-induced secretion of λ
are mimicked by 11-deoxycortisol, 11-deoxycorticone, 11 β -hydroxypr be inactive. However, the delayed inhibitory effect corticosterone on the stress-induced secretion of AC are mimicked by 11-deoxycortisol, 11-deoxycortico one, 11β -hydroxyprogesterone, and 11β , 17α -dihydroxyester corticosterone on the stress-induced secretion of ACTI
are mimicked by 11-deoxycortisol, 11-deoxycorticoster
one, 11β -hydroxyprogesterone, and 11β ,17 α -dihydroxy
progesterone but not by 11-epicortisol, while 17-hy are mimicked by 11-deoxycortisol, 11-deoxycorticoster-
one, 11β -hydroxyprogesterone, and 11β ,17 α -dihydroxy-
progesterone but not by 11-epicortisol, while 17-hydroxy-
progesterone and 18-hydroxy-11-deoxycorticoste one, 11β -hydroxyprogesterone, and 11β ,17 α -dihydroxy- (5
progesterone but not by 11-epicortisol, while 17-hydroxy- vi
progesterone and 18-hydroxy-11-deoxycorticosterone op-
feose these actions of the glucocorticoi progesterone but not by 11-epicortisol, while 17-hydroprogesterone and 18-hydroxy-11-deoxycorticosterone
pose these actions of the glucocorticoids (143). In vi
studies suggest that the actions of these steroids, l
those of progesterone and 18-hydroxy-11-deoxycorticosterone op-
pose these actions of the glucocorticoids (143). In vitro
studies suggest that the actions of these steroids, like
potl
those of cortisol and corticosterone, are exert pose these actions of the glucocorticoids (143). In vitro adenticies suggest that the actions of these steroids, like pothose of cortisol and corticosterone, are exerted predominantly on the hypothalamus and to a lesser ex mineralocorticoid, 18-hydroxy-li-deoxycorticosterone, those of cortisol and corticosterone, are exerted predom-
inantly on the hypothalamus and to a lesser extent on
intervalse secretion of CRF by isolated rat hypothalami in
inantly on the hypothalamus and to a lesser extent inantly on the hypothalamus and to a lesser extent on
the adenohypophysis (172). With the exception of the
mineralocorticoid, 18-hydroxy-11-deoxycorticosterone,
none of these steroids either mimicked or opposed the
"rapid" the adenohypophysis (172). With the exception of the mineralocorticoid, 18-hydroxy-11-deoxycorticosterone, none of these steroids either mimicked or opposed the "rapid" feedback effects of the glucocorticoids (139, 143). 1 mineralocorticoid, 18-hydroxy-11-deoxycorticosterone, of
none of these steroids either mimicked or opposed the
"rapid" feedback effects of the glucocorticoids (139, 143). en
18-Hydroxy-11-deoxycorticosterone antagonised th none of these steroids either mimicked or opposed the either inpid" feedback effects of the glucocorticoids (139, 143). exp. 18-Hydroxy-11-deoxycorticosterone antagonised this action of corticosterone (139, 143). On the ba "rapid" feedback effects of the glucocorticoids (139, 143).
18-Hydroxy-11-deoxycorticosterone antagonised this action of corticosterone (139, 143). On the basis of these
findings, it was suggested (139, 143) that only tho 18-Hydroxy-11-deoxycorticosterone antagonised this action of corticosterone (139, 143). On the basis of thes findings, it was suggested (139, 143) that only thos adrenocortical steroids that possess both the 21-hydroxy gr tion of corticosterone (139, 143). On the basis of these system
findings, it was suggested (139, 143) that only those and
adrenocortical steroids that possess both the 21-hydroxyl
group and 11β -hydroxyl group activate findings, it was suggested (139, 143) that only those a
adrenocortical steroids that possess both the 21-hydroxyl
group and 11 β -hydroxyl group activate the "rapid" feed-
back mechanism while the delayed feedback mechan adrenocortical steroids that possess both the 21-hydroxy
group and 11β -hydroxyl group activate the "rapid" feed
back mechanism while the delayed feedback mechanism
is stimulated by those steroids that possess either th group and 11 β -hydroxyl group activate the "rapid" feed-
back mechanism while the delayed feedback mechanism
is stimulated by those steroids that possess either the 21-
hydroxyl or the 11 β -hydroxyl group. However, th back mechanism while the delayed feedback mechanism
is stimulated by those steroids that possess either the 21-
hydroxyl or the 11 β -hydroxyl group. However, the find-
costerone (both of which possess 21-hydroxyl groups is stimulated by those steroids that possess either the 21-
hydroxyl or the 11 β -hydroxyl group. However, the find-
ings with 11-epicortisol and 18-hydroxy-11-deoxycorti-
costerone (both of which possess 21-hydroxyl gro hydroxyl or the 11 β -hydroxyl group. However, the find-
ings with 11-epicortisol and 18-hydroxy-11-deoxycorti-
costerone (both of which possess 21-hydroxyl groups) are able
hard to reconcile with this hypothesis. Aldost ings with 11-epicortisol and 18-hydroxy-11-deoxycor
costerone (both of which possess 21-hydroxyl groups) a
hard to reconcile with this hypothesis. Aldosterone h
also been implicated in the control of HPA activity.
concentr costerone (both of which possess 21-hydroxyl groups) are ables hard to reconcile with this hypothesis. Aldosterone has activity also been implicated in the control of HPA activity. In trace concentrations approaching the u hard to reconcile with this hypothesis. Aldosterone halso been implicated in the control of HPA activity. I
concentrations approaching the upper end of the physological range, aldosterone inhibits the secretion of CR
by ra

than is the CRF content of the hypothalamus. However, be greater than those of corticosterone. This is surprising, the absolute hormone content of a tissue does not nec-
essarily reflect its secretory capacity (123, 132) a GHAM
stimulated production of ACTH by pituitary segments in
vitro (32). Birmingham (18) suggested that the inhibitory GHAM
stimulated production of ACTH by pituitary segments in
vitro (32). Birmingham (18) suggested that the inhibitory
effects of this mineralocorticoid on ACTH secretion may GHAM
stimulated production of ACTH by pituitary segments in
vitro (32). Birmingham (18) suggested that the inhibitory
effects of this mineralocorticoid on ACTH secretion may
be greater than those of corticosterone. This is stimulated production of ACTH by pituitary segments in
vitro (32). Birmingham (18) suggested that the inhibitory
effects of this mineralocorticoid on ACTH secretion may
be greater than those of corticosterone. This is surp stimulated production of ACTH by pituitary segments in
vitro (32). Birmingham (18) suggested that the inhibitory
effects of this mineralocorticoid on ACTH secretion may
be greater than those of corticosterone. This is surp vitro (32). Birmingham (18) suggested that the inhibitory
effects of this mineralocorticoid on ACTH secretion may
be greater than those of corticosterone. This is surprising,
since, to my knowledge, there is no evidence of hyperaldosteronism. greater than those of corticosterone. This is surprising,
nce, to my knowledge, there is no evidence of severe
pairment of HPA activity in patients with primary
peraldosteronism.
The possibility that the sex steroids influ

respectively, are exaggerated by adrenalectomy and re-
functional activity of the HPA system has been consid-
duced by corticosteroid treatment, possibly as a result of ered. It is unlikely that androgenic steroids are act the hypothalamus is the beginning of the final common
progenic steroids affect the functional activity of the
pathway leading to ACTH secretion. Much further work
hypothalamo-pituitary complex. For example, both the
on thi since, to my knowledge, there is no evidence of severel impairment of HPA activity in patients with prime hyperaldosteronism.
The possibility that the sex steroids influence to functional activity of the HPA system has bee impairment of HPA activity in patients with primary
hyperaldosteronism.
The possibility that the sex steroids influence the
functional activity of the HPA system has been consid-
ered. It is unlikely that androgenic steroi hyperaldosteronism.
The possibility that the sex steroids influence
functional activity of the HPA system has been con
ered. It is unlikely that and
rogenic steroids are active
this respect. The abilities of hypothalami an The possibility that the sex steroids influence t
functional activity of the HPA system has been cons
ered. It is unlikely that androgenic steroids are active
this respect. The abilities of hypothalami and adenot
pophysial functional activity of the HPA system has been considered. It is unlikely that androgenic steroids are active it this respect. The abilities of hypothalami and adenohy pophysial segments to secrete CRF and ACTH respectivel ered. It is unlikely that androgenic steroids are active in
this respect. The abilities of hypothalami and adenohy-
pophysial segments to secrete CRF and ACTH respec-
tively in vitro in response to trophic stimuli were una this respect. The abilities of hypothalami and adenoh
pophysial segments to secrete CRF and ACTH respectively in vitro in response to trophic stimuli were una
fected by the presence of testosterone, androsterone,
androsten pophysial segments to secrete CRF and ACTH respectively in vitro in response to trophic stimuli were unaffected by the presence of testosterone, androsterone, o androsterodione in the incubation medium (32). More over, the tively in vitro in response to trophic stimuli were unaffected by the presence of testosterone, androsterone, or androstenedione in the incubation medium (32). Moreover, the corticotrophin releasing activity of hypothalami fected by the presence of testosterone, androsterone, or
androstenedione in the incubation medium (32). More-
over, the corticotrophin releasing activity of hypothalami
removed from rats was not affected by pretreatment w androstenedione in the incubation medium (32). More-
over, the corticotrophin releasing activity of hypothalami
removed from rats was not affected by pretreatment with
either testosterone or dehydroepiandrosterone (139). A over, the corticotrophin releasing activity of hypothalami
removed from rats was not affected by pretreatment with
either testosterone or dehydroepiandrosterone (139). A
great deal of circumstantial evidence suggests that removed from rats was not affected by pretreatment with
either testosterone or dehydroepiandrosterone (139). A
great deal of circumstantial evidence suggests that oes-
trogenic steroids affect the functional activity of th either testosterone or dehydroepiandrosterone (139).
great deal of circumstantial evidence suggests that oe
trogenic steroids affect the functional activity of tl
hypothalamo-pituitary complex. For example, both tl
adrenal great deal of circumstantial evidence suggests that oestrogenic steroids affect the functional activity of the hypothalamo-pituitary complex. For example, both the adrenal weight and the plasma concentration of gluco-corti trogenic steroids affect the functional activity of the hypothalamo-pituitary complex. For example, both the adrenal weight and the plasma concentration of gluco-corticoids are higher in the female than in the male rat and hypothalamo-pituitary complex. For example, both
adrenal weight and the plasma concentration of glu
corticoids are higher in the female than in the male
and are raised still further during the final stages
pregnancy. Furth adrenal weight and the plasma concentration of gluco-
corticoids are higher in the female than in the male rat
and are raised still further during the final stages of
pregnancy. Furthermore, the concentrations of corticoscorticoids are higher in the female than in the male rat
and are raised still further during the final stages of
pregnancy. Furthermore, the concentrations of corticos-
terone in the plasma (33, 212), ACTH in the plasma (3 and are raised still further during the final stages of
pregnancy. Furthermore, the concentrations of corticos-
terone in the plasma (33, 212), ACTH in the plasma (33)
and pituitary gland (55), and CRF in the hypothalamus
 terone in the plasma (33, 212), ACTH in the plasma (3
and pituitary gland (55), and CRF in the hypothalam
(121) are elevated in the female rat during pro-oestros
as also is the plasma concentration of oestradiol. It h
been and pituitary gland (55), and CRF in the hypothalamus

(121) are elevated in the female rat during pro-oestrous

as also is the plasma concentration of oestradiol. It has

been suggested that oestrogens stimulate the biosy (121) are elevated in the female rat during pro-oestrous
as also is the plasma concentration of oestradiol. It has
been suggested that oestrogens stimulate the biosyn-
thesis of ACTH and sensitise the pituitary gland to C as also is the plasma concentration of oestradiol. It has
been suggested that oestrogens stimulate the biosyn-
thesis of ACTH and sensitise the pituitary gland to CRF
(54, 151). More recent studies with pituitary tissue in been suggested that oestrogens stimulate the biosyn-
thesis of ACTH and sensitise the pituitary gland to CRF
(54, 151). More recent studies with pituitary tissue in
vitro have failed to confirm these findings (37). Positiv thesis of ACTH and sensitise the pituitary gland to CRF (54, 151). More recent studies with pituitary tissue in vitro have failed to confirm these findings (37). Positive feedback effects of oestrogenic steroids, with resp (54, 151). More recent studies with pituitary tissue ivitro have failed to confirm these findings (37). Positiveledback effects of oestrogenic steroids, with respect the afternocortical activity, appear to be exerted at th vitro have failed to confirm these findings (37). Positive
feedback effects of oestrogenic steroids, with respect to
adrenocortical activity, appear to be exerted at the hy-
pothalamic level. Although they did not affect t feedback effects of oestrogenic steroids, with respect
adrenocortical activity, appear to be exerted at the h
pothalamic level. Although they did not affect the spo
taneous secretion of CRF by isolated rat hypothalami
vitr adrenocortical activity, appear to be exerted at the hypothalamic level. Although they did not affect the spontaneous secretion of CRF by isolated rat hypothalami in vitro, oestradiol, oestriol, and oestrone potentiated ma pothalamic level. Although they did not affect the spon-
taneous secretion of CRF by isolated rat hypothalami in
vitro, oestradiol, oestriol, and oestrone potentiated mark-
edly both the increases in the synthesis and the taneous secretion of CRF by isolated rat hypothalami in
vitro, oestradiol, oestriol, and oestrone potentiated mark-
edly both the increases in the synthesis and the release
of this hypothalamic hormone that occur in respon vitro, oestradiol, oestriol, and oestrone potentiated markedly both the increases in the synthesis and the release
of this hypothalamic hormone that occur in response to
either acetylcholine or 5-HT (32). Thus the possibil edly both the increases in the synthesis and the release
of this hypothalamic hormone that occur in response to
either acetylcholine or 5-HT (32). Thus the possibility
exists that not only adrenocortical hormones but also of this hypothalamic hormone that occur in response to
either acetylcholine or 5-HT (32). Thus the possibility
exists that not only adrenocortical hormones but also
oestrogenic steroids influence the activity of the HPA
sy either acetylcholine or 5-HT (32). Thus the possibility exists that not only adrenocortical hormones but also oestrogenic steroids influence the activity of the HPA system. The physiological significance of this is not cle Frogenic steroids influence the activity of the Higher Controller Controller Controller Controller Controller
Fram. The physiological significance of this is not cliently requires further investigation.
VI. Mechanism of Ac **Example Internet Incorporation**
 m of Action of Corti
 Releasing Factor
 rations of the mechan

Releasing Factor
Detailed investigations of the mechanisms by which
CRF evokes the secretion of corticotrophin will not be VI. Mechanism of Action of Corticotrophin
Releasing Factor
Detailed investigations of the mechanisms by which
CRF evokes the secretion of corticotrophin will not be
possible until pure preparations of the hormone are avail v1. Mechanism of Action of Corticotrophin
Releasing Factor
Detailed investigations of the mechanisms by whic
CRF evokes the secretion of corticotrophin will not b
possible until pure preparations of the hormone are availab **Example 19 Accor**

Detailed investigations of the mechanisms by which

CRF evokes the secretion of corticotrophin will not be

possible until pure preparations of the hormone are available. Nevertheless, some information Detailed investigations of the mechanisms by which
CRF evokes the secretion of corticotrophin will not be
possible until pure preparations of the hormone are avail-
able. Nevertheless, some information about its mode of
ac CRF evokes the secretion of corticotrophin will not be possible until pure preparations of the hormone are available. Nevertheless, some information about its mode of action has been obtained with impure hypothalamic extra possible until pure preparations of the hormone are available. Nevertheless, some information about its mode of action has been obtained with impure hypothalamic extracts. CRF acts on the corticotrophs in the anterior pitu able. Nevertheless, some information about its mode of
action has been obtained with impure hypothalamic ex-
tracts. CRF acts on the corticotrophs in the anterior
pituitary gland and causes increases in both the amount
of action has been obtained with impure hypothalamic ex-
tracts. CRF acts on the corticotrophs in the anterior
pituitary gland and causes increases in both the amount
of ACTH released and the ACTH content of the cells
(37). T

PHARMACOLOGICAL REVIEWS

aspet

PHARMACOLOGICAL REVIEWS

aspet

CORTICOTROPHIN RE

rise in pituitary ACTH content have not been thoroughly

studied, but the rapidity of this striking response suggests CORTICOTROPHIN RE
studied, but the rapidity of this striking response suggests
that it cannot be due solely to de novo synthesis of the CORTICOTROPHIN RELE

rise in pituitary ACTH content have not been thoroughly

studied, but the rapidity of this striking response suggests

that it cannot be due solely to de novo synthesis of the

hormone. ACTH is stored rise in pituitary ACTH content have not been thoroughly the studied, but the rapidity of this striking response suggests phenome. ACTH is stored in the corticotrophs in the form of a biologically inactive precursor molecul rise in pituitary ACTH content have not been thoroughly
studied, but the rapidity of this striking response suggests
that it cannot be due solely to de novo synthesis of the
hormone. ACTH is stored in the corticotrophs in studied, but the rapidity of this striking response suggests
that it cannot be due solely to de novo synthesis of the
hormone. ACTH is stored in the corticotrophs in the
form of a biologically inactive precursor molecule (that it cannot be due solely to de novo synthesis of the hormone. ACTH is stored in the corticotrophs in the form of a biologically inactive precursor molecule (162) and it is probable that the rapid CRF-induced increase i hormone. rm of a biologically inactive precursor molecule (162)
d it is probable that the rapid CRF-induced increase
ACTH content reflects merely breakdown of the pro-
rmone.
It is widely believed that the action of CRF, like that
 and it is probable that the rapid CRF-induced increase
in ACTH content reflects merely breakdown of the pro-
hormone.
It is widely believed that the action of CRF, like that
root other hypophysiotrophic hormones, is mediat

in ACTH content reflects merely breakdown of the pro-
hormone.
It is widely believed that the action of CRF, like that
of other hypophysiotrophic hormones, is mediated via
cyclic adenosine 3',5'-monophosphate (cyclic AMP)
 hormone.

It is widely believed that the action of CRF, like that

of other hypophysiotrophic hormones, is mediated via

gyclic adenosine $3',5'$ -monophosphate (cyclic AMP)

(163). A variety of cyclic AMP derivatives, subs It is widely believed that the action of CRF, like that rc
of other hypophysiotrophic hormones, is mediated via
cyclic adenosine 3',5'-monophosphate (cyclic AMP) m
(163). A variety of cyclic AMP derivatives, substituted a of other hypophysiotrophic hormones, is mediated vicyclic adenosine $3',5'$ -monophosphate (cyclic AMP (163). A variety of cyclic AMP derivatives, substituted a N^6 and C^8 , have been shown to evoke the secretion c
ACTH cyclic adenosine $3'$,5'-monophosphate (cyclic AMP) m
(163). A variety of cyclic AMP derivatives, substituted at a
N⁶ and C⁸, have been shown to evoke the secretion of (3
ACTH by pituitary tissue in vitro (74). Simila (163). A variety of cyclic AMP derivatives, substituted at a N^6 and C^8 , have been shown to evoke the secretion of (3) ACTH by pituitary tissue in vitro (74). Similarly, theophylline, a drug that inhibits phosphodies N^6 and C^8 , have been shown to evoke the secretion of (23,
ACTH by pituitary tissue in vitro (74). Similarly, theostor
phylline, a drug that inhibits phosphodiesterase and thus (56)
the metabolism of cyclic AMP, stim ACTH by pituitary tissue in vitro (74) . Similarly, theosphylline, a drug that inhibits phosphodiesterase and thus (56) the metabolism of cyclic AMP, stimulates ACTH release neu (74) . Adenyl cyclase in the pituitary phylline, a drug that inhibits phosphodiesterase and thus
the metabolism of cyclic AMP, stimulates ACTH release
(74). Adenyl cyclase in the pituitary gland is activated by
prostaglandins (298, 299) and thus the possibility the metabolism of cyclic AMP, stimulates ACTH release neu (74). Adenyl cyclase in the pituitary gland is activated by dropprostaglandins (298, 299) and thus the possibility has also 276, been raised that prostaglandins are (74) . Adenyl cyclase in the pituitary gland is activated by drepostaglandins $(298, 299)$ and thus the possibility has also 27 been raised that prostaglandins are involved in the setiquence of events within the corticot prostaglandins (298, 299) and thus the possibility has also 276,
been raised that prostaglandins are involved in the se-
quence of events within the corticotroph that lead to bilit
ACTH secretion. More recent studies are n been raised that prostaglandins are involved in the sequence of events within the corticotroph that lead to ACTH secretion. More recent studies are not in accord with this hypothesis for although prostaglandins do evoke th quence of events within the corticotroph that lead to bi
ACTH secretion. More recent studies are not in accord of
with this hypothesis for although prostaglandins do gr
evoke the secretion of corticosteroids when administe ACTH secretion. More recent studies are not in accord of in with this hypothesis for although prostaglandins do groevoke the secretion of corticosteroids when administered to lot intact control animals (102, 205a), the ef with this hypothesis for although prostaglandins do growbe the secretion of corticosteroids when administered to intact control animals $(102, 205a)$, the effect is blocked evaluation in injected or inhibited by pentobarb evoke the secretion of corticosteroids when administered to b
to intact control animals (102, 205a), the effect is blocked et a
or inhibited by pentobarbitone/morphine (205a), and mon
they do not affect ACTH secretion eith to intact control animals (102, 2
or inhibited by pentobarbitor
they do not affect ACTH secret
into the pituitary gland in viv
pituitary tissue in vitro (37).
Until the pure synthetic h inhibited by pentobarbitone/morphine $(205a)$, and mey do not affect ACTH secretion either when injected due to the pituitary gland in vivo (109) or when added to the tuitary tissue in vitro (37) . and Until the pure s

they do not affect ACTH secretion either when injected due into the pituitary gland in vivo (109) or when added to the pituitary tissue in vitro (37). and Until the pure synthetic hormone is available it is ges unlikely th into the pituitary gland in vivo (109) or when adder
pituitary tissue in vitro (37).
Until the pure synthetic hormone is available is
unlikely that any competitive antagonists to CRF wil
found. The ability of corticosteroi pituitary tissue in vitro (37). and in the pure synthetic hormone is available it is get unlikely that any competitive antagonists to CRF will be and found. The ability of corticosteroids to act as physiolog-celler antagon Until the pure synthetic hormone is available it is gualikely that any competitive antagonists to CRF will be a
found. The ability of corticosteroids to act as physiolog-
ical antagonists of CRF has already been discussed unlikely that any competitive antagonists to CRF will be
found. The ability of corticosteroids to act as physiolog-
ical antagonists of CRF has already been discussed. The
actions of CRF at the pituitary level are also inh found. The ability of corticosteroids to act as physiolog-

ical antagonists of CRF has already been discussed. The

actions of CRF at the pituitary level are also inhibited

thy substance P (138). Substance P is present ical antagonists of CRF has already been discussed. The actions of CRF at the pituitary level are also inhibited by substance P (138). Substance P is present in the hypothalamus in relatively high concentrations and thus i actions of CRF at the pituitary level are also inhibited
by substance P (138). Substance P is present in the
hypothalamus in relatively high concentrations and thus
it is possible, if it enters the hypophysial portal vess by substance P (hypothalamus in it is possible, if it that it may act as inhibiting factor. Expossible, if it checks the hypophysial portal vessels,
at it may act as a physiological corticotrophin release
hibiting factor.
VII. Pharmacology of Corticotrophin Releasing
Factor

Factor

VII. Pharmacology of Corticotrophin Releasing
Factor
The secretion of corticotrophin releasing factor is read-
vevoked-by-minor stressful stimuli, e.g. inhalation of **VII. Pharmacology of Corticotrophin Releasing**

Factor

The secretion of corticotrophin releasing factor is read-

ily evoked by minor stressful stimuli, e.g. inhalation of wether vapour. Many substances are capable of b Factor Factor $\frac{1}{2}$ and $\frac{1}{2}$ are secretion of corticotrophin releasing factor is read-
ily evoked by minor stressful stimuli, e.g. inhalation of wether vapour. Many substances are capable of blocking references t Factor
The secretion of corticotrophin releasing factor is read-
ily evoked by minor stressful stimuli, e.g. inhalation of
wether vapour. Many substances are capable of blocking
the response to specific stimuli; for exampl The secretion of corticotrophin releasing factor is read-
ily evoked by minor stressful stimuli, e.g. inhalation of
ether vapour. Many substances are capable of blocking
reading the response to specific stimuli; for exampl ily evoked by minor stressful stimuli, e.g. inhalation of ether vapour. Many substances are capable of blocking the response to specific stimuli; for example, the release of CRF that occurs in response to insulin or histam ether vapour. Many substances are capable of blocking
the response to specific stimuli; for example, the release
of CRF that occurs in response to insulin or histamine is
prevented by pretreatment with glucose or promethaz the response to specific stimuli; for example, the release of CRF that occurs in response to insulin or histamine is prevented by pretreatment with glucose or promethazine respectively. However, there are only a few drugs of CRF that occurs in response to insulin or histamine is suprevented by pretreatment with glucose or promethazine were respectively. However, there are only a few drugs that do abolish the secretion of CRF in response to prevented by pretreatment with glucose or promethazine wespectively. However, there are only a few drugs that dabolish the secretion of CRF in response to *all* stressful m stimuli by inhibiting, either directly or indirec respectively. However, there are only a few drugs that
abolish the secretion of CRF in response to *all* stressful
stimuli by inhibiting, either directly or indirectly, its
release from the hypothalamus. The drugs that hav abolish the secretion of CRF in response to all stressful
stimuli by inhibiting, either directly or indirectly, its
release from the hypothalamus. The drugs that have (
been most widely studied in this respect are essenti stimuli by inhibiting, either directly or indirectly, its Frelease from the hypothalamus. The drugs that have (been most widely studied in this respect are essentially phose that have been employed to prevent the secretion release from the hypothalamus. The drugs that have
been most widely studied in this respect are essential
those that have been employed to prevent the secretic
of endogenous CRF in animals used for the assay of th
hypothal been most widely studied in this respect are essentially pine those that have been employed to prevent the secretion findin of endogenous CRF in animals used for the assay of this mittee hypothalamic hormone, i.e. reserpin

ELEASING FACTOR
the effects of these drugs on the production of cortico
phin releasing factor are considered. ELEASING FACTOR
the effects of these drugs on the proc
phin releasing factor are considered. *A. Reserpine*
A. Reserpine
A. Reserpine
A. single injerging

in releasing factor are considered.

Reserpine

A single injection of reserpine evokes a prolonged

persecretion of ACTH (6, 67, 129, 225, 275, 287), the A. Reserpine
A single injection of reserpine evokes a prolonged
hypersecretion of ACTH (6, 67, 129, 225, 275, 287), the
duration of which depends upon both the dose and the A. Reserpine
A single injection of reserpine evokes a prolonged
hypersecretion of ACTH (6, 67, 129, 225, 275, 287), the
duration of which depends upon both the dose and the
route of administration. The mechanism by which r A single injection of reserpine evokes a prolonge
hypersecretion of ACTH (6, 67, 129, 225, 275, 287), the
duration of which depends upon both the dose and the
route of administration. The mechanism by which rese
pine induc A single injection of reserpine evokes a prolonged
hypersecretion of ACTH (6, 67, 129, 225, 275, 287), the
duration of which depends upon both the dose and the
route of administration. The mechanism by which reser-
pine in hypersecretion of ACTH (6, 67, 129, 225, 275, 287), the
duration of which depends upon both the dose and the
route of administration. The mechanism by which reser-
pine induces this response is not clear. Reserpine causes
 duration of which depends upon both the dose and the
route of administration. The mechanism by which reser-
pine induces this response is not clear. Reserpine causes
marked decreases in the concentrations of 5-HT, nor-
adr route of administration. The mechanism by which respine induces this response is not clear. Reserpine cau marked decreases in the concentrations of 5-HT, n adrenaline, and dopamine in the central nervous syst (23, 135) by pine induces this response is not clear. Reserpine causes
marked decreases in the concentrations of 5-HT, nor-
adrenaline, and dopamine in the central nervous system
 $(23, 135)$ by blocking the Mg^{++} -ATP-dependent uptak marked decreases in the concentrations of 5-HT, nor-
adrenaline, and dopamine in the central nervous system
(23, 135) by blocking the Mg^{++} -ATP-dependent uptake-
storage mechanism in the intraneuronal amine granules
(56 adrenaline, and dopamine in the central nervous syster $(23, 135)$ by blocking the Mg^{++} -ATP-dependent uptake storage mechanism in the intraneuronal amine granule (56) . Since it is widely believed that central noradre (23, 135) by blocking the Mg⁺⁺-ATP-dependent uptakestorage mechanism in the intraneuronal amine granules (56). Since it is widely believed that central noradrenergic neurones inhibit (41, 228–230, 271, 272) and that 5-h storage mechanism in the intraneuronal amine granul (56). Since it is widely believed that central noradrenerg
neurones inhibit (41, 228–230, 271, 272) and that 5-h
droxytryptaminergic nervous pathways inhibit (243, 26
276 (56). Since it is widely believed that central noradrener,
neurones inhibit (41, 228–230, 271, 272) and that 5-b
droxytryptaminergic nervous pathways inhibit (243, 2
276, 277, 282) and stimulate (41, 141, 160, 162) the se neurones inhibit (41, 228–230, 271, 272) and that 5-hy-
droxytryptaminergic nervous pathways inhibit (243, 267,
276, 277, 282) and stimulate (41, 141, 160, 162) the secre-
tion of CRF, it is probable that the alterations i droxytryptaminergic nervous pathways inhibit (243, 267, 276, 277, 282) and stimulate (41, 141, 160, 162) the secretion of CRF, it is probable that the alterations in availability of these monoamines are associated with the 276, 277, 282) and stimulate (41, 141, 160, 162) the secretion of CRF, it is probable that the alterations in availability of these monoamines are associated with the effects of reserpine on pituitary adrenocortical activi tion of CRF, it is probable that the alterations in availability of these monoamines are associated with the effects of reserpine on pituitary adrenocortical activity. Several groups have shown that CRF release is related bility of these monoamines are associated with the effects
of reserpine on pituitary adrenocortical activity. Several
groups have shown that CRF release is related indirectly
to brain monoamine levels (22, 287), For exampl groups have shown that CRF release is related indirectly
to brain monoamine levels $(22, 287)$, For example, Martel
et al. (177) demonstrated that treatment of rats with a
monoamine oxidase inhibitor blocked the reserpi groups have shown that CRF release is related indirectly
to brain monoamine levels (22, 287), For example, Martel
et al. (177) demonstrated that treatment of rats with a
monoamine oxidase inhibitor blocked the reserpine-in to brain monoamine levels (22, 287), For example, Martel
et al. (177) demonstrated that treatment of rats with a
monoamine oxidase inhibitor blocked the reserpine-in-
duced depletion of brain monoamines and prevented
the h et al. (177) demonstrated that treatment of rats with a monoamine oxidase inhibitor blocked the reserpine-in-
duced depletion of brain monoamines and prevented
the hypothalamo-pituitary-adrenocorticotrophic activity
and se monoamine oxidase inhibitor blocked the reserpine-in-
duced depletion of brain monoamines and prevented
the hypothalamo-pituitary-adrenocorticotrophic activity
and sedative effects evoked by the alkaloid. They sug-
gested and sedative effects evoked by the alkaloid. They suggested that the actions of the drug on the HPA system are an integral part of its pharmacological effects on the central nervous system and not the result of direct acthe hypothalamo-pituitary-adrenocorticotrophic activity
and sedative effects evoked by the alkaloid. They sug-
gested that the actions of the drug on the HPA system
are an integral part of its pharmacological effects on th and sedative effects evoked by the alkaloid. They suggested that the actions of the drug on the HPA system are an integral part of its pharmacological effects on the central nervous system and not the result of direct acti gested that the actions of the drug on the HPA system
are an integral part of its pharmacological effects on the
central nervous system and not the result of direct ac-
tions on the adenohypophysis. It is not yet clear whe are an integral part of its pharmacological effects on the central nervous system and not the result of direct actions on the adenohypophysis. It is not yet clear whether the reserpine-induced discharge of CRF is related t central nervous system and not the result of direct actions on the adenohypophysis. It is not yet clear whether
the reserpine-induced discharge of CRF is related to
changes in brain noradrenaline, 5-HT, or both. It seems
u the reserpine-induced discharge of CRF is related to changes in brain noradrenaline, 5-HT, or both. It seems unlikely that reserpine exerts its effects by reducing the tonic inhibitory noradrenergic input to the hypothalam the reserpine-induced discharge of CRF is related to changes in brain noradrenaline, 5-HT, or both. It seems unlikely that reserpine exerts its effects by reducing the tonic inhibitory noradrenergic input to the hypothala changes in brain noradrenaline, 5-HT, or both. It seems
unlikely that reserpine exerts its effects by reducing the
tonic inhibitory noradrenergic input to the hypothalamus
since rats pretreated with α -methyl-paratyrosi unlikely that reserpine exerts its effects by reducing the tonic inhibitory noradrenergic input to the hypothalamus since rats pretreated with α -methyl-paratyrosine (a drug that selectively inhibits tyrosine hydroxylas tonic inhibitory noradrenergic input to the hypothalamus
since rats pretreated with α -methyl-paratyrosine (a drug
that selectively inhibits tyrosine hydroxylase) respond
normally to reserpine. On the basis of these fin that selectively inhibits tyrosine hydroxylase) respond
normally to reserpine. On the basis of these findings
Martel et al. (177) suggested that reserpine exerts its normally to reserpine. On the basis of these findings normally to reserpine. On the basis of these findings
Martel et al. (177) suggested that reserpine exerts its
effects on CRF secretion by actions on central inhibitory
5-hydroxytryptaminergic pathways but convincing evi-
d Martel et al. (177) suggested that reserpine exerts its
effects on CRF secretion by actions on central inhibitory
5-hydroxytryptaminergic pathways but convincing evi-
dence for this hypothesis has not been forthcoming. It
 (bb). Since it witely believed that central not
accretise on the system and the system of the system of the system of CRF, as
271, 272) and thin (243, 267, 272) and thin (243, 267, 276) and structions in a
value (41, 141, dence for this hypothesis has not been forthcoming. It
was anticipated that direct evidence that the actions of
reserpine are related to changes in cerebral 5-HT would
be obtained by the use of parachlorophenylalanine (a
s dence for this hypothesis has not been forthcoming. It
was anticipated that direct evidence that the actions of
reserpine are related to changes in cerebral 5-HT would
be obtained by the use of parachlorophenylalanine (a
s was anticipated that direct evidence that the actions of
reserpine are related to changes in cerebral 5-HT would
be obtained by the use of parachlorophenylalanine (a
substance that depletes the brain of the indoleamine
wit reserpine are related to changes in cerebral 5-HT would
be obtained by the use of parachlorophenylalanine (a
substance that depletes the brain of the indoleamine
without affecting the concentrations of noradrenaline or
dop be obtained by the use of parachlorophenylalanine (a substance that depletes the brain of the indolearmine without affecting the concentrations of noradrenaline or dopamine). However, this drug is not specific, and simulta substance that depletes the brain of the indoleamine
without affecting the concentrations of noradrenaline or
dopamine). However, this drug is not specific, and si-
multaneous fluctuations in the concentrations of brain 5without affecting the concentrations of noradrenaline dopamine). However, this drug is not specific, and a multaneous fluctuations in the concentrations of brain HT, noradrenaline, and dopamine have been describe (188, 262 dopamine). However, this drug is not specific, and si-
multaneous fluctuations in the concentrations of brain 5-
HT, noradrenaline, and dopamine have been described
(188, 262, 285). The interpretation of the effects of res multaneous fluctuations in the concentrations of bra
HT, noradrenaline, and dopamine have been descreent (188, 262, 285). The interpretation of the effects of r
pine on CRF secretion are further complicated by
finding that HT, noradrenaline, and dopamine have been described (188, 262, 285). The interpretation of the effects of reserpine on CRF secretion are further complicated by the finding that the alkaloid also influences other neurotrans (188, 262, 285). The interpretation of the effects of reserpine on CRF secretion are further complicated by the finding that the alkaloid also influences other neurotransmitter substances implicated in the regulation of i pine on CRF secretion are further complicated by the finding that the alkaloid also influences other neurotransmitter substances implicated in the regulation of its secretion. Reserpine has been reported to increase the co

PHARMACOLOGICAL REVIEWS

aspet

266
to deplete the brain of GABA (11), both of which may am
lead to enhanced CRF production. due 266
to deplete the brain of GABA (1)
lead to enhanced CRF production.
The hypothalamo-pituitary-adi

BUCKINGHA
to deplete the brain of GABA (11), both of which may am
lead to enhanced CRF production. due
The hypothalamo-pituitary-adrenocorticotrophic re- in t
sponse to a single injection of reserpine is reduced and pin
ul to deplete the brain of GABA (11), both of which may lead to enhanced CRF production.
The hypothalamo-pituitary-adrenocorticotrophic response to a single injection of reserpine is reduced and lultimately disappears if the lead to enhanced CRF production.
The hypothalamo-pituitary-adrenocorticotrophic response to a single injection of reserpine is reduced and
ultimately disappears if the injections are repeated at
daily intervals (129, 150, The hypothalamo-pituitary-adrenocorticotrophic re-
sponse to a single injection of reserpine is reduced and
ultimately disappears if the injections are repeated at
widaily intervals (129, 150, 286). Furthermore, the stress sponse to a single injection of reserpine is reduced and ultimately disappears if the injections are repeated at daily intervals (129, 150, 286). Furthermore, the stress-
induced activity of the system is also inhibited on ultimately disappears if the injections are repeated at v
daily intervals (129, 150, 286). Furthermore, the stress-
induced activity of the system is also inhibited once
preserpine-adaptation is achieved (129, 152, 173, 28 daily intervals (129, 150, 286). Furthermore, the stress-
induced activity of the system is also inhibited once
reserpine-adaptation is achieved (129, 152, 173, 286).
Several authors have attempted to explain this inhibiti induced activity of the system is also inhibited of reserpine-adaptation is achieved (129, 152, 173, 2
Several authors have attempted to explain this inhibit
but the precise mechanism whereby it is effected is
understood. reserpine-adaptation is achieved (129, 152, 1
Several authors have attempted to explain this i
but the precise mechanism whereby it is effect
understood. The observation that rats bearing
lamic lesions exhibit a delayed hy Several authors have attempted to explain this inhibition c
but the precise mechanism whereby it is effected is not
inderstood. The observation that rats bearing hypotha-
lamic lesions exhibit a delayed hypothalamo-pituit but the precise mechanism whereby it is effected is not understood. The observation that rats bearing hypothalamic lesions exhibit a delayed hypothalamo-pituitary-
adrenocorticotrophic response to stress (25, 26) prompted
 understood. The observation that rats bearing hypotha-
lamic lesions exhibit a delayed hypothalamo-pituitary-
adrenocorticotrophic response to stress (25, 26) prompted
the suggestion that the apparent inhibition of CRF selamic lesions exhibit a delayed hypothalamo-pituitary-
adrenocorticotrophic response to stress (25, 26) prompted
the suggestion that the apparent inhibition of CRF se-
cretion in rats that had received prolonged reserpine
 adrenocorticotrophic response to stress (25, 26) prompted
the suggestion that the apparent inhibition of CRF se-
cretion in rats that had received prolonged reserpine
treatment is due to an alteration in the time-course of the suggestion that the apparent inhibition of CRF secretion in rats that had received prolonged reserpine hibit
treatment is due to an alteration in the time-course of plet
the response. This seems unlikely since Vellucci cretion in rats that had received prolonged reserpine
treatment is due to an alteration in the time-course of
the response. This seems unlikely since Vellucci (275)
found no evidence of increased ACTH secretion up to 40
mi treatment is due to an alteration in the time-course of pl
the response. This seems unlikely since Vellucci (275) va
found no evidence of increased ACTH secretion up to 40 fu
minutes after the final injection of reserpine. the response. This seems unlikely since Vellucci (275) vario
found no evidence of increased ACTH secretion up to 40 funct
minutes after the final injection of reserpine. Kitay et al. simul
 (152) reported that repeated found no evidence of increased ACTH secretion up to 40 funct
minutes after the final injection of reserpine. Kitay et al. simul
(152) reported that repeated injections of reserpine cause respo
a sustained release of ACTH minutes after the final injection of reserpine. Kitay et al. sin (152) reported that repeated injections of reserpine cause res a sustained release of ACTH and a fall in pituitary ACTH mecontent. They proposed that the re (152) reported that repeated injections of reserpine cause
a sustained release of ACTH and a fall in pituitary ACTH
content. They proposed that the reduction in ACTH
content would diminish the ability of the pituitary glan a sustained release of ACTH and a fall in pituitary ACTH
content. They proposed that the reduction in ACTH
content would diminish the ability of the pituitary gland
to respond to the CRF secreted in response to an addi-
ti content. They proposed that the reduction in ACTH content would diminish the ability of the pituitary gland B .
to respond to the CRF secreted in response to an additional stress. However, there are convincing reports th content would diminish the ability of the pituitary gland
to respond to the CRF secreted in response to an addi-
tional stress. However, there are convincing reports that
show that a fall in pituitary ACTH content cannot b to respond to the CRF secreted in response to an additional stress. However, there are convincing reports that show that a fall in pituitary ACTH content cannot be correlated with an inability to respond to stress (123, 27 show that a fall in pituitary ACTH content cannot be correlated with an inability to respond to stress (123, 273). Moreover, Hodges and Vellucci (129) found that the inhibition of ACTH release after adaptation to reser-
pi show that a fall in pituitary ACTH content cannot be chreated with an inability to respond to stress (123, cer
273). Moreover, Hodges and Vellucci (129) found that the inhibition of ACTH release after adaptation to reser-
 correlated with an inability to respond to stress (123, 273). Moreover, Hodges and Vellucci (129) found that the inhibition of ACTH release after adaptation to reserpine occurs at a time when the pituitary stores are the s 273). Moreover, Hodges and Vellucci (129) found that the inhibition of ACTH release after adaptation to reservine occurs at a time when the pituitary stores are the same as those in the corresponding vehicle-treated contro the inhibition of ACTH release after adaptation to reser-
pine occurs at a time when the pituitary stores are the
same as those in the corresponding vehicle-treated con-
trols, while others (273) showed that the adrenocort pine occurs at a time when the pituitary stores are the Easame as those in the corresponding vehicle-treated controls, while others (273) showed that the adrenocortical to response to aspirin or histamine was normal in rat same as those in the corresponding vehicle-treated controls, while others (273) showed that the adrenocortical to response to aspirin or histamine was normal in rats given an a single large dose of reserpine at a time when trols, while others (273) showed that the adrenocortical
response to aspirin or histamine was normal in rats given
a single large dose of reserpine at a time when the
pituitary ACTH stores must have been depleted. The
poss response to aspirin or histamine was norm
a single large dose of reserpine at a tipituitary ACTH stores must have been
possibility has been raised that the rese
suppression of hypothalamo-pituitary-
trophic activity is due a single large dose of reserpine at a time when the as the sedative effects of the drug. However, experiments pituitary ACTH stores must have been depleted. The in which corticotrophin was measured directly show possibilit pituitary ACTH stores must have been depleted. The in
possibility has been raised that the reserpine-induced cla
suppression of hypothalamo-pituitary-adrenocortico-
cortophic activity is due to a "feedback" effect exerted possibility has been raised that the reserpine-indu
suppression of hypothalamo-pituitary-adrenocort
trophic activity is due to a "feedback" effect exerted
the elevated levels of corticosteroids previously evo
by the drug (trophic activity is due to a "feedback" effect exerted by
the elevated levels of corticosteroids previously evoked
by the drug (93). However, although very high, nonphys-
iological doses of corticosteroids inhibit the stre trophic activity is due to a "feedback" effect exerted by before the elevated levels of corticosteroids previously evoked chlow by the drug (93). However, although very high, nonphys- by cological doses of corticosteroids the elevated levels of corticosteroids previously evoked compared by the drug (93). However, although very high, nonphysiological doses of corticosteroids inhibit the stress-induced release of CRF and do so more effectivel by the drug (93). However, although very high, nonphy
iological doses of corticosteroids inhibit the stress-i
duced release of CRF and do so more effectively 18 to
hours after administration than during the first few hou
(iological doses of corticosteroids inhibit the stress-in-
duced release of CRF and do so more effectively 18 to 20
hours after administration than during the first few hours
persist for (12), it is unlikely that any "feedb duced release of CRF and do so more effectively 18 to 20
hours after administration than during the first few hours
(12), it is unlikely that any "feedback" effect from endog-
enous corticosteroids would be so effective or hours after administration than during the first few hours (12), it is unlikely that any "feedback" effect from endogenous corticosteroids would be so effective or persist for so long. The bulk of the evidence available in (12), it is unlikely that any "feedback" effect from endog-
enous corticosteroids would be so effective or persist for
so long. The bulk of the evidence available indicates that,
eike its stimulatory effects, the inhibito enous corticosteroids would be so effective or persist for
so long. The bulk of the evidence available indicates that, eff
like its stimulatory effects, the inhibitory actions of re-
serpine are exerted at the level of the so long. The bulk of the evidence available indicates that, like its stimulatory effects, the inhibitory actions of reserpine are exerted at the level of the hypothalamus or on centres higher in the brain. Reserpine reduce like its stimulatory effects, the inhibitory actions of serpine are exerted at the level of the hypothalamus
on centres higher in the brain. Reserpine reduces
corticotrophin releasing activity of the hypothalan
(16) probab Serpine are exerted at the level of the hypothalamus or
on centres higher in the brain. Reserpine reduces the
corticotrophin releasing activity of the hypothalamus
(16) probably either by altering the balance of stimula-
t on centres higher in the brain. Reserpine reduces the corticotrophin releasing activity of the hypothalamus (16) probably either by altering the balance of stimulatory and inhibitory nervous inputs to the CRF neurones or b corticotrophin releasing activity of the hypothalamus cholinomimetic agents (257), increases the biosynthesis (16) probably either by altering the balance of stimula-
of acetylcholine (268), and raises the concentration of (16) probably either by altering the balance of stime tory and inhibitory nervous inputs to the CRF neuro or by interfering with the CRF storage mechanism. Meroups favour the former hypothesis since, despite report to the tory and inhibitory nervous inputs to the CRF neuron
or by interfering with the CRF storage mechanism. Me
groups favour the former hypothesis since, despite of
report to the contrary (252), it appears that the reserpin
ind or by interfering with the CRF storage mechanism. Mogroups favour the former hypothesis since, despite of report to the contrary (252), it appears that the reserpined induced decrease in hypothalamic corticotrophin releasi

amine content. Since noradrenaline inhibits CRF proin this respect $(29, 81, 141)$, it is unlikely that the reser-FIAM
amine content. Since noradrenaline inhibits CRF production $(41, 68, 80, 81, 229)$ and dopamine is ineffective
in this respect $(29, 81, 141)$, it is unlikely that the reser-
pine-induced inhibition of CRF secretion amine content. Since noradrenaline inhibits CRF production (41, 68, 80, 81, 229) and dopamine is ineffective in this respect (29, 81, 141), it is unlikely that the reserpine-induced inhibition of CRF secretion is associate amine content. Since noradrenaline inhibits CRF production (41, 68, 80, 81, 229) and dopamine is ineffective
in this respect (29, 81, 141), it is unlikely that the reser-
pine-induced inhibition of CRF secretion is associa duction (41, 68, 80, 81, 229) and dopamine is ineffective
in this respect (29, 81, 141), it is unlikely that the reser-
pine-induced inhibition of CRF secretion is associated
with the fall in brain catecholamines. However, in this respect $(29, 81, 141)$, it is unlikely that the reserpine-induced inhibition of CRF secretion is associated with the fall in brain catecholamines. However, the possibility that the stimulatory effects of 5-HT on pine-induced inhibition of CRF secretion is associated
with the fall in brain catecholamines. However, the pos-
sibility that the stimulatory effects of 5-HT on CRF
production are impaired or even abolished as a result of
 with the fall in brain catecholamines. However, the possibility that the stimulatory effects of 5-HT on CRF production are impaired or even abolished as a result of the decrease in the brain content of the indoleamine cann sibility that the stimulatory effects of 5-HT on CRF
production are impaired or even abolished as a result of
the decrease in the brain content of the indoleamine
cannot be disregraded. It appears that reserpine exerts
its production are impaired or even abolished as a result of
the decrease in the brain content of the indoleamine
cannot be disregraded. It appears that reserpine exerts
its effects on CRF release predominantly by depleting
br the decrease in the brain content of the indolean
cannot be disregraded. It appears that reserpine ex
its effects on CRF release predominantly by deple
brain monoamines that are involved in the control o
production. This a cannot be disregraded. It appears that reserpine exerts
its effects on CRF release predominantly by depleting
brain monoamines that are involved in the control of its
production. This action may take place at the hypothalits effects on CRF release predominantly by depleting
brain monoamines that are involved in the control of its
production. This action may take place at the hypothal-
amus or at centres higher in the brain. As a result, CR brain monoamines that are involved in the control of its
production. This action may take place at the hypothal-
amus or at centres higher in the brain. As a result, CRF
production is initially stimulated and subsequently production. This action may take place at the hypothal-
amus or at centres higher in the brain. As a result, CRF
production is initially stimulated and subsequently in-
hibited as monoamine stores become progressively de-
 amus or at centres higher in the brain. As a result, CRF
production is initially stimulated and subsequently in-
hibited as monoamine stores become progressively de-
pleted. However, it is only when the turnover rates of t production is initially stimulated and subsequently in-
hibited as monoamine stores become progressively de-
pleted. However, it is only when the turnover rates of the
various central neurotransmitter substances and the
fu hibited as monoamine stores become progressively de-
pleted. However, it is only when the turnover rates of the
various central neurotransmitter substances and the
functional activity of the hypothalamus are assessed
simul pleted. However, it is only when the turnover rates of the various central neurotransmitter substances and the functional activity of the hypothalamus are assessed simultaneously that it will be possible to ascribe the res mechanisms.

B. *Chlorpromazine*

sponse to specific effects on brain monoamine storage
echanisms.
Chlorpromazine
Although there are some reports to the contrary (148,
1), it is generally agreed that a single injection of mechanisms.

171), it is generally agreed that a single injection of

171), it is generally agreed that a single injection of

chlorpromazine causes a marked rise in the plasma con-B. Chlorpromazine
Although there are some reports to the contrary (148,
171), it is generally agreed that a single injection of
chlorpromazine causes a marked rise in the plasma con-
centrations of ACTH and corticosterone B. Chlorpromazine

Although there are some reports to the contrary (1

171), it is generally agreed that a single injection

chlorpromazine causes a marked rise in the plasma c

centrations of ACTH and corticosterone and c Although there are some reports to the contrary (14
171), it is generally agreed that a single injection
chlorpromazine causes a marked rise in the plasma content
tant fall in the content of CRF and ACTH in the hypo-
thala chlorpromazine causes a marked rise in the plasma concentrations of ACTH and corticosterone and concomitant fall in the content of CRF and ACTH in the hypothalamus and anterior pituitary gland respectively (16).
Early stud chlorpromazine causes a marked rise in the plasma concentrations of ACTH and corticosterone and concom
tant fall in the content of CRF and ACTH in the hyperchalamus and anterior pituitary gland respectively (16
Early studi centrations of ACTH and corticosterone and concomitant fall in the content of CRF and ACTH in the hypothalamus and anterior pituitary gland respectively (16).
Early studies, in which indirect indices of ACTH secretion were tant fall in the content of CRF and ACTH in the hypothalamus and anterior pituitary gland respectively (16).
Early studies, in which indirect indices of ACTH secretion were used, suggested that the hypothalamic response
to thalamus and anterior pituitary gland respectively (16).
Early studies, in which indirect indices of ACTH secre-
tion were used, suggested that the hypothalamic response
to chlorpromazine, like that to reserpine, is prolon Early studies, in which indirect indices of ACTH secretion were used, suggested that the hypothalamic response
to chlorpromazine, like that to reserpine, is prolonged,
and one group (255) proposed that it persisted for as tion were used, suggested that the hypothalamic response
to chlorpromazine, like that to reserpine, is prolonged,
and one group (255) proposed that it persisted for as long
as the sedative effects of the drug. However, ex to chlorpromazine, like that to reserpine, is prolonged, and one group (255) proposed that it persisted for as long as the sedative effects of the drug. However, experiments in which corticotrophin was measured directly sh and one group (255) proposed that it persisted for as long
as the sedative effects of the drug. However, experiments
in which corticotrophin was measured directly show
clearly that this is not the case and that the plasma
 as the sedative effects of the drug. However, experiments
in which corticotrophin was measured directly show
clearly that this is not the case and that the plasma
concentration of ACTH returns to normal some time
before th in which corticotrophin was measured directly show
clearly that this is not the case and that the plasma
concentration of ACTH returns to normal some time
before the sedative effects disappear. The actions of
chlorpromazin clearly that this is not the case and that the plasma
concentration of ACTH returns to normal some time
before the sedative effects disappear. The actions of
chlorpromazine on CRF secretion are probably caused
by changes i concentration of ACTH returns to normal some time
before the sedative effects disappear. The actions of
chlorpromazine on CRF secretion are probably caused
by changes in neurotransmitter activity in the brain. The
drug in before the sedative effects disappear. The actions of chlorpromazine on CRF secretion are probably caused by changes in neurotransmitter activity in the brain. The drug interferes with catecholamine neurotransmission by ca chlorpromazine on CRF secretion are probably caused
by changes in neurotransmitter activity in the brain. The
drug interferes with catecholamine neurotransmission by
causing postsynaptic blockade of the receptors for do-
p by changes in neurotransmitter activity in the brain. The
drug interferes with catecholamine neurotransmission by
causing postsynaptic blockade of the receptors for do-
pamine and noradrenaline (4, 49). Since it is believe drug interferes with catecholamine neurotransmission by
causing postsynaptic blockade of the receptors for do-
pamine and noradrenaline (4, 49). Since it is believed
that noradrenergic pathways inhibit the secretion of
CRF causing postsynaptic blockade of the receptors for do-
pamine and noradrenaline (4, 49). Since it is believed
that noradrenergic pathways inhibit the secretion of
CRF, it is tempting to postulate that the stimulatory
effec pamine and noradrenaline (4, 49). Since it is believed
that noradrenergic pathways inhibit the secretion of
CRF, it is tempting to postulate that the stimulatory
effects of chlorpromazine on ACTH secretion are due
simply t that noradrenergic pathways inhibit the secretion of CRF, it is tempting to postulate that the stimulatory effects of chlorpromazine on ACTH secretion are due simply to its actions on adrenoceptors (16, 291). However, chlo CRF, it is tempting to postulate that the stimulatory
effects of chlorpromazine on ACTH secretion are due
simply to its actions on adrenoceptors $(16, 291)$. However,
chlorpromazine also increases the turnover (15) and effects of chlorpromazine on ACTH secretion are due
simply to its actions on adrenoceptors (16, 291). However,
chlorpromazine also increases the turnover (15) and syn-
thesis (14) of 5-HT, antagonises the actions of variou simply to its actions on adrenoceptors (16, 291). However,
chlorpromazine also increases the turnover (15) and syn-
thesis (14) of 5-HT, antagonises the actions of various
cholinomimetic agents (257), increases the biosynt chlorpromazine also increases the turnover (15) and synthesis (14) of 5-HT, antagonises the actions of various cholinomimetic agents (257), increases the biosynthesis of acetylcholine (268), and raises the concentration of thesis (14) of 5-HT, antagonises the actions of various
cholinomimetic agents (257), increases the biosynthesis
of acetylcholine (268), and raises the concentration of
GABA in the cerebellum and the cortex (116). Thus the
 cholinomimetic agents (257), increases the biosynthesis
of acetylcholine (268), and raises the concentration of
GABA in the cerebellum and the cortex (116). Thus the
effects of chlorpromazine on CRF secretion are probably
 of acetylcholine (268), and raises the concentration GABA in the cerebellum and the cortex (116). The effects of chlorpromazine on CRF secretion are prothe result of alterations in the balance of stimulator inhibitory sign GABA in the cerebellum and the cortex (116). Thus the
effects of chlorpromazine on CRF secretion are probably
the result of alterations in the balance of stimulatory and
inhibitory signals from cholinergic and 5-hydroxytry effects of chlorproma:
the result of alteration
inhibitory signals fro
taminergic neurones
neurones respectively

CORTICOTROPHIN RELEASING FACTOR 267

Downloaded from pharmrev.aspetjournals.org at Thammasart University on December 8, 2012

inhibition of the hypothalamo-pituitary-adrenocortico-COI
Several groups have suggested that a s
of chlorpromazine causes partial (103) or
inhibition of the hypothalamo-pituitary-
trophic response to stress. These findings Several groups have suggested that a single injection vio
of chlorpromazine causes partial (103) or total (10, 171) act
inhibition of the hypothalamo-pituitary-adrenocortico-
theoremonic response to stress. These findings Several groups have suggested that a single injectic
of chlorpromazine causes partial (103) or total (10, 17
inhibition of the hypothalamo-pituitary-adrenocortic
trophic response to stress. These findings have not bee
conf of chlorpromazine causes partial (103) or total (10, 171)
inhibition of the hypothalamo-pituitary-adrenocortico-
trophic response to stress. These findings have not been
confirmed. Hodges and Witek (133) showed that chlorinhibition of the hypothalamo-pituitary-adrenocortico-
trophic response to stress. These findings have not been
enfirmed. Hodges and Witek (133) showed that chlor-
promazine-treated rats respond to stress with a normal
per trophic response to stress. These findings have not been
confirmed. Hodges and Witek (133) showed that chlor-
promazine-treated rats respond to stress with a normal
perise in plasma ACTH concentration, thus confirming the
 confirmed. Hodges and Witek (133) showed that chlor-
promazine-treated rats respond to stress with a normal pen
rise in plasma ACTH concentration, thus confirming the pote
earlier findings of Holzbauer and Vogt (134) and O promazine-treated rats respond to stress with a normal
rise in plasma ACTH concentration, thus confirming the
earlier findings of Holzbauer and Vogt (134) and Olling
and de Wied (201). However, there can be no
doubt that c rise in plasma ACTH concentration, thus confirming the earlier findings of Holzbauer and Vogt (134) and Ollir and de Wied (201). However, there can be redoubt that chlorpromazine prevents the stress-induce release of CRF w earlier findings of Holzbauer and Vogt (134) and Olling and de Wied (201) . However, there can be no the doubt that chlorpromazine prevents the stress-induced tirelease of CRF when given to pentobarbitone-treated to ra doubt that chlorpromazine prevents the stress-induced
release of CRF when given to pentobarbitone-treated
rats (201). This interesting drug interaction is discussed
in the following section.
C. Pentobarbitone/Chlorpromazin *C. Pentobarbitonerats (201).* This interesting due in the following section.
C. Pentobarbitone/Chlorpromaxyoneration.
C. Pentobarbitone/Chlorpromaxyoneration

ts (201). This interesting drug interaction is discussed
the following section.
Pentobarbitone/Chlorpromazine
Olling and de Wied (201) were the first to show that
lorpromazine abolishes the hypothalamo-pituitary-adin the following section.
C. Pentobarbitone/Chlorpromazine
Olling and de Wied (201) were the first to
chlorpromazine abolishes the hypothalamo-pit
renocorticotrophic response to stress in rats C. Pentobarbitone/Chlorpromazine
Olling and de Wied (201) were the first to show the
chlorpromazine abolishes the hypothalamo-pituitary
renocorticotrophic response to stress in rats anaestheed with sodium pentobarbitone. T C. *Fentooarouone*/*Churpromazine*

Colling and de Wied (201) were the first to show that

chlorpromazine abolishes the hypothalamo-pituitary-ad-

renocorticotrophic response to stress in rats anaesthe-

pitsed with sod Olling and de Wied (201) were the first to show that
chlorpromazine abolishes the hypothalamo-pituitary-ad-
renocorticotrophic response to stress in rats anaesthe-
tised with sodium pentobarbitone. This observation was
sub chlorpromazine abolishes the hypothalamo-pituitary-ad-
renocorticotrophic response to stress in rats anaesthe-
pitised with sodium pentobarbitone. This observation was
foubsequently confirmed by using both direct and indir renocorticotrophic response to stress in rats anaesthe-
tised with sodium pentobarbitone. This observation was
fous subsequently confirmed by using both direct and indirect
indices of ACTH secretion (133, 241, 290, 291). T tised with sodium pentobarbitone. This observation was followed subsequently confirmed by using both direct and indirect laiding indices of ACTH secretion (133, 241, 290, 291). The tidentechanisms whereby this drug combina subsequently confirmed by using both direct and indirect later indices of ACTH secretion (133, 241, 290, 291). The tidenchanisms whereby this drug combination inhibits the sibstress response are not understood. Several gro indices of ACTH secretion (133, 241, 290, 291). The tidenchanisms whereby this drug combination inhibits the sitess-induced release of CRF but experiments in which Find CTH was determined by bioassay (133) and radioimmechanisms whereby this drug combination inhibits
stress response are not understood. Several groups has
suggested that pentobarbitone anaesthesia prevents
stress-induced release of CRF but experiments in wh
ACTH was deter stress response are not understood. Several groups have
suggested that pentobarbitone anaesthesia prevents the
stress-induced release of CRF but experiments in which
ACTH was determined by bioassay (133) and radioim-
munoa suggested that pentobarbitone anaesthesia prevents the best
ress-induced release of CRF but experiments in which Fir
ACTH was determined by bioassay (133) and radioim-
the munoassay (97) techniques respectively demonstrate ACTH was determined by bioassay (133) and radioim-
munoassay (97) techniques respectively demonstrate are concentration-dependent (159). Secondly, the recent
that pentobarbitone-treated rats respond to stress with demonstr munoassay (97) techniques respectively demonstrate
that pentobarbitone-treated rats respond to stress with
a normal rise in plasma ACTH concentration. Olling and
de Wied (201) and Sevy et al. (241) proposed that pen-
tobar munoassay (97) techniques respectively demonstrat
that pentobarbitone-treated rats respond to stress wit
a normal rise in plasma ACTH concentration. Olling an
de Wied (201) and Sevy et al. (241) proposed that per
tobarbito that pentobarbitone-treated rats respond to stress with de
a normal rise in plasma ACTH concentration. Olling and op
de Wied (201) and Sevy et al. (241) proposed that pen-
tobarbitone prevents the chlorpromazine-induced hy a normal rise in plasma ACTH concentration. Olling
de Wied (201) and Sevy et al. (241) proposed that probarbitone prevents the chlorpromazine-induced
persecretion of CRF but the results of Hodges and W
(133) did not suppor tobarbitone prevents the chlorpromazine-induced hypersecretion of CRF but the results of Hodges and Witek (133) did not support this hypothesis. Since corticotro-
phin release is readily evoked in pentobarbitone/chlor-
pro tobarbitone prevents the chlorpromazine-induced
persecretion of CRF but the results of Hodges and Wi
(133) did not support this hypothesis. Since cortico
phin release is readily evoked in pentobarbitone/ch
promazine-treate persecretion of CRF but the results of Hodges and Wite (133) did not support this hypothesis. Since corticotro
phin release is readily evoked in pentobarbitone/chlor
promazine-treated rats by injection of either hypotha
la (133) did not support this hypothesis. Since corticot phin release is readily evoked in pentobarbitone/chlopromazine-treated rats by injection of either hypot lamic extracts or lysine vasopressin $(165, 241)$ it is predom phin release is readily evoked in pentobarbitone/chlor-
promazine-treated rats by injection of either hypotha-
scilamic extracts or lysine vasopressin (165, 241) it is prob-
able that the drugs exert their inhibitory effec promazine-treated rats by injection of either hypotha-
lamic extracts or lysine vasopressin (165, 241) it is prob-
no
able that the drugs exert their inhibitory effects predom-
intently on the hypothalamus or on centres hi lamic extracts or lysine vasopressin $(165, 241)$ it is probable that the drugs exert their inhibitory effects predominantly on the hypothalamus or on centres higher in the cobrain. According to de Wied (290) pituitary able that the drugs exert their inhibitory effects predominantly on the hypothalamus or on centres higher in the celorain. According to de Wied (290) pituitary function is conormal in pentobarbitone/chlorpromazine-treated inantly on the hypothalamus or on centres higher in the brain. According to de Wied (290) pituitary function i
normal in pentobarbitone/chlorpromazine-treated rat
but other workers have shown a reduction in the ability
of brain. According to de Wied (290) pituitary function is cornormal in pentobarbitone/chlorpromazine-treated rats are
but other workers have shown a reduction in the ability recof pituitary glands from rats treated with this normal in pentobarbitone/chlorpromazine-treated rats are
but other workers have shown a reduction in the ability recoficializing glands from rats treated with this drug com-
bination to secrete ACTH in response to CRF in v but other workers have shown a reduction in the ability rece
of pituitary glands from rats treated with this drug com-
bination to secrete ACTH in response to CRF in vivo the
(M. T. Jones, personal communication) and in vi of pituitary glands from rats treated with this drug combination to secrete ACTH in response to CRF in vivo (M. T. Jones, personal communication) and in vitro (133). This loss of sensitivity is probably due both to direct bination to secrete ACTH in response to CRF in vivo
(M. T. Jones, personal communication) and in vitro
(133). This loss of sensitivity is probably due both to
the trophic drive the trophic drive action the trophic drive ac (M. T. Jones, personal communication) and in vitro spit (133). This loss of sensitivity is probably due both to that direct inhibitory actions of chlorpromazine on the pituior the hypothalamus. Both the hypothalamic CRF di (133). This loss of sensitivity is probably due both to that direct inhibitory actions of chlorpromazine on the pitui-
tary gland (295) and to the removal of the trophic drive adression the hypothalamus. Both the hypothal direct inhibitory actions of chlorpromazine on the pitui-
tary gland (295) and to the removal of the trophic drive
from the hypothalamus. Both the hypothalamic CRF
content and the capacity of the organ to secrete CRF in
vi from the hypothalamus. Both the hypothalamic CRF content and the capacity of the organ to secrete CRF in vitro in response to trophic stimuli are reduced by pentobarbitone/chlorpromazine treatment (133). These effects are from the hypothalamus. Both the hypothalamic CRF diarcontent and the capacity of the organ to secrete CRF in of μ vitro in response to trophic stimuli are reduced by pentable to barbitone/chlorpromazine treatment (133) content and the capacity of the organ to secrete CRF in of μ vitro in response to trophic stimuli are reduced by pen-
tobarbitone/chlorpromazine treatment (133). These ef-
more fects are probably the result of actions vitro in response to trophic stimuli are reduced by pentobarbitone/chlorpromazine treatment (133). These effects are probably the result of actions of the drug on centres higher in the brain rather than direct actions on t to barbitone/chlorpromazine treatment (133). These ef-
fects are probably the result of actions of the drug on
pentres higher in the brain rather than direct actions on
he hypothalamus since the addition of chlorpromazine
 fects are probably the result of actions of the drug on
centres higher in the brain rather than direct actions on
the hypothalamus since the addition of chlorpromazine
to the incubation medium does not affect the secretory centres higher in the brain rather than direct actions on
the hypothalamus since the addition of chlorpromazine
to the incubation medium does not affect the secretory
capacity of hypothalami removed from normal or pen-
tob

Several groups have suggested that a single injection vious section, chlorpromazine influences markedly the of chlorpromazine causes partial (103) or total (10, 171) activity of cholinergic and monoaminergic neurones in in vious section, chlorpromazine influences markedly the LEASING FACTOR
vious section, chlorpromazine influences markedly the
activity of cholinergic and monoaminergic neurones in
the central nervous system. Since such neurones influence the secretion of CRF, it is probable that the effects vious section, chlorpromazine influences markedly the activity of cholinergic and monoaminergic neurones in the central nervous system. Since such neurones influence the secretion of CRF, it is probable that the effects of vious section, chlorpromazine influences markedly the activity of cholinergic and monoaminergic neurones in the central nervous system. Since such neurones influence the secretion of CRF, it is probable that the effects of activity of cholinergic and monoaminergic neurones in the central nervous system. Since such neurones influence the secretion of CRF, it is probable that the effects of the drug are related to these actions. The role of pe the central nervous system. Since such neurones influ-
ence the secretion of CRF, it is probable that the effects
of the drug are related to these actions. The role of
pentobarbitone remains to be explained. Chlorpromazine ence the secretion of CRF, it is probable that the effects of the drug are related to these actions. The role of pentobarbitone remains to be explained. Chlorpromazine potentiates the actions of central depressant drugs (2 of the drug are related to these actions. The role opentobarbitone remains to be explained. Chlorpromazire potentiates the actions of central depressant drugs (2 and, accordingly, it has been proposed that it potentiate "i pentobarbitone remains to be explained. Chlorpromazine
potentiates the actions of central depressant drugs (24)
and, accordingly, it has been proposed that it potentiates
the "inhibitory" effect of pentobarbitone on CRF se potentiates the actions of central depressant drugs (24
and, accordingly, it has been proposed that it potentiate
the "inhibitory" effect of pentobarbitone on CRF secretion
(255, 291). Certainly the two drugs need to be gi and, accordingly, it has been proposed that it potentia
the "inhibitory" effect of pentobarbitone on CRF section (255, 291). Certainly the two drugs need to be give
together to block CRF secretion effectively. They pr
ably tion (255, 291). Certainly the two drugs need to be given
together to block CRF secretion effectively. They prob-
ably act synergistically and reduce the ratio of stimula-
tory and inhibitory impulses controlling the secre CRF. Ably act synergistically and reduce the ratio of stimulatory and inhibitory impulses controlling the secretion of CRF.
 D. Opioids

It has been known for many years that hypothalamo-

It has been known for many years that hypothalamo-
It has been known for many years that hypothalamore.
It has been known for many years that hypothalamore. CRF.
D. Opioids
It has been known for many years that hypothalamo-
pituitary-adrenocorticotrophic activity is influenced pro-
foundly by opiate substances and hence the recent iso-*D. Opioids*
It has been known for many years that hypothalamo-
pituitary-adrenocorticotrophic activity is influenced pro-
foundly by opiate substances and hence the recent iso-
lation and identification of the endogenous Let has been known for many years that hypothalamo-
pituitary-adrenocorticotrophic activity is influenced pro-
foundly by opiate substances and hence the recent iso-
lation and identification of the endogenous opioid pep-
 It has been known for many years that hypothalamo-
pituitary-adrenocorticotrophic activity is influenced pro-
foundly by opiate substances and hence the recent iso-
lation and identification of the endogenous opioid pep-
t pituitary-adrenocorticotrophic activity is influenced profoundly by opiate substances and hence the recent isolation and identification of the endogenous opioid peptides, enkephalins and endorphins, have raised the possibi foundly by opiate substances and hence the recent isolation and identification of the endogenous opioid peptides, enkephalins and endorphins, have raised the possibility that opioid receptors are involved in the control of lation and identification of the endogenous opioid peptides, enkephalins and endorphins, have raised the possibility that opioid receptors are involved in the control of CRF secretion. The actions of the opiate drugs have tides, enkephalins and endorphins, have raised the pos-
sibility that opioid receptors are involved in the control
of CRF secretion. The actions of the opiate drugs have
been the subject of controversy, probably for two re sibility that opioid receptors are involved in the control
of CRF secretion. The actions of the opiate drugs have
been the subject of controversy, probably for two reasons.
Firstly, morphine, the drug most widely employed of CRF secretion. The actions of the opiate drugs have
been the subject of controversy, probably for two reasons.
Firstly, morphine, the drug most widely employed in
these studies, is only a partial agonist and thus its ef Firstly, morphine, the drug most widely employed in Firstly, morphine, the drug most widely employed in
these studies, is only a partial agonist and thus its effects
are concentration-dependent (159). Secondly, the recent
demonstration of the existence of more than one type these studies, is only a partial agonist and thus its effects
are concentration-dependent (159). Secondly, the recent
demonstration of the existence of more than one type of
opioid receptor has raised the possibility that are concentration-dependent (159). Secondly, the recent
demonstration of the existence of more than one type of
opioid receptor has raised the possibility that different
receptors mediate different effects and that the ove demonstration of the existence of more than one type of
opioid receptor has raised the possibility that different
receptors mediate different effects and that the overall
response depends on the balance of stimulated recep opioid receptor has raised the possibility that different
receptors mediate different effects and that the overall
response depends on the balance of stimulated receptors
(284). However, although only indirect indices of C receptors mediate different effects and that the overall
response depends on the balance of stimulated receptors
(284). However, although only indirect indices of CRF
and ACTH secretion have been employed, it is generally
 response depends on the balance of stimulate (284). However, although only indirect indicand ACTH secretion have been employed, it agreed that acute administration of morphiscious animals stimulates hypothalamo-pitunocorti (284). However, although only indirect indices of CRF
and ACTH secretion have been employed, it is generally
agreed that acute administration of morphine to con-
scious animals stimulates hypothalamo-pituitary-adre-
nocort and ACTH secretion have been employed, it is generally agreed that acute administration of morphine to conscious animals stimulates hypothalamo-pituitary-adre-
nocorticotrophic activity. A single injection of morphine
into agreed that acute administration of morphine to conscious animals stimulates hypothalamo-pituitary-adre-
nocorticotrophic activity. A single injection of morphine
into rats causes a fall in the adrenal ascorbic acid con-
c scious animals stimulates hypothalamo-pituitary-adre-
nocorticotrophic activity. A single injection of morphine
into rats causes a fall in the adrenal ascorbic acid con-
centration (21, 84, 198) and a rise in the concentra nocorticotrophic activity. A single injection of morphine
into rats causes a fall in the adrenal ascorbic acid con-
centration (21, 84, 198) and a rise in the concentration of
corticosterone in the plasma (83, 158, 167, 19 into rats causes a fall in the adrenal ascorbic acid c
centration (21, 84, 198) and a rise in the concentration
corticosterone in the plasma (83, 158, 167, 197). Its effe
are antagonised by nalorphine (84). Moreover, opi
r centration (21, 84, 198) and a rise in the concentration of corticosterone in the plasma (83, 158, 167, 197). Its effects are antagonised by nalorphine (84). Moreover, opioid receptor agonists, normorphine and methionine e corticosterone in the plasma (83, 158, 167, 197). Its effects
are antagonised by nalorphine (84). Moreover, opioid
receptor agonists, normorphine and methionine enkeph-
alin (administered intracerebroventricularly), potent are antagonised by nalorphine (84). Moreover, opioid
receptor agonists, normorphine and methionine enkeph-
alin (administered intracerebroventricularly), potentiate
the adrenocortical response to ether stress (87, 88). Dereceptor agonists, normorphine and methionine enkephalin (administered intracerebroventricularly), potentiate
the adrenocortical response to ether stress (87, 88). Despite one report to the contrary (203), it seems unlikel alin (administered intracerebroventricularly), potentiate
the adrenocortical response to ether stress (87, 88). De-
spite one report to the contrary (203), it seems unlikely
that the drugs act directly on either the adrena the adrenocortical response to ether stress (87, 88). Despite one report to the contrary (203), it seems unlikely that the drugs act directly on either the adrenal cortex or the anterior pituitary gland. Opioids do not inf spite one report to the contrary (203), it seems unlikely
that the drugs act directly on either the adrenal cortex
or the anterior pituitary gland. Opioids do not influence
adrenocortical activity in hypophysectomised (84) that the drugs act directly on either the adrenal cortex
or the anterior pituitary gland. Opioids do not influence
adrenocortical activity in hypophysectomised (84) or me-
dian eminence-lesioned (85) rats. Moreover, the se or the anterior pituitary gland. Opioids do not influence
adrenocortical activity in hypophysectomised (84) or me-
dian eminence-lesioned (85) rats. Moreover, the secretion
of ACTH by anterior pituitary tissue in vitro is adrenocortical activity in hypophysectomised (84) or r
dian eminence-lesioned (85) rats. Moreover, the secret
of ACTH by anterior pituitary tissue in vitro is
affected by the addition to the incubation medium
morphine, met dian eminence-lesioned (85) rats. Moreover, the secretion
of ACTH by anterior pituitary tissue in vitro is not
affected by the addition to the incubation medium of
morphine, methionine- or leucine-enkephalin, β -endor-
 of ACTH by anterior pituitary tissue in vitro is not affected by the addition to the incubation medium of morphine, methionine- or leucine-enkephalin, β -endor-
phin, or naloxone (42, 90). However, receptors in the hypo affected by the addition to the incubation medium of morphine, methionine- or leucine-enkephalin, β -endor-
phin, or naloxone (42, 90). However, receptors in the
hypothalamus may be involved. The secretion of CRF by
iso morphine, methionine- or leucine-enkephalin, β -ephin, or naloxone (42, 90). However, receptors is hypothalamus may be involved. The secretion of Clisolated rat hypothalami in vitro is evoked by loventrations of morphin phin, or naloxone (42, 90). However, receptors in the hypothalamus may be involved. The secretion of CRF isolated rat hypothalami in vitro is evoked by low concentrations of morphine, leucine-, and methionine-exhapplin. hypothalamus may be involved. The secretion of CRF by isolated rat hypothalami in vitro is evoked by low concentrations of morphine, leucine-, and methionine-en-
kephalin. β -Endorphin alone does not affect CRF secretio

SUCKINGH
actions of morphine and enkephalin (42). These findings me
suggest that endogenous enkephalins are involved in the the
control of CRF secretion and that their actions are mod- 268
actions of morphine and enkephalin (42). These finding
suggest that endogenous enkephalins are involved in th
control of CRF secretion and that their actions are mod
ulated by endorphin. β -Lipotrophin, the parent actions of morphine and enkephalin (42). These findings m
suggest that endogenous enkephalins are involved in the
control of CRF secretion and that their actions are mod-
ulated by endorphin. β -Lipotrophin, the parent actions of morphine and enkephalin (42). These findings
suggest that endogenous enkephalins are involved in the
control of CRF secretion and that their actions are mod-
ulated by endorphin. β -Lipotrophin, the parent pr suggest that endogenous enkephalins are involved in the the control of CRF secretion and that their actions are mod-
repulated by endorphin. β -Lipotrophin, the parent protein Dall
of β -endorphin, is released from th control of CRF secretion and that their actions are mod-
vertical by endorphin, β -Lipotrophin, the parent protein Dal
of β -endorphin, is released from the adenohypophysis at due
the same time as ACTH and thus it see ulated by endorphin. β -Lipotrophin, the parent protein Let of β -endorphin, is released from the adenohypophysis at dthe same time as ACTH and thus it seems reasonable to maggest that β -endorphin, like ACTH (195a) the same time as ACTH and thus it seems reasonable to suggest that β -endorphin, like ACTH (195a), exerts a short-loop feedback effect inhibiting the further secretion of CRF. The actions of opioid substances on CRF sec the same time as ACTH and thus it seems reasonable to suggest that β -endorphin, like ACTH (195a), exerts a short-loop feedback effect inhibiting the further secretion of CRF. The actions of opioid substances on CRF sec suggest that β -endorphin, like ACTH (195a), exerts a niss
hort-loop feedback effect inhibiting the further secretion mu
of CRF. The actions of opioid substances on CRF secre-
hy
ion are probably also affected by action short-loop feedback effect inhibiting the further secretion
of CRF. The actions of opioid substances on CRF secre-
tion are probably also affected by actions on centres
higher in the central nervous system. Certainly they
 of CRF. The actions of opioid substances on CRF secre-
tion are probably also affected by actions on centres
higher in the central nervous system. Certainly they
influence the activity of cholinergic and noradrenergic
neu tion are probably also affected by actions on centres sately
higher in the central nervous system. Certainly they
influence the activity of cholinergic and noradrenergic E .
neurones, both of which are implicated in the higher in the central nervous system. Certainly they
influence the activity of cholinergic and noradrenergic
neurones, both of which are implicated in the control of
CRF secretion. Morphine and β -endorphin inhibit the
 influence the activity of cholinergic and noradrenergic E .
neurones, both of which are implicated in the control of CRF secretion. Morphine and β -endorphin inhibit the to include the turnover of acetylcholine in cert neurones, both of which are implicated in the control of CRF secretion. Morphine and β -endorphin inhibit the release of noradrenaline from the rat cerebral cortex (5) and reduce the turnover of acetylcholine in certain CRF secretion. Morphine and β -endorphin inhibit the release of noradrenaline from the rat cerebral cortex (5) and reduce the turnover of acetylcholine in certain brain nuclei (193, 300). Thus, the effects of opioid sub release of noradrenaline from the rat cerebral cortex (5)
and reduce the turnover of acetylcholine in certain brain
nuclei (193, 300). Thus, the effects of opioid substances
on CRF secretion are probably due partially to d and reduce the turnover of acetylcholine in certain brain modei (193, 300). Thus, the effects of opioid substances to on CRF secretion are probably due partially to direct tinulations on the hypothalamus and partially to a nuclei (193, 300). Thus, the effect
on CRF secretion are probably c
actions on the hypothalamus and
in the ratio of stimulatory and inhi
from higher centres in the brain.
In contrast to the effects of a s In CRF secretion are probably due partially to direct the effects on the hypothalamus and partially to alterations in the ratio of stimulatory and inhibitory signals received $\frac{1}{2}$ on higher centres in the brain.
In c

actions on the hypothalamus and partially to alteration
in the ratio of stimulatory and inhibitory signals receive
from higher centres in the brain.
In contrast to the effects of a single injection, Brigg
and Munson (21) s in the ratio of stimulatory and inhibitory signals received
from higher centres in the brain.
In contrast to the effects of a single injection, Briggs
and Munson (21) showed that chronic morphine treat-
ment blocked the ad from higher centres in the brain.
In contrast to the effects of a single injection, Brigg
and Munson (21) showed that chronic morphine treat
ment blocked the adrenocortical response to histamin
stress and suggested that to In contrast to the effects of a single injection, Briggs shand Munson (21) showed that chronic morphine treat-
ment blocked the adrenocortical response to histamine nastress and suggested that tolerance develops to the sti and Munson (21) showed that chronic morphine treat- (46a).

ment blocked the adrenocortical response to histamine natior

stress and suggested that tolerance develops to the stim-

ulatory actions of the drug. Another grou ment blocked the adrenocortical response to histamine na
stress and suggested that tolerance develops to the stim-
will ulatory actions of the drug. Another group (158) found ex
that after repeated daily injections of morp stress and suggested that tolerance develops to the stim-
ulatory actions of the drug. Another group (158) found
that after repeated daily injections of morphine the HPA
dsystem was no longer stimulated by the drug but the ulatory actions of the drug. Another group (158) found
that after repeated daily injections of morphine the HPA
system was no longer stimulated by the drug but the
response to stress (cold or insulin) persisted. The bulk o that after repeated daily injections of morphine the HPA disystem was no longer stimulated by the drug but the aresponse to stress (cold or insulin) persisted. The bulk of the evidence available suggests that chronic morph system was no longer stimulated by the drug but the amu
response to stress (cold or insulin) persisted. The bulk of this
the evidence available suggests that chronic morphine It is
treatment causes impairment but not total response to stress (cold or insulin) persisted. The bulk of
the evidence available suggests that chronic morphine
treatment causes impairment but not total inhibition of
HPA activity (202). It seems unlikely that this is d the evidence available suggests that chronic morphine
treatment causes impairment but not total inhibition of
HPA activity (202). It seems unlikely that this is due to
direct actions of the opiate on the adrenal cortex (83 treatment causes impairment but not total inhibition HPA activity (202). It seems unlikely that this is due direct actions of the opiate on the adrenal cortex (83)
Two mechanisms of action have been proposed. Firstle that HPA activity (202). It seems unlikely that this is due to ner
direct actions of the opiate on the adrenal cortex (83). con
Two mechanisms of action have been proposed. Firstly, that
that prolonged morphine treatment inhib direct actions of the opiate on the adrenal cortex (83). contr
Two mechanisms of action have been proposed. Firstly, that if
that prolonged morphine treatment inhibits CRF secre-
with ition and secondly, that chronic treat Two mechanisms of action have been proposed. Firstly,
that prolonged morphine treatment inhibits CRF secre-
tion and secondly, that chronic treatment increases CRF
secretion to such an extent that the pituitary ACTH
stores that prolonged morphine treatment inhibits CRF secretion and secondly, that chronic treatment increases CRF secretion to such an extent that the pituitary ACTH stores become depleted. George (83) favoured the latter theory secretion to such an extent that the pituitary ACTH
stores become depleted. George (83) favoured the latter
theory because prolonged treatment with morphine re-
sulted in adrenal hypertrophy and hyperplasia (258),
effects secretion to such an extent that the pituitary ACT
stores become depleted. George (83) favoured the latt
theory because prolonged treatment with morphine r
sulted in adrenal hypertrophy and hyperplasia (258
effects that ar stores become depleted. George (83) favoured the latter $F \cdot G$ theory because prolonged treatment with morphine re-
sulted in adrenal hypertrophy and hyperplasia (258) , secreffects that are probably due to excessive A theory because prolonged treatment with morphine resulted in adrenal hypertrophy and hyperplasia (258), seeffects that are probably due to excessive ACTH secre-
pion, and reduces the pituitary ACTH content to such an wexte sulted in adrenal hypertrophy and hyperplasia (258), effects that are probably due to excessive ACTH secretion, and reduces the pituitary ACTH content to such an extent that ACTH is released only in response to severe stre effects that are probably due to excessive ACTH secre-
tion, and reduces the pituitary ACTH content to such an
extent that ACTH is released only in response to severe
is
stressful stimuli. However, this argument is not ten tion, and reduces the pituitary ACTH content to such an wite
value of the act of the substressful stimuli. However, this argument is not tenable. 126
It is well known that animals in which the pituitary pit
ACTH content is stressful stimuli. However, this argument is not tenable.
It is well known that animals in which the pituitary
ACTH content is substantially reduced respond to mild
stressful stimuli with a marked hypersecretion of ACTH
(1 It is well known that animals in which the pituitary
ACTH content is substantially reduced respond to mild
stressful stimuli with a marked hypersecretion of ACTH
(123, 278). At the present time there is little information
 ACTH content is substantially reduced respond to mild
stressful stimuli with a marked hypersecretion of ACTH
(123, 278). At the present time there is little information
available concerning the functional activity of the stressful stimuli with a marked hypersecretion of ACTH assotiated as a stressful stimular with present time there is little information 131, available concerning the functional activity of the hypothalamo-hypophysial compl (123, 278). At the present time there is little information 13
available concerning the functional activity of the hy-
pothalamo-hypophysial complex in rats given prolonged the
treatment with morphine. Preliminary experim available concerning the functional activity of the hypothalamo-hypophysial complex in rats given prolonged
treatment with morphine. Preliminary experiments in
the Royal Free laboratory indicate that the capacity of
hypoth pothalamo-hypophysial complex in rats given prolonged
treatment with morphine. Preliminary experiments in
the Royal Free laboratory indicate that the capacity of
hypothalami to secrete CRF in vitro is impaired after
prolon treatment with morphine. Preliminary experiments in a
the Royal Free laboratory indicate that the capacity of
hypothalami to secrete CRF in vitro is impaired after A
prolonged incubation with morphine. Furthermore, re-
duc the Royal Free laboratory indicate that the capacity of hypothalami to secrete CRF in vitro is impaired after prolonged incubation with morphine. Furthermore, reduced plasma corticosterone levels have been described after hypothalami to secrete CRF in vitro is impaired after
prolonged incubation with morphine. Furthermore, re-
duced plasma corticosterone levels have been described
after chronic morphine treatment (243), which suggests
that

actions of morphine and enkephalin (42). These findings ment with the opiate. In this event it is difficult to explain
suggest that endogenous enkephalins are involved in the the adrenal hypertrophy and hyperplasia induced the adrenal hypertrophy and hyperplasia induced by GHAM
ment with the opiate. In this event it is difficult to explain
the adrenal hypertrophy and hyperplasia induced by
repeated injections of morphine. However, according to GHAM
ment with the opiate. In this event it is difficult to explain
the adrenal hypertrophy and hyperplasia induced by
repeated injections of morphine. However, according to
Dallman et al. (57) adrenal hypertrophy is not n ment with the opiate. In this event it is difficult to explain
the adrenal hypertrophy and hyperplasia induced by
repeated injections of morphine. However, according to
Dallman et al. (57) adrenal hypertrophy is not necess ment with the opiate. In this event it is difficult to explain
the adrenal hypertrophy and hyperplasia induced by
repeated injections of morphine. However, according to
Dallman et al. (57) adrenal hypertrophy is not necess the adrenal hypertrophy and hyperplasia induced
repeated injections of morphine. However, according
Dallman et al. (57) adrenal hypertrophy is not necessar
due to elevated circulating levels of ACTH but may
mediated by a n repeated injections of morphine. However, according to
Dallman et al. (57) adrenal hypertrophy is not necessarily
due to elevated circulating levels of ACTH but may be
mediated by a neural mechanism. Perhaps this mecha-
ni Dallman et al. (57) adrenal hypertrophy is not necessarily
due to elevated circulating levels of ACTH but may be
mediated by a neural mechanism. Perhaps this mecha-
nism also operates in morphine-treated rats. Clearly
much due to elevated circulating levels of ACTH but may mediated by a neural mechanism. Perhaps this mech
nism also operates in morphine-treated rats. Clear
much further work in which the functional activity of t
hypothalamo-hy mediated by a neural mechanism. Perhaps this me
nism also operates in morphine-treated rats. Cle
much further work in which the functional activity of
hypothalamo-hypophysial complex is studied is ne
sary to explain the tr much further work in which
hypothalamo-hypophysia
sary to explain the true m
E. Pentobarbitone/Morpi
The ability of morphin hypothalamo-hypophysial complex is studied is necessary to explain the true mode of action of morphine.

E. Pentobarbitone/Morphine

The ability of morphine to inhibit the HPA response

to explain the true mode of action of morphine.

E. Pentobarbitone/Morphine

The ability of morphine to inhibit the HPA response

to stress in anaesthetized rats was first reported by Briggs

and Munson (21). It was shown E. Pentobarbitone/Morphine
The ability of morphine to inhibit the HPA response
to stress in anaesthetized rats was first reported by Briggs
and Munson (21). It was shown that a single dose of
morphine given to rats anaesth E. Pentooarottone/Morphine
The ability of morphine to inhibit the HPA response
to stress in anaesthetized rats was first reported by Briggs
and Munson (21). It was shown that a single dose of
morphine given to rats anaesth The ability of morphine to inhibit the HPA respon
to stress in anaesthetized rats was first reported by Brig
and Munson (21). It was shown that a single dose
morphine given to rats anaesthetized with sodium pe
tobarbitone and Munson (21). It was shown that a single dose of morphine given to rats anaesthetized with sodium pentobarbitone prevented the adrenal ascorbic acid depletion normally produced by laparotomy, unilateral adrenalectomy, o and Munson (21). It was shown that a single dose of morphine given to rats anaesthetized with sodium pen tobarbitone prevented the adrenal ascorbic acid depletion normally produced by laparotomy, unilateral adrenalectomy, morphine given to rats anaesthetized with sodium pentobarbitone prevented the adrenal ascorbic acid depletion normally produced by laparotomy, unilateral adrenalectomy, or by low doses of histamine or vasopressin.
This inh tobarbitone prevented the adrenal ascorbic acid depletion normally produced by laparotomy, unilateral adrenalectomy, or by low doses of histamine or vasopressin.
This inhibitory action of morphine was subsequently confirme tion normally produced by laparotomy, unilateral adre-
nalectomy, or by low doses of histamine or vasopressin.
This inhibitory action of morphine was subsequently
confirmed both in the rat (200) and in man (185) and was
sh nalectomy, or by low doses of histamine or vasopress
This inhibitory action of morphine was subsequen
confirmed both in the rat (200) and in man (185) and w
shown to be competitively antagonised by nalorphi
(46a). The site This inhibitory action of morphine was subsequently
confirmed both in the rat (200) and in man (185) and was
shown to be competitively antagonised by nalorphine
(46a). The site and mode of action of this drug combi-
nation confirmed both in the rat (200) and in man (185) and was
shown to be competitively antagonised by nalorphine
(46a). The site and mode of action of this drug combi-
nation are not understood. The finding that rats treated
w shown to be competitively antagonised by nalorphine (46a). The site and mode of action of this drug combination are not understood. The finding that rats treated with pentobarbitone/morphine respond to hypothalamic extract (46a). The site and mode of action of this drug condition are not understood. The finding that rats tree with pentobarbitone/morphine respond to hypothala extracts with a rise in ACTH secretion suggest that drugs exert the and Munson (21). It was shown that a single dose of
morphine given to rats anasesthetized with solume ne-
tobarbitone prevented the adrenal ascorbic acid deple-
tion normally produced by laparotomy, unilateral adre-
tion extracts with a rise in ACTH secretion suggest that the extracts with a rise in ACTH secretion suggest that the
drugs exert their effects predominantly on the hypothal-
amus or on centres higher in the brain. No studies on
this aspect of the pharmacology of CRF have been made.
 drugs exert their effects predominantly on the hypothal-
amus or on centres higher in the brain. No studies on
this aspect of the pharmacology of CRF have been made.
It is known that opioid substances influence the activit amus or on centres higher in the brain. No studies on
this aspect of the pharmacology of CRF have been made.
It is known that opioid substances influence the activity
of cholinergic and noradrenergic neurones in the centra this aspect of the pharmacology of CRF have been made.
It is known that opioid substances influence the activity
of cholinergic and noradrenergic neurones in the central
nervous system, both of which are implicated in the
 It is known that opioid substances influence the activity
of cholinergic and noradrenergic neurones in the central
nervous system, both of which are implicated in the
control of CRF secretion. It seems reasonable to sugges of cholinergic and noradrenergic neurones in the central
nervous system, both of which are implicated in the
control of CRF secretion. It seems reasonable to suggest
that morphine, like chlorpromazine, acts synergistically nervous system, both of which a
control of CRF secretion. It seems
that morphine, like chlorpromazin
with pentobarbitone to modulate the
controlling the secretion of CRF. **Facture Theoryton Charles Controlling the second F. Glucocorticoids**
F. Glucocorticoids
The pharmacolo with pentobarbitone to modulate the activity of neurones
controlling the secretion of CRF.
F. Glucocorticoids
The pharmacological effects of corticosteroids on the
secretion of CRF are essentially exaggerations of their

Downloaded from pharmrev.aspetjournals.org at Thammasart University on December 8, 2012

extent that ACTH is released only in response to severe ishes the stress-induced release of ACTH (36, 95, 124, stressful stimuli. However, this argument is not tenable. 126) and the normal circadian excursion in hypothalam controlling the secretion of CRF.

F. Glucocorticoids

The pharmacological effects of corticosteroids on the

secretion of CRF are essentially exaggerations of their

physiological actions. Treatment of either rats or man F. Glucocorticoids
The pharmacological effects of corticosteroids on the
secretion of CRF are essentially exaggerations of their
physiological actions. Treatment of either rats or man
with high, nonphysiological doses of c *F. Guteocorticolas*
The pharmacological effects of corticosteroids on the
secretion of CRF are essentially exaggerations of their
physiological actions. Treatment of either rats or man
with high, nonphysiological doses of The pharmacological effects of corticosteroids on the
secretion of CRF are essentially exaggerations of their
physiological actions. Treatment of either rats or man
with high, nonphysiological doses of corticosteroids abol secretion of CRF are essentially exaggerations of
physiological actions. Treatment of either rats or
with high, nonphysiological doses of corticosteroids
ishes the stress-induced release of ACTH (36, 95
126) and the normal physiological actions. Treatment of either rats or n
with high, nonphysiological doses of corticosteroids al
ishes the stress-induced release of ACTH (36, 95, 1
126) and the normal circadian excursion in hypothalar
pituita with high, nonphysiological doses of corticosteroids abolishes the stress-induced release of ACTH (36, 95, 124, 126) and the normal circadian excursion in hypothalamo-
pituitary-adrenal activity (95, 124). Many of the semisyn-
thetic corticosteroids (e.g. betamethasone and dexam 126) and the normal circadian excursion in hypothalamo-
pituitary-adrenal activity (95, 124). Many of the semisyn-
thetic corticosteroids (e.g. betamethasone and dexameth-
asone) are considerably more potent in this respec pituitary-adrenal activity (95, 124). Many of the set
thetic corticosteroids (e.g. betamethasone and dexa
asone) are considerably more potent in this respec
131, 244) than the naturally occurring corticoids
corticosteroidthetic corticosteroids (e.g. betamethasone and dexameth-
asone) are considerably more potent in this respect (124,
131, 244) than the naturally occurring corticoids. The
corticosteroid-induced suppression of hypothalamo-pi asone) are considerably more potent in this respect (124, 131, 244) than the naturally occurring corticoids. The corticosteroid-induced suppression of hypothalamo-pituitary-adrenocorticotrophic activity is associated with 131, 244) than the naturally occurring corticoids. The corticosteroid-induced suppression of hypothalamo-pituitary-adrenocorticotrophic activity is associated with adrenal atrophy (36, 125), a reduction in the plasma conce corticosteroid-induced suppression of hypothalamo-pi-
tuitary-adrenocorticotrophic activity is associated with
adrenal atrophy (36, 125), a reduction in the plasma
concentrations of corticosterone (cortisol in man) and
ACT tuitary-adrenocorticotrophic activity is associated with adrenal atrophy (36, 125), a reduction in the plasma
concentrations of corticosterone (cortisol in man) and
ACTH (36, 95), and a fall in the contents of ACTH and
CRF in the anterior pituitary gland and the hypothala-
mus r concentrations of corticosterone (cortisol in man) and
ACTH (36, 95), and a fall in the contents of ACTH and
CRF in the anterior pituitary gland and the hypothala-
mus respectively (38). The sensitivities of the adrenal
co ACTH (36, 95), and a fall in the contents of ACTH and CRF in the anterior pituitary gland and the hypothalamus respectively (38). The sensitivities of the adrenal cortex (17, 95, 124, 128, 189), the adenohypophysis (38) a **CORTICOTROPHIN RELEASING FACTOR** ²⁶⁹

CORTICOTROPHIN RELI

impaired. Endocrine tissue, unlike neural tissue, rapidly

loses its secretory capacity when deprived of trophic CORTICOTROPHIN REI

impaired. Endocrine tissue, unlike neural tissue, rapidly

loses its secretory capacity when deprived of trophic

stimuli. Thus the apparent insensitivity of the individual CORTICOTROPHIN
impaired. Endocrine tissue, unlike neural tissue, rapidly
loses its secretory capacity when deprived of trophic
stimuli. Thus the apparent insensitivity of the individual
components of the HPA system is prob impaired. Endocrine tissue, unlike neural tissue, rapidly must loses its secretory capacity when deprived of trophic existimuli. Thus the apparent insensitivity of the individual also components of the HPA system is probab impaired. Endocrine tissue, unlike neural tissue, rapidly

loses its secretory capacity when deprived of trophic

stimuli. Thus the apparent insensitivity of the individual

also components of the HPA system is probably pa loses its secretory capacity when deprived of trophic existimuli. Thus the apparent insensitivity of the individual also components of the HPA system is probably partially due CH cost to the absence of positive stimuli. Di stimuli. Thus the apparent insensitivity of the individual components of the HPA system is probably partially du
to the absence of positive stimuli. Direct actions of the
steroid on the tissue itself are also important. Th to the absence of positive stimuli. Direct actions of the
steroid on the tissue itself are also important. There are
numerous reports in the literature that show that corti-
numerous reports in the literature that show tha to the absence of positive stimuli. Direct actions of the steroid on the tissue itself are also important. There are numerous reports in the literature that show that corticosteroids act directly on both the hypothalamus a steroid on the tissue itself are also important. There a
numerous reports in the literature that show that cor
costeroids act directly on both the hypothalamus and t
adenohypophysis to inhibit the secretion of CRF (31, 3
1 numerous reports in the literature that show that corticosteroids act directly on both the hypothalamus and the adenohypophysis to mhibit the secretion of CRF (31, 39 142, 172) and ACTH (6, 37, 75, 76, 142, 172, 220), resp costeroids act directly on both the hypothalamus and the
adenohypophysis to mhibit the secretion of CRF $(31, 39, 142, 172)$ and ACTH $(6, 37, 75, 76, 142, 172, 220)$, respec-
tively, that occurs in response to trophic st adenohypophysis to mhibit the secretion of CRF (31, 39, role 142, 172) and ACTH (6, 37, 75, 76, 142, 172, 220), respectively, that occurs in response to trophic stimulation, (e.g although it is unlikely that they affect th 142, 172) and ACTH $(6, 37, 75, 76, 142, 172, 220)$, respectively, that occurs in response to trophic stimulation, (ealthough it is unlikely that they affect the secretory netrivity of the adrenal cortex (124). Steroids a tively, that occurs in response to trophic stimulation,
although it is unlikely that they affect the secretory
activity of the adrenal cortex (124). Steroids also act on
higher centres in the brain to modulate the activity although it is unlikely that they affect the s
activity of the adrenal cortex (124). Steroids als
higher centres in the brain to modulate the ac
neurones that control the secretion of cortic
releasing factor (59, 60, 71, 1 es in the brain to modulate the
at control the secretion of concording Comments
VIII. Concluding Comments
vears that have elansed since

urones that control the secretion of corticotrophin
easing factor (59, 60, 71, 149, 154, 187, 297).
VIII. Concluding Comments
In the 43 years that have elapsed since Harris first
oposed that the secretory activity of the a releasing factor (59, 60, 71, 149, 154, 187, 297).

VIII. Concluding Comments

In the 43 years that have elapsed since Harris

proposed that the secretory activity of the adenohy

ysis is controlled by chemical transmitter VIII. Concluding Comments
In the 43 years that have elapsed since Harris first
proposed that the secretory activity of the adenohypoph-
ysis is controlled by chemical transmitter substances
produced by the hypothalamus, on Fig. Concluding Comments
In the 43 years that have elapsed since Harris first
proposed that the secretory activity of the adenohypoph-
ysis is controlled by chemical transmitter substances
produced by the hypothalamus, onl In the 43 years that have elapsed since Harris first
proposed that the secretory activity of the adenohypoph-
ysis is controlled by chemical transmitter substances
produced by the hypothalamus, only three of these reg-
ula proposed that the secretory activity of the adenohypophysis is controlled by chemical transmitter substances inconduced by the hypothalamus, only three of these regulatory hormones (thyrotrophin releasing hormone, gonadotr ysis is controlled by chemical transmitter substances
produced by the hypothalamus, only three of these reg-
ulatory hormones (thyrotrophin releasing hormone, go-
nadotrophin releasing hormone, and growth hormone
release i produced by the hypothalamus, only three of these reg-
ulatory hormones (thyrotrophin releasing hormone, go-
nadotrophin releasing hormone, and growth hormone with
release inhibiting hormone) have been successfully iso-
h ulatory hormones (thyrotrophin releasing hormone, gonadotrophin releasing hormone, and growth hormon
release inhibiting hormone) have been successfully is
lated and identified. These hypothalmic hormones an
their synthetic mentuation in releasing hormone, and growth hormone wive
release inhibiting hormone) have been successfully iso-
hated and identified. These hypothalmic hormones and
their synthetic analogues have been effective in the tre release inhibiting hormone) have been successfully isolated and identified. These hypothalmic hormones and their synthetic analogues have been effective in the treatment of certain endocrine disorders as also have a variet lated and identified. These hypothalmic hormones and
their synthetic analogues have been effective in the treat-
ment of certain endocrine disorders as also have a variety
of drugs that influence their secretion. Thyrotrop their synthetic analogues have been effective in the treat-
ment of certain endocrine disorders as also have a variety
of drugs that influence their secretion. Thyrotrophin
releasing hormone (TRH) and gonadotrophin releasi ment of certain endocrine disorders as also have a variety
of drugs that influence their secretion. Thyrotrophin
releasing hormone (TRH) and gonadotrophin releasing
hormone (GnRH) are employed to assess the capacity of
the of drugs that influence their secretion. Thyrotrophin
releasing hormone (TRH) and gonadotrophin releasing
hormone (GnRH) are employed to assess the capacity of
the adenohypophysis to secrete the appropriate trophic
hormone releasing hormone (TRH) and gonadotrophin releasing hormone (GnRH) are employed to assess the capacit
the adenohypophysis to secrete the appropriate trop
hormones, thus facilitating accurate differentiation
tween diseases the adenohypophysis to secrete the appropriate trophic
hormones, thus facilitating accurate differentiation be-
tween diseases of the pituitary gland and the hypothal-
amus as causes of thyroid or gonadal dysfunction. Clin the adenohypophysis to secrete the appropriate trophic
hormones, thus facilitating accurate differentiation be-
tween diseases of the pituitary gland and the hypothal-
amus as causes of thyroid or gonadal dysfunction. Clin hormones, thus facilitating accurate differentiation be-
tween diseases of the pituitary gland and the hypothal-
amus as causes of thyroid or gonadal dysfunction. Clinical
neuroendocrinology with respect to HPA function is tween diseases of the pituitary gland and the hypothal-
amus as causes of thyroid or gonadal dysfunction. Clinical
neuroendocrinology with respect to HPA function is
rather limited. There are reports of successful attempts amus as causes of thyroid or gonadal dysfunction. Clinical
neuroendocrinology with respect to HPA function is
rather limited. There are reports of successful attempts
to treat patients with Cushing's disease of hypothalami neuroendocrinology with respect to HPA function is
rather limited. There are reports of successful attempts
to treat patients with Cushing's disease of hypothalamic
origin with the 5-HT and acetylcholine antagonist, cy-
pr rather limited. There are reports of successful attempts
to treat patients with Cushing's disease of hypothalamic
origin with the 5-HT and acetylcholine antagonist, cy-
proheptadine (e.g., 160). However, since pure CRF is to treat patients with Cushing's disease of hypothalamic
origin with the 5-HT and acetylcholine antagonist, cy-
proheptadine (e.g., 160). However, since pure CRF is not
available it is not possible at the present time to s origin with the 5-HT and acetylcholine antagonist, cy-
proheptadine (e.g., 160). However, since pure CRF is not
available it is not possible at the present time to study
directly the capacity of the pituitary gland to secr proheptadine (e.g., 160). However, since pure CRF is not available it is not possible at the present time to study directly the capacity of the pituitary gland to secrete ACTH. Vasopressin is sometimes used clinically as a available it is not possible at the present time to stud
directly the capacity of the pituitary gland to secret
ACTH. Vasopressin is sometimes used clinically as a test
of pituitary ACTH reserve but since it is not chemica rectly the capacity of the pituitary gland to secrete

TH. Vasopressin is sometimes used clinically as a test

pituitary ACTH reserve but since it is not chemically

entical with CRF the validity of the test is questionabl

ACTH. Vasopressin is sometimes used clinically as a test
of pituitary ACTH reserve but since it is not chemically
identical with CRF the validity of the test is questionable.
There is no reason to assume that the so-called of pituitary ACTH reserve but since it is not chemically
identical with CRF the validity of the test is questionable.
There is no reason to assume that the so-called "hy-
pothalamic hormones" are concerned only with endo-
 identical with CRF the validity of the test is questionable.
There is no reason to assume that the so-called "hypothalamic hormones" are concerned only with endo-
crine function. Immunofluorescence techniques have
demonstr There is no reason to assume that the so-called "hy-
pothalamic hormones" are concerned only with endo-
crine function. Immunofluorescence techniques have
demonstrated the presence of some hypothalamic hor-
mones both in e pothalamic hormones" are concerned only with endo-
crine function. Immunofluorescence techniques have
demonstrated the presence of some hypothalamic hor-
mones both in extrahypothalamic sites within the central
nervous sy crine function. Immunofluorescence techniques have
demonstrated the presence of some hypothalamic hor-
mones both in extrahypothalamic sites within the central
nervous system $(9, 211)$ and in the gut (169) . It has been demonstrated the presence of some hypothalamic hormones both in extrahypothalamic sites within the central nervous system (9, 211) and in the gut (169). It has been suggested that these peptides may be involved in the cont mones both in extrahypothalamic sites within the cent
nervous system (9, 211) and in the gut (169). It has been
suggested that these peptides may be involved in
control of physiological functions as diverse as behavier
(TR nervous system $(9, 211)$ and in the gut (169) . It has been
suggested that these peptides may be involved in the
control of physiological functions as diverse as behaviour
(TRH, GnRH) $(146, 194)$, glucose metabolism (s suggested that these peptides may be involved in the control of physiological functions as diverse as behaviour (TRH, GnRH) (146, 194), glucose metabolism (somatotistatin) (265), and memory (vasopressin) (274). As yet no e control of physiological functions as diverse as behaved (TRH, GnRH) (146, 194), glucose metabolism (som statin) (265), and memory (vasopressin) (274). As year
trapituitary effects of CRF have been described has the "hormo

LEASING FACTOR
mus. However the possibility has been raised that an
extrahypothalamic tissue-corticotrophin releasing factor LEASING FACTOR
mus. However the possibility has been raised that an
extrahypothalamic tissue-corticotrophin releasing factor
also exists (170). Tissue CRF has been distinguished from 269
mus. However the possibility has been raised that an
extrahypothalamic tissue-corticotrophin releasing factor
also exists (170). Tissue CRF has been distinguished from
CRF of hypothalamic origin on the basis of physico mus. However the possibility has been raised the
extrahypothalamic tissue-corticotrophin releasing f
also exists (170). Tissue CRF has been distinguished
CRF of hypothalamic origin on the basis of physicoc
ical properties, mus. However the possibility has been raised that a
extrahypothalamic tissue-corticotrophin releasing factor
also exists (170). Tissue CRF has been distinguished from
CRF of hypothalamic origin on the basis of physicochem
 extrahypothalamic tissue-corticotrophin releasing factor
also exists (170). Tissue CRF has been distinguished from
CRF of hypothalamic origin on the basis of physicochem-
ical properties, potency, prolonged action on the p also exists (170). Tissue CRF has been distinguished from
CRF of hypothalamic origin on the basis of physicochem-
ical properties, potency, prolonged action on the pitui-
tary-adrenal system, and existence in the blood lon CRF of hypothalamic origin on the basis of physicochemical properties, potency, prolonged action on the pituitary-adrenal system, and existence in the blood long after the hypothalamus has been removed. The factor, which a ical properties, potency, prolonged action on the pitui-
tary-adrenal system, and existence in the blood long after
the hypothalamus has been removed. The factor, which
appears to originate from damaged tissue, may play a
 tary-adrenal system, and existence in the blood long after
the hypothalamus has been removed. The factor, which
appears to originate from damaged tissue, may play a
role in the pituitary-adrenocortical response to stress. the hypothalamus has been removed. The factor, which
appears to originate from damaged tissue, may play a
role in the pituitary-adrenocortical response to stress. It
appears that during chronic stress of severe intensity
(appears to originate from damaged tissue, may play
role in the pituitary-adrenocortical response to stress.
appears that during chronic stress of severe intensi
(e.g. extensive surgery) the needs of the organism m
not be m appears that during chronic stress of severe intensity (e.g. extensive surgery) the needs of the organism may not be met by the hypothalamic-CRF and that tissue-CRF may be necessary to sustain prolonged pituitary-
adrenal appears that during chronic stress of severe intensity (e.g. extensive surgery) the needs of the organism may not be met by the hypothalamic-CRF and that tissue-CRF may be necessary to sustain prolonged pituitary-
adrenal (e.g. extensive surgery) the needs of the
not be met by the hypothalamic-CRF a
CRF may be necessary to sustain prolon
adrenal activity (27). This fascinating
cently been extensively reviewed (28).
A further understanding t be met by the hypothalamic-CRF and that tissue-
RF may be necessary to sustain prolonged pituitary-
renal activity (27). This fascinating subject has re-
ntly been extensively reviewed (28).
A further understanding of th

CRF may be necessary to sustain prolonged pituitary-
adrenal activity (27). This fascinating subject has re-
cently been extensively reviewed (28).
A further understanding of the chemistry, physiology,
and pharmacology of adrenal activity (27). This fascinating subject has recently been extensively reviewed (28).
A further understanding of the chemistry, physiology,
and pharmacology of CRF should ultimately lead to the
development of tests cently been extensively reviewed (28).

A further understanding of the chemistry, physiology,

and pharmacology of CRF should ultimately lead to the

development of tests that enable differentiation between

dysfunction of A further understanding of the chemistry, physiology,
and pharmacology of CRF should ultimately lead to the
development of tests that enable differentiation between
dysfunction of the hypothalamus and anterior pituitary
gl and pharmacology of CRF should ultimately lead to the development of tests that enable differentiation between dysfunction of the hypothalamus and anterior pituitary gland as causes of adrenal disease, to the synthesis of development of tests that enable differentiation between
dysfunction of the hypothalamus and anterior pituitary
gland as causes of adrenal disease, to the synthesis of
"super-active" CRF receptor agonists and antagonists
t dysfunction of the hypothalamus and anterior pituitary
gland as causes of adrenal disease, to the synthesis of
"super-active" CRF receptor agonists and antagonists
that may be of therapeutic value, and possibly to the
succ gland as causes of adrenal disease, to the synthesis of "super-active" CRF receptor agonists and antagonists
that may be of therapeutic value, and possibly to the
successful treatment of diseases of hypothalamic origin
wit "super-active" ϵ
that may be of
successful treatn
with drugs that
hormone cells. *Acknowledgments.* **I** am grateful to Mrs. **J.** Dobson and Miss A. Fletcher for their help with the literature search. REFERENCES

- Acknowledgments. 1 am graterul to MIS. J. Dobson and MISS A.

etcher for their help with the literature search.

REFERENCES

1. ABE, K., AND HIROSHIGE, T.: Changes in plasma corticosterone and hypo-

thalamic CRF levels fo **EXEMPLE BRAIN BIOGENCES**
 **of brain biogenic amines in plasma corticosterone and hypothalamic CRF levels following intraventricular injection or drug-induced

changes of brain biogenic amines in the rat. Neuroendocrinolog 2. ALAGHBAND-ZADEH,** J., DALY, J. R., BITENSKY, L., AND CHAYEN, J.: The 2.1, 1974.
 2. ALAGHBAND-ZADEH, J., DALY, J. R., BITENSKY, L., AND CHAYEN, J.: The cytochemical section assay for corticotrophin. Clin. Endocri
- 21, 1974.

2. ALAGHBAND-ZADEH, J., DALY, J. R., BITENSKY, L., AND CHAYEN, J.: The

cytochemical section assay for corticotrophin. Clin. Endocrinol. 3: 319-

327, 1974.

3. ALESHIN, B. V., AND Us, L. A.: Catecholamine conce
-
- Eksp. Biol. Med. (Transl.) 82: 353-965, 1976.

3. ALESHIN, B. V., AND Us, L. A.: Catecholamine concentration in the hypothelalamus during changes in pituitary-adrenocorticotropic function. Byull.

Eksp. Biol. Med. (Transl.
-
- thalamus during changes in pituitary-adrenocorticotropic function. Byull.

Eksp. Biol. Med. (Transl.) 82: 953-955, 1976.

4. ANDÉN, N., DAHLSTRÖM, A., FUXE, K., AND HOKFELT, T.: The effect of

haloperiol and cholopromazine of noradrenaline from cerebral cortex but not of dopamine from rat
striatum. Nature (London) 271: 559-561, 1978.
6. ARIMURA, A., BOWERS, C. Y., SCHALLY, A. V., SAITO, M., AND MILLER, M.
C.: The effect of corticorophin-rele
- release of CRF) using rates treated with morphine, chlorpromazine, and activation in rats with hereditary hypothalamic diabetes insipidus.
Acta endocrinol. 54: 155-165, 1967.

8. ARIMURA, A., SAITO, T., AND SCHALLY, A. V.:
- releasing factor (CRF) using rats treated with morphine, chlorpromazine,
- and GIF. *In* Hypothalamic Hormones, ed. by M. Motta, P. G. Crosignani, and L. Martini, pp. 27–42, Academic Press, London, 1977.
10. ARON, E., Снамвон, Y., AND VOISIN, A.: Action d'un végétativolytique sur dexamethasone and nembutal. Endocrinology 81: 235-245, 1967.

9. ARIMURA, A., AND SCHALLY, A. V.: Immunological studies on hypothalamic

hormones with special reference to radioirmunoassays for TRH, LHRH

and GIF. In Hypot
- la réaction hypophyso-surrénalienne du rat blanc. Application au dosage
pratique des substances corticotropes. Bull. Acad. nat. Méd. (Paris) 137:
11. BALZER, H., HOLTZ, P., AND PALM, D.: Reserpine and α-aminobuttersäure-
g
-
- 417-420, 1953.

11. BALZER, H., HOLTZ, P., AND PALM, D.: Reserpine and *a*-aminobuttersäure-

gehalt de Gehirns. Experientia (Basel) 17: 38-40, 1961.

12. BARRETT, A. M.: The effect of cortisone and hydrocortisone on the p
- RRETT, A. M.: The effect of cortisone and hydrocortisone on the plasma
macol. 13: 20–25, 1961.
nnacol. 13: 20–25, 1961.
**RRETT, A. M., AND HODGES, J. R.: The level of adrenocorticotrophin in
the plasma of normal and adre**

Downloaded from pharmrev.aspetjournals.org at Thammasart University on December 8, 2012

Downloaded from pharmrev aspetjournals org at Thammasart University on December 8, 2012

NANH

- **14. BENDER, D. A.: The effects of chlorpromazine on serum tryptophan, brain tryptophan uptake and brain serotonin synthesis in the rat. Biochem.

Pharmacol. 28:** 1743–1746, 1976.
 15. BHATFACHARYA, S. P.: Actions of atr
- induced changes in rat brain monoamines. Can. J.

HATNAGER, S. P.: Actions of atropine, hemicholinium-3, and physostigmine

on chlorpromazine-induced changes in rat brain monoamines. Can. J.

HATTACHARYA, A. N., AND MARKS, 2000. 108-116, 1974.

108. BHATTACHARYA, A. N., AND MARKS, B. H.: Reserpine- and chlorpromazine-

induced changes in hypothalamo-hypophyseal-adrenal system in rats in

the presence and absence of hypothermia. J. Pharmacol.
- the presence and absence of hypothermia. J. Pharmacol. Exp. Ther. 165:
108-116, 1969.
17. BIERICH, J. R., KERSTEN, I., AND MARUEKTAD, S.: Plasma corticosteroids
and their responsiveness to corticotrophin after long term th
- **hydroxylation. J. Steroid Biochem. Acta endocrinol. 31: 40–48, 1959.**
 hydroxylation. Acta endocrinol. 31: 40–48, 1959.
 hydroxylation. J. Steroid Biochem. 5: 789-794, 1974.
 hydroxylation. J. Steroid Biochem. 5: 789
- **structures in the hormonal feedback action ofcorticosteroids. Acts physiol.**
- **vitro.** J. Physiol. (London) 239. 269-283, 1974.
 20. BRADBURY, M. W. B., BURDEN, J., HILLHOUSE, E., AND JONES, M. T.: Stimulation electrically and by acetylcholine of the rat hypothalamus *in vitro.* J. Physiol. (Lon
- **of ACTH secretically and by active-20.** BRADBURY, M. W. B., BURDEN, J., HILLHOUSE, E., AND JONES, M. T.: 2011
 oitro. J. Physiol. (London) **239:** 269-283, 1974.

21. BRIGGS, F. N., AND MUNSON, P. L.: Studies on the mech
- **on Pitulical system through Sympo-Lice action** of ACTH secretion with the aid of morphine as a blocking agent. Endocrinology 57: 205-219, 1955.
 RIGGS, F. N., AND MUNSON, P. L.: Studies on the mechanism of stimulation o orinology 57: 205-219, 1955.

RODIE, B. B., MAICKEL, R. P., AND WESTERMANN, E. O.: Action of reserpine

on pituitary-adrenocortical system through possible action on hypothala-

mus. In Proceedings of the Fourth Internatio Xety and J. Eikes, pp. 361-361, Pergamon Press, Oxford, 1961.

Registered in the Pourth International Neurochemical Symposium, June 1960, Varenna, Italy, Regional Neurochemical Symposium, June 1960, Varenna, Italy, Regiona mus. *In* Proceedings of the Fourth International Neurochemical Symposium, June 1960, Varenna, Italy, Regional Neurochemistry, ed by S. S.
Kety and J. Eikes, pp. 351-361, Pergamon Press, Oxford, 1961.
23. BRODIE, B. B., OL
- **by** reserpine. Science 125: 1293-1294, **1957.** interrelationship between release of brain norepinephrine and serotonin
- 24. **BRODIE, B. B., SHORE, P. A., SILVER,** S. L., **AND PULVER,** R.: Potentiating 24. BRODIE, B. B., SHORE, P. A., SILVER, S. L., AND PULVER, R.: Potentiating
action of chlorpromazine and reserpine. Nature (London) 175: 1133-1134,
1955.
25. BRODISH, A.: Delayed secretion of ACTH in rats with hypothalami
- Headler, N. 26. BRODISH, A.: Delayed secretion of ACTH in rats with hypothalamic lesions.
 Endocrinology 74: 28-34, 1964.

26. BRODISH, A.: Effect of hypothalamic lesions on the time-course of corticoe-

terone secretion
-
-
- Endocrinology 74: 28-34, 1964.

26. BRODISH, A.: Effect of hypothalamic lesions on the time-course of corticos-

terme secretion. Neuroendocrinology 5: 33-47, 1969.

27. BRODISH, A.: Extra-CNS corticotropin releasing facto
-
- 27. BRODISH, A.: Extra-CNS corticotropin releasing factors. Ann. N.Y. Acad.

26. **297: 420-435, 1977.**

28. BRODISH, A.: Control of ACTH secretion by corticotropin releasing factor(s).

29. BRODISH, A., AND LONG, C. N. H.: 29. BRODISH, A., AND LONG, C. N. H.: ACTH-releasing hypothalamic neurohumor in peripheral blood. Endocrinology 71: 298-306, 1962.
30. BROOKS, C. McC.: A study of the mechanism whereby coitus excites the ovulation-producing 29. ВRODISH, A., AND LONG, C. N. H.: ACTH-releasing hypothalamic neurohumor in peripheral blood. Endocrinology 71: 298-306, 1962.

30. BROOKS, C. McC.: A study of the mechanism whereby coitus excites the

ovulation-produc
-
- 31. BUCKINGHAM, J. C.: The influence of corticosteroids on the secretion of
corticotrophin and its hypothalamic releasing hormone. J. Physiol. (Lon-
don) 286: 331-342, 1979.
32. BUCKINGHAM, J. C.: The influence of various
- cycle of corticotrophin releasing hormone and corticotrophin. J. Endocrinol. 83: 38P, 1979.

33. BUCKINGHAM, J. C., DÖHLER, K-D, AND WILSON, C. A.: Activity of the pituitary-adrenocortical system and thyroid gland during t
- plasma corticotrophin and plasma corticosterone in adrenalectomised pointing the onestrous cycle of the rat. J. Endocrinol. 78: 359-366, 1978.
cycle of the rat. J. Endocrinol. 78: 359-366, 1978.
plasma corticostrophin and Stressed, adrenalectomised rats. J. Endocrinol. Assembly adrenably to the pituitary-adrenocortical system and thyroid gland during the oestrous cycle of the rat. J. Endocrinol. 78: 359-366, 1978.

34. BUCKINGHAM, J. C., AN
-
- 34. BUCKINGHAM, J. C., AND HODGES, J. R.: Interrelationships of pituitary and
plasma corticotrophin and plasma corticosterone in adventateomised and
stressed, adrenated rates. J. Endocrinol. 63: 213-222, 1974.
BUCKINGHAM,
- **by and the detection in the detection and estimation**
cortical function in the rat after treatment with betamethasone. Brit. J.
Pharmacol. 56: 235-239, 1976.
ucan by adenohypophysial tissue *in vitro* for the detection an 37. BUCKINGHAM, J. C., AND HODGES, J. R.: The use of corticotrophin production by adenohypophysial tissue in vitro for the detection and estimation of potential corticotrophin releasing factors. J. Endocrinol. 72: 187-193,
- **EXAMPLE TO THE ISOCITY OF THE ISOLATE ISOLATE AND HOREAL SET ALSO DETERMINED ASSEMBLE DETERMINED IN EXAMPLE DETERMINED IN THE PHONOREAL THE PHONOREAL THE PHONOREAL THE PHONORE THE PHONORE THE PHONORE PHONORE PHONORE PHONO**
- (a) Doc. Doc. Determines, v.c., we have the rat after betamethasone treatment. J.
 274: 287-302, 1977.

29. BUCKINGHAM, J. C., AND HODGEs, J. R.: Production of corticotrophin

releasing hormone by the isolated hypothalam **39.** BUCKINGRAM, J. C., AND HODGES, J. R.: Production of corticotrophin releasing hormone by the isolated hypothalamus of the rat. J. Physiol. (London) **372:** 469-479, 1977.
 40. BUCKINGRAM, J. C., AND HODGES, J. R.: Hy
-
- 40. BUCKINGHAM, J. C., AND HODGES, J. K.: Hypothalamo-pituitary activity in
the betamethasone-treated rat. J. Endocrinol. 78: 29P, 1977.
41. BUCKINGHAM, J. C., AND HODGES, J. R.: Hypothalamic receptors influencing
the sec
-
-
- Brattleboro rat. J. Endocrinol. 81: 126P, 1979.
44. BUCKINGHAM, J. C., AND LEACH, J. H.: Vasopressin and hypothalamo-
pituitary-adrenocorticotrophic activity. J. Physiol. (London) 296: 87P,
1979. **pituitary-adrenocorticotrophic activity. J. Physiol. (London) 296: 87P, 1979.** Brattleboro rat. J. Endocrinol. 81: 126P, 1979.

44. BUCKINGHAM, J. C., AND LEACH, J. H.: Vasopressin and hypothalamo-

pituitary-adrenocorticotrophic activity. J. Physiol. (London) 296: 87P,

1979.

45. BUCKINGHAM, J. C.,
-
- 46. BURDEN, J. L.: The control and nature of corticotrophin releasing hormone.
- physial hormones and their analogues on corticotrophin release. J. Endocrinol. 72: 9P, 1977.

URDEN, J. L.: The control and nature of corticotrophin releasing hormone.

Thesis, University of London, 1975.

B. H., LEEMAN, S **IRDEN, J. L.: The control and nature of corticotrophin releasing hormone.**
Thesis, University of London, 1975.
 NURDETTE, B. H., LEEMAN, S., AND MUNSON, P. L.: The reversal by
 nalorphine of the inibilitory effect of m 46a. BURDETTE, B. H., LEEMAN, S., AND MUNSON, P. L.: The reversal nalorphine of the inhibitory effect of morphine on the secretion of admocorticotropic hormone in stress. J. Pharmacol. Exp. Ther. 132: 323-3
1961.
1961. BUR malorphine of the inhibitory effect of morphine on the secretion of adremocorticotropic hormone in stress. J. Pharmacol. Exp. Ther. 132: 323-328,
1961.
The Burns of Marmacology. In A. S. V., AND MITCHELL, J. F.: Quantitati
-
- T. H., OLIVER, J. T., AND POSSANZA, G.: Biological consequences of 18-
hydroxylation. J. Steroid Biochem. 5: 789–794, 1974.
19. BOHUS, B., NYAKAS, C., AND LISSÁK, K.: Involvement of suprahypothalamic
19. BOHUS, B., NYAKAS 47. BURGEN, A. S. V., AND MITCHELL, J. F.: Quantitative and human pharmacology. In A. S. V. Burgen and J. F. Mitchell: Gaddum's Pharmacology, pp. 229-247, Oxford Medical Publications, London, 1978.
48. CAMPBELL, H. J., FE
	- **48. CAMPBELL, H. J., FEUER, G., AND HARRIS, G. W.: The effect of intrapituitary** infusion of median eminence and other brain extracts on anterior pituitary gonadotrophic secretion. J. Physiol. (London) 170: 474–486, 1964. gonadotrophic secretion. J. Physiol. (London) 170: 474–486, 1964.
49. CARLSSON, A., AND LINDQVIST, M.: Effect of chlorpromazine or haloperidol
on formation of 3-methoxytyramine and normetanephrine in mouse brain.
Acta phar
	- phin-release and ACTH in the rhesus monkey: Effects of biogenic amines. Endocrinology 98: 420-428, 1976.

	51. CHAN, L. T., SCHAAL, S. M., AND SAFFRAN, M.: Properties of the corticotrophin-releasing factor of the rat median
	- 51. CHAN, L. T., SCHAAL, S. M., AND SAFFRAN, M.: Properties of the corticotro-
phin-releasing factor of the rat median eminence. Endocrinology 85: 644-
651. 1969. EXA, L. T., SCHAAL, S. M., AND SAFFRAN, M.: Properties of the cortiphin-releasing factor of the rat median eminence. Endocrinology 84651, 1969.
1651, 1969. L. T., DE WIED, D., AND SAFFRAN, M.: Comparison of assa A. L. T.,
	-
	- **53. CHAITA, C., T., DE WIED, D., AND SAFFRAN, M.: Comparison of assays for** corticotropin releasing activity. Endocrinology 84: 967-972, 1969.
 53. CHIHARA, K., KATO, Y., MAEDA, K., MATSUKURA, S., AND IMURA, H.: Suppres S2. CHAN, L. T., DE WIED, D., AND SAFFRAN, M.: Comparison of assays for
corticotropin releasing activity. Endocrinology 84: 967-972, 1969.
53. CHIHARA, K., KATO, Y., MAEDA, K., MATSUKURA, S., AND IMURA, H.:
Suppression by Suppression by cyproheptadine of human growth hormone and cortisol secretion during sleep. J. Clin. Invest. 57: 1393-1402, 1976.
54. COYNE, M. D., AND KITAY, J. I.: Effect of ovariectomy on pituitary secretion of ACTH. End Suppression by cyproheptadine of human growth hormone and cortisol
secretion during sleep. J. Clin. Invest. 57: 1393-1402, 1976.
54. Coyne, M. D., AND KITAY, J. I.: Effect of ovariectomy on pituitary secretion
of ACTH. End
	-
	-
	-
	-
	- secretion during sleep. J. Clin. Invest. 57: 1393-1402, 1976.

	54. Coyne, M. D., AND Krray, J. I.: Effect of ovariectomy on pituitary secretion

	of ACTH. Endocrinology 85: 1097-1102, 1969.

	55. CRITENDOW, V., LIEBELT, R. A 373-392, 1977.

	58. DALLMAN, M. F., JONES, M. T., VERNIKOS-DANELLIS, J., AND GANONG, W.

	F.: Corticoid feedback control of ACTH secretion: Rapid effects of bilateral

	adrenalectomy on plasma ACTH in the rat. Endocrinology
	-
	- bition of CRF secretion. Fed. Proc. 26: 315, 1967.
ALLMAN, M. F., AND YATES, F. E.: Anatomical and functional mapping of central neural input and feedback pathways of the adrenocortical system.
Mem. Soc. Endocrinol. 17: 39 60. DALLMAN, M. F., AND YATES, F. E.: Anatomical and functional mapping of central neural input and feedback pathways of the adrenocortical system.
Mem. Soc. Endocrinol. 17: 39-72, 1968.
61. DALMAN, M. F., AND YATES, F. E.
	-
	- central neural input and feedback pathways of the adrenocortical system.
Mem. Soc. Endocrinol. 17: 39-72, 1968.
61. DALLMAN, M. F., AND YATES, F. E.: Dynamic asymmetries in the cortico-
steroid feedback path and distributi **85:** 861-866, 1969. the adrenocortical system. Ann. N.Y. Acad. Sci. 156: 696-721, 1969.
62. DAVID-NELSON, M. A., AND BRODISH, A.: Evidence for a diurnal rhythm of
corticotropin-releasing factor (CRF) in the hypothalamus. Endocrinology
65: 861
- pituitary-adrenocortical system and thyroid gland during the oestrous controls. A., AND BRODISH, A.: Evidence for a diurnal rhythm of cycle of the rat. J. Endocrinol. 78: 359-366, 1978.

34. BUCKINGHAM, J. C., AND HODGES, Collistic Cortocotrophi-releasing factor (CRF) in the hypothalamus. Endocrinology

85: 861-866, 1969.

63. DELITALA, G., MASALA, A., ALAGNA, S., AND DEVILLA, L.: Effect of cypro-

heptadine on the spontaneous diurnal varia
	- and ACTH-GH secretion induced by L-dopa. Biomedicine 23: 406-409,
1975.
64. DHARWAL, A. P. S., ANTUNES-RODRIGUES, J., REESER, F., CHOWERS, I.,
AND MCCANN, S. M.: Purification of hypothalamic corticotrophin-releas-
ing fact
	-
	- 65. DHARIWAL, A. P. S., RUSSELL, S. M., MCCANN, S. M., AND YATES, F. E.:
Assay of corticotropin releasing factors by injection into the anterior
pituitary of intact rats. Endocrinology 84: 544-556, 1969.
66. DUBE, D., LECL Eminence of normal and adrenalectomised rats. Amer. **J.** Ann and adventuation of vasopressin and neurophysin in the median eminence of normal and adrenalectomised rats. Amer. J. Anat. 147: 103-108, 1976.
 108, 1976.
 10 66. DUBE, D., LECLERC, R., AND PELLETIER, G.: Electron microscopic immunohistochemical localisation of vasopressin and neurophysin in the median eminence of normal and adrenalectomised rats. Amer. J. Anat. 147: 103-67. EGD
	-
- (London) **372:** 469-479, 1977.

40. BUCKINGHAM, J. C., AND HODGES, J. R.: Hypothalamo-pituitary activity in influence on the hypothalamo-pituitary-adrenal axis in the rat. Neuroen-

the betamethesone-treated rat. J. Endocr eminence of normal and adrenalectomised rats. Amer. J. Anat. 147: 103-
108, 1976.

GDAHL, R. H., RICHARDS, J. B., AND HUME, D. M.: Effect of reserpine on

adrenocortical function in unanaesthetized dogs. Science 123: 418,
	- 69. ENDRÖCZI, E., AND LISSÁK, K.: Interrelations between palaeocortical activity and pituitary-adrenocortical function. Acta. physiol. acad. sci. hung. 21: 257-263. 1962.
	- 68. EISENBERG, R. M.: Further evidence of a central alpha-adrenergic inhibitory
influence on the hypothalamo-pituitary-adrenal axis in the rat. Neuroen-
docrinology 17: 154-166, 1975.
69. ENDRÖCZI, E., AND LISÁR, K.: Inter
- **tion. Acts physiol. acad.** sci. hung. **24: 211-221, 1963.** 71. **FELDMAN, S.: The interaction of neural and endocrine factors regulating** CONTROVERCE HEN REGIST

tion. Acta physiol. acad. sci. hung. 24: 211-221, 1963. 100.

71. FELDMAN, S.: The interaction of neural and endocrine factors regulating

hypothalamic activity. In Brain-Pituitary Interrelationship
- LDMAN, S.: The interaction of neural and endocrine factors regulating hypothalamic activity. In Brain-Pituitary Interrelationships, ed. by A. Brodish and E. S. Redgate, pp. 224-238, Karger, Basel, 1973.
LDMAN, S., CONFORTI **Acts endocrinol. 73: 660-664, 1973.** I. Effect of dexamethasone on advenocrical responses in intact and hypothalamic deafferented rats.
Acta endocrinol. 73: 660-664, 1973.
Acta endocrinol. 73: 660-664, 1973.
T. FELDMAN, S
- adrenocortical responses in intact and hypothalamic deafferented rats.
Acta endocrinol. 73: 660-664, 1973.
TSLEMAN, S., CONFORTH, N., CHOWERS, I., AND DAVIDSON, J. M.: Inhibitory
effect of hypothalamic implants of corticos
-
- effect of hypothalamic implants of corticosterone on adrenocortical response to auditory stimulation. Israel J. Med. Sci. 3: 915-917, 1967.

74. FLEISCHER, N., DONALD, R. A., AND BUTCHER, R. W.: Involvement of adenosine 3%
- (GC). Clin. Res. 18: 300, 1970.
 105. Sone. Clin. Res. 18: 30, 1970.

76. FLEISCHER, N., AND RAWLS, W.: Adrenocorticotrophin (ACTH) synthesis and release in rat pituitary monolayer culture: The effect of glucocorticoids
- 76. FLEISCHER, N., AND RAWLS, W.: Adrenocorticotrophin (ACTH) synthesis
and release in rat pituitary monolayer culture: The effect of glucocorticoids
(GC). Clin. Res. 18: 360, 1970.
77. FORTIER, C., AND DE GROOT, J.: Adeno
-
- (GC). Clin. Res. 18: 360, 1970.

The method of remote control stimulation. Phil. Trans.

To mark a plasma free corticosteroids during regeneration of the enucleated adrenal

Pay. Soc. London Ser. Biol. Sci. 248: 385-441, 1 80. GANONG, W. F.: Evidence for a central noradrenergic system that inhibits
ACTH secretion. In Brain-Endocrine Interaction. Median Eminence:
Structure and Function, ed. by K.M. Knigge, pp. 254–266, Karger, Basel,
1972.
80 ACTH secretion. In Brain-Endocrine Interaction. Median Eminence:
Structure and Function, ed. by K.M. Knigge, pp. 254-266, Karger, Basel,
1972.
Prog. Brain Res. 38: 41-57, 1972.
Prog. Brain Res. 38: 41-57, 1972.
B1. GANONG,
-
-
- SCAPAGNINI, P.: Brain amines and the control of ACTH and growth hormone secretion. In Hypothalamic Hormones, ed. by M. Motta, P.G. Crosignani, 112. High and L. Martini, pp. 237-248, Academic Press, London, 1977.

EVINORE, and L. Martini, pp. 237-248, Academic Press, London, 1977.

82. GANONG, W. F., KRAMER, N., SALMON, J., REID, I. A., LOVINGER, R., SCAPAGNINI, U., BORYCZKA, A. T., AND SHAKELFORD, R.: Pharmacological

evidence for inhibitio
- evidence for inhibition of ACTH secretion by a central adrenergic system
in the dog. Neuroscience 1: 167-174, 1976.
83. GEORGE, R.: Pituitary: Hypothalamus. In Biochemical Pharmacology on
New York, 1971.
84. GEORGE, R., AN
-
- 83. GEORGE, R.: Pituitary: Hypothalamus. In Biochemical Pharmacology of
Records. R.: Pituitary: Hypothalamus. In Biochemical Pharmacology of
Narcotic Analgesic Drugs, pp. 283-296, ed. by D.H. Louet, Plenum Press,
New York, activation by morphine. Brit. J. Pharmacol. Chemother. 10: 260–264, 1955.
86. GEORGE, R., AND WAY, E. L.: The role of the hypothalamus in pituitary-adrenal activation and antidiuresis by morphine. J. Pharmacol. Exp. Ther.

-
- 86. GEORGE, K., AND WAT, E. L.: The role of the hypothalamus in pituitary-
adrenal activation and antidiuresis by morphine. J. Pharmacol. Exp. Ther.
126: 111-115, 1969.
86. GIBBS, F. P., AND SCOTT, D. E.: The influence of 1966. GIBBS, F. P., AND SCOTT, D. E.: The influence of glucocorticoids on the fine structure of the rat median eminence. Endocrinology 94: 303-308, 1974.

187. GIBSON, A., GINSBURG, M., HALL, M., AND HART, S. L.: The effec
- intericular administration of one interior of correction of correction of correction of methionic secretion of methionic secretion of corticosterone in mice. Brit. J. Pharmacol. **66:** 164-166, 1979.
 Example 20: 164-166, 88. **GIBBON, A., GINBBURG, M., HALL, M., AND HART, S. L.:** The effect of intracerebroventricular administration of methionine enkephalin on the stress-induced secretion of corticosterone in mice. Brit. J. Pharmacol. 66: 11
- 164-166, 1979.

194-166, 1979.

194-166, 1979.

20. GILLUES, G., **ESTIVARIZ, F. E.**, AND LOWRY, P. J.: Investigations on the

nature of corticotrophin releasing factor using the perfused isolated rat

20. GILLUES, G., AND **column as a bioassay for factor (s)** controllations on that the perfused isolated anterior pituitary cell column J. Endocrinol. 80: 56P, 1979.
 column as a bioassay for factor(s) controllation anterior pituitary (column
- mature of corticotrophin releasing factor using the perfused isolated rate
anterior pituitary cell column. J. Endocrinol. 80: 56P, 1979.
90. GILLIES, G., AND LOWRY, P. J.: Perfused rat isolated anterior pituitary cell
colu
-
- 90. GILLES, G., AND LOWRY, P. J.: Perfused rat isolated anterior pituitary cell
column as a bioassay for factor(s) controlling release of adrenocorticotropin:
Validation of a technique. Endocrinology 103: 521-527, 1978.
91 in adrenocorticotropin release. Endocrinology 103: 528-534, 1978.
-
- acterisation of rat stalk median eminence vasopressin and its involvement
in adrenocorticotropin release. Endocrinology 103: 528-534, 1978.
HULLANI, G., MOTTA, M., AND MARTINI, L.: Reserpine and corticotrophin
secretion. A blood perfusing the adenohypophysis. Experientia (Basel) 18: 279-281,
- **94.** GOLDMAN, H., AND LINDNER, L.: Antidiuretic hormone concentration in 123. Holood perfusing the adenohypophysis. Experientia (Basel) 18: 279-281, following long perfusing the adenohypophysis. Experientia (Basel) 18: 27 **suppression with corticosteroids. J. Clin. Endocrinol. Metab. 25: 11-16,** 1949. 96. GRABER, A. L., NET, R. L., NICHOLSON, W. E., ISLAND, D. P., AND LIDD G. W.: Natural history of pituitary-adrenal recovery following long to suppression with corticosteroids. J. Clin. Endocrinol. Metab. 25: 11-1949.

96
-
- 1949.

1949.

2008. GREEN, J. D., AND HARRIS, G. W.: Observation of the hypophysioportal

vessels of the living rat. J. Physiol. (London) 108: 359-361, 1949.

37. GREER, M. A., AND ALLEN, C. F.: The effect of pentobarbital
-
- Neuroendocrinology 17: 258-264, 1975.

Neuroendocrinology 17: 258-264, 1975.

98. DE GROOT, J., AND HARRIS, G. W.: Hypothalamic control of the anterior 127. Figure 127. AND HARRIS, G. W.: Hypothalamic control of the anteri
- 100. GUHLEMIN, R., AND ROSENBERG, B.: Humoral hypothalamic control of

anterior pituitary: A study with combined tissue cultures. Endocrinology

57: 599-607, 1955. **57:** 599-607, 1965. **101. R., AND ROSENBERG, B.:** Humoral hypothalamic control of anterior pituitary: A study with combined tissue cultures. Endocrinology 57: 599-607, 1965. .
101. GUILLEMIN, R., AND SCHALLY, A. V.: Con **luming factor (CRF)** in action of anterior pituitary: A study with combined tissue cultures. Endocrinology $57:599-607$, 1965.
 (CRF) in acid extracts of sheep hypothalamus by gel filtration

leasing factor (CRF) in a
- anterior pituitary: A study with combined tissue cultures. Endocrinology
57: 599-607, 1955.
UILLEMIN, R., AND SCHALLY, A. V.: Concentration of corticotrophin re-
leasing factor (CRF) in acid extracts of sheep hypothalamus
- 102. HARE, H. A. D. SCHALLY, A. V.: Concentration of corticotrophin releasing factor (CRF) in acid extracts of sheep hypothalamus by gel filtration leasing factor (CRF) in acid extracts of sheep hypothalamus by gel filtrat
- 101. GUILLEMIN, R., AND SCHALLY, A. V.: Concentration of corticotrophin re-
leasing factor (CRF) in acid extracts of sheep hypothalamus by gel filtration
and counter current distribution. Texas Rep. Biol. Med. 21: 541-545, 104. HARRIS, G. W.: The induction of pseudo-pregnancy in the rat by electrical stimulation through the head. J. Physiol. (London) 88: 361-367, 1936.
290, 1956.
HARRIS, G. W.: The induction of pseudo-pregnancy in the rat by
-
- chlorpromazine in the assay of corticotrophin. Acta endocrinol. 20: 283-290, 1965.
290, 1965.
104. Haraus, G. W.: The induction of peeudo-pregnancy in the rat by electrical
106. Haraus, G. W.: The induction of ovulation in
- 106. HARRIS, G. W.: The induction of ovulation in the rabbit, by electrical
stimulation of the hypothalamo-hypophysial mechanism. Proc. Roy. Soc.
Ser. B Biol. Sci. 122: 374-394, 1937.
106. HARRIS, G. W.: The innervation an **the ration of the rat. J. Physiol. (London) 111:** 347-360, 1960. IMARIS, G. U. Physiol. (Rondon) Ser. B Biol. Sci. 232: 365-441, 1947.
 RARRIS, G. W.: Oestrus rhythm. Pseudopregnancy and the pituitary stalk in the rat.
-
-
- Roy. Soc. London Ser. B Biol. Sci. 232: 385-441, 1947.

107. HARRIS, G. W.: Oestrus rhythm. Pseudopregnancy and the pituitary stalk in

the rat. J. Physiol. (London) 111: 347-360, 1950.

108. HARRIS, G. W., AND JACOBSOHN,
-
- intuitary gland. Proc. Roy. Soc. Ser. B Biol. Sci. 139: 263-276, 1962.

109. HEDGE, G. A.: The effects of prostaglandins on ACTH secretion. Endocrinology 91: 925-933, 1972.

110. HEDGE, G. A., AND SMELIK, P. G.: Corticotro nology 91: 925-933, 1972.

110. HEDGE, G. A., AND SMELIE, P. G.: Corticotrophin release. Inhibition by

intrahypothalamic implantation of atropine. Science 159: 891, 1968.

111. HEDGE, G. A., VAN REE, J. M., AND VERSTEEG,
- and L. Martini, pp. 237-248, Academic Press, London, 1977.

and L. Martini, pp. 237-248, Academic Press, London, 1977.

82. GANONG, W. F., KRAMER, R., SALMON, J., REID, I. AND SEARCHER, R., SALMON, J., REID, I., CONDON, J. after thy pothalamic catecholamine synthesis and ether stress-induced
detween hypothalamic catecholamine synthesis and ether stress-induced
ACTH secretion. Neuroendocrinology 81: 236-246, 1976.
113. **HEDGE,** G. A., YATES,
	-
	- 112. HEDGE, G. A., AND DE WIED, L.: COTGOGTOPHIN and Vasopressin secretion
after hypothalamic implantation of atropine. Endocrinology 88: 1257-1259,
1976.
1976.
1986.
1986.
1986.
1986.
A., YATES, M. B., MARCUS, R., AND YAT **and normalism is complementated in the series of control of the series of the series of the series of the series of control and normalism of the rate in intero. Effect of acetylcholine and order and intervalse of the rate**
	- putative neurotransmitters on the release of corticotrophin releasing hor-
mone from the hypothalamus of the rat in vitro. Effect of acetylcholine
and noradrenaline. Neuroendocrimology 17: 1-11, 1975.
115. HILLHOUSE, E. W.
	-
	- 30, 1976.

	116. HIMWICH, W. A., AND DAVIES, J. M.: Brain amino acids as affected by acute

	and chronic administration of chlorpromazine. Biol. Psychiat. 5: 89-98,

	1972.

	117. HIROSHIOR, T.: CRF assay by intrapituitary inj HARGER, T.: CRF assay by intrapituitary injection through the para-
pharyngeal approach and its physiological validation. In Brain-Pituitary-
Adrenal Interrelationships, ed. by A. Brodish and E.S. Redgate, pp. 57-78,
Karge
	- intracerebroventricular administration of methionine enkephalin on the
stress-induced secretion of corticoterone in mice. Brit. J. Pharmacol. 66: 118. HIROSHIGE, T., AND ITOH, S.: Studies on the release of corticotropin by pharyngeal approach and its physiological valuation. *In* Brain-Pitultary-
Adrenal Interrelationships, ed. by A. Brodish and E.S. Redgate, pp. 57-78,
Karger, Basel, 1972.
118. HIROSHIGE, T., AND ITOH, S.: Studies on the re means of intrapituitary microinjection. In Integrative Mechanism of Neuronnocorine System, ed. by S. Itoh, pp. 21-40, Hokkaido University School of Medicine, Sapporo, 1968.
119. HIROSHIGE, T., KUNITA, H., YOSHIMURA, K., AN
		-
		- of Medicine, Sapporo, 1968.

		119. HIROSHIGE, T., KUNITA, H., YOSHIMURA, K., AND ITOH, S.: An assay method

		for corticotropin-releasing activity by intrapituitary microinjection in the

		rat. Jap. J. Physiol. 18: 179-189, 19
- Validation of a technique. Endocrinology 103: 521-527, 1978.

91. GILLIES, G., AND LOWRY, P. J.: Corticotrophin releasing factor may be

modulated vasopressin. Nature (London) 278: 463-464, 1979.

92. GILLIES, G., AND WORK for corticotropin-releasing activity by intrapituitary microinjection in the
rat. Jap. J. Physiol. 18: 179–189, 1968.
120. HIROSHIGE, T., SATO, T., OTA, R., AND ITOH, S.: Increase of corticotropin-
releasing activity in th 121. HIROSHIGE, T., AND WADA-OKADA, S.: Diurnal changes of hypothalamic content of corticotrophin-releasing activity in female rats at various stages of the estrous cycle. Neuroendocrinology 12: 316-319, 1973.
122. Honces,
	-
	- function in the adrenalectomial and contribution of pituitary
 function of *advenaling* in the production of *advenaling* adreno-corticotrophic activity. J. Endocrinol. 9: 342-350, 1953.

	123. HoDGES, J. R., AND JONES, M
	- and the advertiser and the same of the production in the advertiser of the production in the advertised rat. J. Physiol. (London) 173: 190–200, 1964.

	124. Hoogas, J. R., AND MITCHLEY, S.: The effect of betamethasone on ci
- 98. GREEN, J. D., AND HARRIS, G. W.: Observation of the hypophysioportal and function in the rat after prolonged treatment with betamethasone.

97. GREEN, J. D., AND ALLEN, C. F.: The effect of pentobarbital on basal and
 125. HODGES, J. R., AND MITCHLEY, S.: Recovery of hypothalamo-pituitary-
adrenal function in the rat after prolonged treatment with betamethasone.
Brit. J. Pharmacol. 40: 732-739, 1970.
126. HODGES, J. R., AND MITCHLEY, S.
	-
	-
	- Pharmacol. 41: 640-647, 1971.

	27. Honors, J. R., AND SADOW, J.: Impairment of pituitary adrenocorticotrophic

	function by corticosterone in the blood. Brit. J. Pharmacol. Chemother.

	30: 385-391, 1967.

	28. Honors, J.: R.

Downloaded from pharmrev.aspetjournals.org at Thammasart University on December 8, 2012

Downloaded from pharmrev aspetjournals org at Thammasart University on December 8, 2012

ARMACOLO

- 129.
129. Hodges, J. R., AND VELLUCCI, S. V.: The effect of reserpine on hypothalamotic
139. Hodges, J. R., AND VELLUCCI, S. V.: The effect of reserpine on hypotha
139. Moreo-Cortical function in the rat. Brit. J. Pharmaco **BUCKIN**
pituitary adrenocortical function in the rat. Brit. J. Pharmacol. 53: 555-
561, 1975. 129. HODGES, J. R., AND VELLUCCI, S. V.: The effect of reserpine on hypothalamo-
pituitary adrenocortical function in the rat. Brit. J. Pharmacol. 53: 555-
561, 1975.
130. HODGES, J. R., AND VERNIKOS, J.: Circulating corti 129. HODGES, J. R., AND VELLUCCI, S. V.: The effect of reserpine on hypothalamo-
pituitary adrenocortical function in the rat. Brit. J. Pharmacol. 53: 555-
561, 1975.
130. HODGES, J. R., AND VERNIKOS, J.: Circulating cort
-
- Chemotromischer. 13: 98-102, 1968. 132. Honours, J.: Circulating corticotrophin in normal and
adrenalectomised rate after stress. Acta endocrinol. **30:** 188-196, 1959.
131. Hopors, J. R., AND VzENIEOS, J.: A comparison of
- 131. HODGES, J. R., AND VERNIEOS, J.: A comparison of the pituitary inhibitory
effects of prednisone, prednisolone and hydrocortisone. Brit. J. Pharmacol.
Chemother. 13: 98-102, 1958.
132. HODGES, J. R., AND VERNIEOS, J.: chalcorromazine-treat. J. Endocrinol. 77: 54-55P, 1978.
132. Hopozs, J. R., AND VERNIKOS, J.: The effects of hydrocortisone on the level of corticotrophin in the blood and pituitary glands of adrenalectomised a of stressed
-
- of stressed adrenaiectomised rats. J. Physiol. (London) 199: 683-683, 196
Chlorpromazine-treated rat. J. Endocrinol. 77: 54-55P, 1978.
Collorpromazine-treated rat. J. Endocrinol. 77: 54-55P, 1978.
[ol.zBAUER, M., AND VOGT, chlorpromazine-treated rat. J. Endocrinol. 77: 54-55P, 1978.

134. HOLZBAUER, M., AND VOGT, M.: The action of chlorpromazine on die

phalic sympathetic activity and on the release of adrenocorticotro

hormone. Brit. J. Pha
- lolar concentration in the hypothalamus of the concentration in the hypothalamus **of** the hypothesis of a chemical 136. INURA, H., NAKAI, Y., AND YOGHIMI, T.: Effect of 5-hydroxytryptophan (5-HTP) on growth hormone and ACTH release in man. J. Clin. Endocrinol.
-
- 136. HOLZBAUER, M., AND VOGT, M.: Depression by reserpine of the noradrena-
line concentration in the hypothalamus of the cat. J. Neurochem. 1: 8-11,
1956.
IMURA, H., NAKAI, Y., AND YOSHIMI, T.: Effect of 5-hydroxytryptoph 489-497, **1972.** Metab. 36: 204-206, 1973.

137. JONES, M. T., BRUSH, F. R., AND NEAME, R. L. B.: Characteristics of fast

feedback of corticotrophin release by corticosteroids. J. Endocrinol. 55:

489-497, 1972.

138. JONES, M. T., GILLHA
-
- Feedback of corticotrophin release by corticosteroids. J. Endocrinol. 55:

489-497, 1972.

138. JONES, M. T., GILLHAM, B., HOLMES, M. C., HODGES, J. R., AND BUCK-

INGHAM, J. C.: Influence of substance P on hypothalamo-pit
- 139. JONES, M. T., AND HILLHOUSE, E. W.: Structure-activity relationship and
the mode of action of corticosteroid feedback on the secretion of cortico-
trophin-releasing factor (corticoliberin). J. Steroid Biochem. 7: 1189 140. JONES, M. T., HILLHOUSE, E., AND BURDEN, J.: Secretion of corticotropin-
releasing hormone in vitro. In Frontiers in Neuroendocrinology, ed. by L.
Martini and W.F. Ganong, vol. 4, pp. 195-226, Raven Press, New York,
1 releasing hormone in vitro. In Frontiers in Neuroendocrinology, ed. by L.
Martini and W.F. Ganong, vol. 4, pp. 195-226, Raven Press, New York,
1976.
news, M. T., HILLHOUSE, E. W., AND BURDEN, J.: Effect of various putative
- Martini and W.F. Ganong, vol. 4, pp. 195-226, Raven Press, New Yorl 1976.
1976.

ONES, M. T., HILLHOUSE, E. W., AND BURDEN, J.: Effect of various putative

neurotransmitters on the secretion of corticotrophin-releasing hor 1976.

141. JoNES, M. T., HILLHOUSE, E. W., AND BURDEN, J.: Effect of various putative

neurotransmitters on the secretion of corticotrophin-releasing hormone

from the rat hypothalamus *in vitro*—A model of the neurotrans
-
- from the rat hypothalamus in vitro—A model of the neurotransmitters
involved. J. Endocrinol. 69: 1-10, 1976.
142. JONES, M. T., HILLHOUSE, E. W., AND BURDEN, J.: Dynamics and mechanics
of corticosteroid feedback at the hyp decries and all the states of the states of the states of the states of the states. A. T., AND TIPTAFT, E. M.: Structure-activity relationship of various corticosteroids on the feedback control of corticostrophin secretion
- corticosteroids on the feedback control of corticotrophin secretion. Brit. J.
Pharmacol. **59:** 35–41, 1977.
ONES, M. T., TIPTAFT, E. M., BRUSH, F. R., FERGUSSON, D. A. N., AND
NEAME, R. L. B.: Evidence for dual corticoster 144. JONES, M. T., TIPTAFT, E. M., BRUSH, F. R., FERGUSSON, D. A. N., AND
NEAME, R. L. B.: Evidence for dual corticosteroid receptor mechanisms in
the feedback control of adrenocorticotrophin secretion. J. Endocrinol. 60:
 SINEAME, R. L. B.: Evidence for dual corticosteroid receptor mechanisms in
the feedback control of adrenocorticotrophin secretion. J. Endocrinol. 60:
223–233, 1974.
KAPLANSEKI, J., AND SMELIK, P. G.: Analysis of the inhibi
- 659, **1973.** 223-233, 1974.

223-233, 1974.

146. KAPLANSKI, J., AND SMELIK, P. G.: Analysis of the inhibition of the AC

release by hypothalamic implants of atropine. Acta endocrinol. 73: 6

659, 1973.

446. KASTIN, A. J., PLOTNIKOFF,
- LAPLANSKI, J., AND SMELIK, P. G.: Analysis of the inhibition of the ACTH
release by hypothalamic implants of atropine. Acta endocrinol. 73: 651-
659, 1973.
AETIN, A. J., PLOTNIKOFF, N. P., HALL, R., AND SCHALLY, A. V.: Hyp Academic Press, London, 1977.

HACAMIN, A. J., PLOTNIKOFF, N. P., HALL, R., AND SCHALLY, A. V.: Hypotha-

147. KawaKaMI: Dimones and the central nervous system. In Hypothalamic Hormones, ed. by M. Motta, P.G. Crosignani, a
- lamic hormones and the central nervous system. *In* Hypothalamic Hormones, ed. by M. Motta, P.G. Crosignani, and L. Martini, pp. 261-268, Academic Press, London, 1977.
KAWAKAMI, M., SETO, K., KIMURA, F., AND YANASE, M.: Di for Press, London, 1977.
 KAWAKAMI, M., SETO, K., KIMURA, F., AND YANASE, M.: Difference in the buffer action between the limbic structures and the hypothalamus to the buffer action between in abbits. *In* **Proceedings of** Immobilization streas in rabbits. In Proceedings of the International Society
for Psychoneuroendocrinology, Brooklyn, 1970, Influence of Hormones on
the Central Nervous System, ed. by D. H. Ford, pp. 107-120, Karger, Basel
- the Central Nervous System, ed. by D. H. Ford, pp. 107-120, Karger, Basel,
1971.
148. KEIM, K. L., AND Stoc, E. B.: Plasma corticosterone and brain catecholamines in stress. Effect of psychotropic drugs. Pharmacol. Biochem COM. K. L., AND SIGG, E. B.: Plasma corticosterone and brainmes in stress: Effect of psychotropic drugs. Pharmacol. Bioch 6: 79-85, 1977.

ENDALL, J. W., AND ALLEN, C.: Studies of the glucocorticoirontrol of ACTH secretion
-
- 149. KENDALL, J. W., AND ALLEN, C.: Studies of the glucocorticoid feedback control of ACTH secretion. Endocrinology 82: 397–405, 1968.
150. KENDALL, J. W., AND ALLEN, C.: Studies of the glucocorticoid feedback control of A Soc. Exp. Biol. Med. 106: 579-581, 1961. In the rat after gonadectom and the REALMAN, N., SULMAN, F. G., AND WINNIE, H. Z.: Activity of pituitary-adrenal contex axis during acute and chronic reserpine treatment. Proc. Soc. 150. KHAZAN, N., SULMAN, F. G., AND WINNIE, H. Z.: Activity of pituitary-
adrenal cortex axis during acute and chronic reserpine treatment. Proc.
Soc. Exp. Biol. Med. 106: 579-581, 1961.
151. KITAY, J. I.: Pituitary-adrena
-
- nology 65: 548-554, 1959. 1959. 1959. 1959. 1959. 1959. 1959. ISBN 977-747, J. I., Hotter, D. A., AND JAILER, J. W.: "Inhibition" of pituitary ACTH release after administration of reserpine or epinephrine. Endocri-
ACTH re
- gramm continues with correlation and dexamethason of principal correlation of primary and ACTH release after administration of reserpine or epinephrine. Endocrinology 65: 548-554, 1969.

EXLORT, E. R., AND MCEWEN, B. S.: D from rat brain. Biochim. Biophys. Acts 421: Department of reserves between cytosol receptor complexes with corticosterone and dexamethasone in hippocampal tissue from rat brain. Biochim. Biophys. Acts 421: 124-132, 1976. 1 163. DE KLOET, E. R., AND MCEWEN, B. S.: Differences between cytosol receptor
from rat brain. Biochim. Biophys. Acta 421: 124-132, 1976.
164. DE KLOET, R., WALLACH, G., AND MCEWEN, B. S.: Differences in corticos-
terone an
- now in the hippocampus and amygdala. Fed. Proc. 20: 185, 1960. ISB KLOFT, R., WALLACH, G., AND MCEWEN, B. S.: Differences in corticos-
ogy 96: 596-609, 1975.
185. KNIGGE, K. M.: Adrenocortical response to immobilization in
-
-

- hippocampus and amygdala. Proc. Soc. Exp. BioL Med. 108:18-21,1961. **157.** KrnGoE, K. M., **AND HAYS, M.:** Evidence of inhibitive role of hippocampus **M**
hippocampus and amygdala. Proc. Soc. Exp. Biol. Med. 108: 18–21, 1961.
KNIGGE, K. M., AND HAYS, M.: Evidence of inhibitive role of hippocampus
in neural regulation of ACTH release. Proc. Soc. Exp. Biol. Med. 114: 67-
6
- hippocampus and amygdala. Proc. Soc. Exp. Biol. Med. 108: 18-21, 1961.

157. KNIGGE, K. M., AND HAYS, M.: Evidence of inhibitive role of hippocampus

in neural regulation of ACTH release. Proc. Soc. Exp. Biol. Med. 114: 67 ERRA, N., GARCIA, J. F., AND ELLIOTT, H. W.: Effects of acute and chronic administration of narcotic analgesics on growth hormone and corticotre phin (ACTH) secretion in rats. Progr. Brain Res. 39: 347-360, 1973.
159. Kors
-
-
- phin (ACTH) secretion in rats. Progr. Brain Res. 39: 347-360, 1973.
159. KOSTERLITZ, H. W., AND WATT, A. J.: Kinetic parameters of narcotic drugs.
Brit. J. Pharmacol. 33: 266-276, 1968.
160. KRIEGER, D. T., AMOROSA, L., AN deafferent and Cousting's disease. N. Engl. J. Med. 293: 893-896, 1975.

161. KRIEGER, D. T., LIOTTA, A. AND BROWNSTEIN, M. J.: Corticotropin releasing

factor distribution in normal and Brattleboro rat brain, and effect o **of Plasma 17-hydroxycorticoateroids.** Amer. J. Corticotropin releasing factor distribution in normal and Brattleboro rat brain, and effect of deafferentation, hypophysectomy and steroid treatment in normal animals.
Endocr
-
- S., PELLETIER, D., AND RIZZO, F.: Serotonin mediation of circadian periodicity
of plasma 17-hydroxycorticosteroids. Amer. J. Physiol. 217: 1703-1707,
1969.
ABRIER, F., BORGEAT, P., FERLAND, L., LEMAY, A., DUPONT, A., LEMAI hypothalamic hypothalamic hormones. **In Hypothalamic Hormones,** ABRIE, F., BORGEAT, P., FERLAND, L., LEMAY, A., DUPONT, A., LEMAIRE, S., PELLETIER, G., BARDEN, N., DROUIN, J., DELEAN, A., BELANGER, A., AND JOLICOEUR, P.: M hypothalamic hypophysiotropic hormones. *In* Hypothalamic Hormones, ed. by M. Motta, P. G. Crosignani, and L. Martini, pp. 109–123, Academic Press, London, 1977.
164. LAMMERS, J. R. G.: De invloed van chlorpromazine op net hypothalamic hypophysiotropic hormones. In Hypothalamic Hormones,
ed. by M. Motta, P. G. Crosignani, and L. Martini, pp. 109-123, Academic
Press, London, 1977.
164. LAMMERS, J. R. G.: De invloed van chlorpromazine op net h
-
- 165. LAMMERS, J. G. R., AND DEWIED, D.: The blocking action of chlorpromazine on stress-induced pituitary-adrenal activity in nembutalized rats. Acta Physiol. Pharmacol.. Néer. 13: 103, 1964.
166. LENGVARI, I., AND HALASZ, on stress-induced pituitary-adrenal activity in nembutalized rats. Acta

Physiol. Pharmacol.. Néer. 13: 103, 1964.

166. LENGVARI, I., AND HALASZ, B.: On the site of action of reserpine on ACTH

secretion. J. Neural Transm
-
- Fhysiol. Pharmacol.. Néer. 13: 103, 1964.
166. LENGVARI, I., AND HALASZ, B.: On the site of action of reserpine on ACTH
secretion J. Neural Transm. 33: 289-300, 1972.
167. LOTT, V. J., KOKKA, N., AND GEOROE, R.: Pituitary
- **biology 4: 326-332, 1969.**
 hiosynthesis of peptides related to corticotropins and β **-melanotropins.**
 biosynthesis of peptides related to corticotropins and β **-melanotropins.**
 Ann. N.Y. Acad. Sci. 2977: 49-62,
- nology 4: 326-332, 1969.

nology 4: 326-332, 1969.

168. Loway, P. J., SILMAN, R. E., Hore, J., AND SCOTT, A. P.: Structure and

biosynthesis of peptides related to corticotropins and β -melanotropins.

Ann. N.Y. Acad. S Ann. N.Y. Acad. Sci. 297: 49-62, 1977.

169. LUFT, R., EFENDIC, S., HOKFELT, T., JOHANSSON, O., AND ARIMURA, A.:

Immunohistochemical evidence for the localization of somatostatin-like

immunohistochemical evidence for the
-
- **EVANGROVER, J., AND BRODISH, A.: Tissue-CRF—an extrahypothalamic** corticotrophin releasing factor (CRF) in the peripheral blood of stressed rats. Neuroendocrinology 12: 225-235, 1973.
 ALIFOUZ, M., AND Exp. E. A.: The e 39-42, 1958.
172. MAHMOUD, S., AND JONES, M. T.: Relative importance of corticosteroid **171. MAHFOUZ, M., AND EZZ, E. A.: The effect of reserpine and chlorpromazine**
271. MAHFOUZ, M., AND EZZ, E. A.: The effect of reserpine and chlorpromazine
39–42, 1958.
39–42, 1958.
MAHMOUD, S., AND JONES, M. T.: Relative negative-feedback at the hypothalamus and chlorpromazine on the response of the rat to acute stress. J. Pharmacol. Exp. Ther. 123:

39-42, 1958.

172. MAHMOUD, S., AND JONES, M. T.: Relative importance of corticosteroid

n
-
- **EXECUTE:** AND JONES, M. T.: Relative importance of corticosteroid negative-feedback at the hypothalamus and anterior pituitary gland. J. Endocrinol. 75: 29-30P, 1977.
AACKEL, R. P., WESTERMANN, E. O., AND BRODER, B. B.: E
- **Endocrinol. 76: 29-30P, 1977.**

173. MAICKEL, R. P., WESTERMANN, E. O., AND BRODIE, B. B.: Effects of

reserpine and cold exposure on pituitary adrenocortical function in rats. J.
 Pharma-aminobutyric acid (GABA)

and G Pharmacol. Exp. Ther. 134: 167-175, 1961.

174. MAKARA, G. B., AND STARK, E.: Effect of gamma-aminobutyric acid (GABA)

and GABA antagonist drugs on ACTH release. Neuroendocrinology 16:

178-190, 1974.

175. MALHOTRA, C. L
-
-
- 175. MALHOTRA, C. L., AND PUNDLIE, P. G.: The effect of reserpine on the
acetylcholine content of different areas of the central nervous system of
the dog. Brit. J. Pharmacol. Chemother. 14: 46-47, 1959.
176. MARSHALL, F. 178. MARTEL, R. R., WESTERMANN, E. O., AND MAICKEL, R. P.: Dissociation of reserpine-induced sedation and ACTH hypersecretion. Life Sci. 4: 151-155, 1962.
1962.
188. MARTINI, L., AND MORPURGO, C.: Neurohumoral control of t
-
- **179. MARTINI, L., AND MORPURGO, C.: Neurohumoral control of the release of adrenocorticotrophic hormone. Nature (London) 175: 1127-1128, 1955.

179. MARTINI, L., AND MORPURGO, C.: Neurohumoral control of the release of a** 178. MARTINI, L., AND MORPURGO, C.: Neurohumoral control of the release of
adrenocorticotrophic hormone. Nature (London) 175: 1127-1128, 1955.
179. MASON, J. W.: Plasma 17-hydroxycorticosteroid levels during electrical
sti
- **lobe of pitulitary** *in**incluses and radioimmunoassay of plasma in adrenalectomised rats.* **Endocrinology 88: 696-701, 1971.

iii** *i* Bioassay and radioimmunoassay of plasma in adrenalectomised rats.
 iiii *inclearing*
-
- 182. McCANN, S. M.: The corticotrophin releasing activity of extracts of posterial and and and the role of the role of the role of the role of the supration-hypophysial system in the regulation of adrenocorticotrophin secr 181. McCANN, S. M.: The corticotrophin releasing activity of extracts of posterior
lobe of pituitary in vivo. Endocrinology **60:** 664–676, 1957.
182. McCANN, S. M., AND BROBECR, J. R.: Evidence for the role of the supraop-
-
- tico-hypophysial system in the regulation of adrenocorticotrophin secretion. Proc. Soc. Exp. Biol. Med. 87: 318-324, 1954.
183. McCaNN, S. M., aND FRUIT, A.: Effect of vasopressin on release of adrenocorticotrophin in rats 184. McCANN, S. M., AND HABERLAND, P.: Relative abundance of vasopressin and corticotrophin releasing factor in neurohypophysial extracts. Proc. Soc. Exp. Biol. Med. 102: 319-325, 1959.
185. McDoNALD, R. K., Evans, F. T.,
-

spet

- **of morphine and nalorphine on plasma hydrocortisone levels in man. J.**

Pharmacol. Exp. Ther. 125: 241-247, 1959.

186. McDoNALD, R. K., WAGNER, H. N., AND WEISE, V. K.: Relationships

between exogenous antidiuretic hormo of morphine and nalorphine on plasma hydrocortisone levels in man. J.
Pharmacol. Exp. Ther. 125: 241-247, 1959.
CCDONALD, R. K., WAGNER, H. N., AND WEISE, V. K.: Relationships
between exogenous antidiuretic hormone activit man. Pharmacol. Exp. Ther. 125: 241-247, 1959.

186. McDoNALD, R. K., WAGNER, H. N., AND WEISE, V. K.: Relationshet between exogenous antidiuretic hormone activity and ACTH release man. Proc. Soc. Exp. Biol. Med. 96: 566-5 186. MCDONALD, R. K., WAGNER, H. N., AND WEISE, V. K.: Relationships
between exogenous antidiuretic hormone activity and ACTH release in
man. Proc. Soc. Exp. Biol. Med. 96: 566-567, 1957.
187. McEwER, B. S., WEISS, J. M.,
- man. Proc. Soc. Exp. Biol. Med. 96: 566-567, 1957.
187. McEwEN, B. S., WEISS, J. M., AND SCHWARTZ, L. S.: Retention of cortico-
terone by cell nuclei from brain regions of adrenalectomized rats. Brain
Res. 17: 471-482, 197
-
-
- 191. MIASLE, AND MARTINI, L.: The central nervous system and the secretion of anterior pituitary trophic hormones. In Recent Advances in Endocrinology, 8th ed, ed. by V.H.T. James, pp. 1–49, Churchill, London, 1968. 19.1.
- of anterior pitchic hormones. **In Recent Advances in Advances in Advances in Recent Advances in Section Advances in Endocri-Controphic Pelessing factor (CRF) and vasopressin in the regulation of** C of anterior pituitary trophic hormones. In Recent Advances in Endocri-
nology, 8th ed, ed. by V.H.T. James, pp. 1-49, Churchill, London, 1968.
191. MIAHLE, C., LUTZ-BUCHER, B., BRIAUD, B., SCHLEIFFER, R., AND KOCH, B.:
Cor corticotropin (ACTH) secretion. In Interaction within the Brain Pituitary-
Adrenocortical System, ed. by M.T. Jones, B. Gillham, M. Dallman, and S.
Chattopadyay, pp. 63-75, Academic Press, London, 1979.
192. MIRSKY, I. A.,
-
-
- 194. Moson, R. C. A., Moreon, M. M. M. AND McCannics and hypothysectomised rats exposed to noxious stimuli. Endocrinology 55: 28-39, 1954.

193. Moreon, F., CHENEY, D. L., AND COSTA, E.: β -Endorphin inhibits acetylcholi choline turnover in nuclei of rat brain. Nature (London) 267: 267-268, 22
1977.

194. Moss, R. L., DUDLEY, C. A., FOREMAN, M. M., AND MCCANN, S. M.:

Synthetic LRF. A potentiator of sexual behaviour in the rat. In Hypotha-Synthetic LRF. A potentiator of sexual behaviour in the rat. In Hypothlamic Hormones, ed. by M. Motta, P.G. Crosignani, and L. Martini, p. 269–278, Academic Prees, London, 1977.
1977. **M., FRASCHINI, F., PIVA, F., AND MART**
- 269–278, Academic Press, London, 1977.

1955. MOTTA, M., FRASCHINI, F., PIVA, F., AND MARTINI, L.: Hypothalamic and

extrahypothalamic mechanisms controlling adrenocorticotrophin secretion.

23. Mem. Soc. Endocrinol. 17: 3
-
- extrahypothalamic mechanisms controlling adrenocorticotrophin secretion.
Mem. Soc. Endocrinol. 17: 3-18, 1968.
196a. MOTTA, M., MANGILI, G., AND MARTINI, L.: A "short" feedback loop in the control of ACTH secretion. Endoc 196. MULDER, G. H., AND SMELIE, P. G.: A superfusion system technique for the study of the sites of action of glucocorticoids in the rat hypothalamus-
pituitary-adrenal system *in vitro* I. Pituitary cell superfusion. Endo
-
- (ACTH) Stress reaction. Progr. A.: Factors influencing the effect of morphine sulphate on the mecific method for the assay of ACTH. Endocrinology 88: 1063-1068, accorbic acid content of rats' adrenal glands. Brit. J. Pharm
- ogy 100: 1143-1152, 1977.

197. MUNSON, P. L.: Effects of morphine and related drugs on the corticotrophin

(ACTH) stress reaction. Progr. Brain Res. 39: 361-372, 1973.

198. NASAYITH, P. A.: Factors influencing the effect **active Multime, depletion** by direct intra-
pituitary infusion of median eminence extracts. Endocrinology 70: 350-
358, 1962.
200. OHLER, E. A., AND SEVY, R. W.: Inhibition of stress-induced adrenal ascorbic
acid deplet
-
-
- more the hypophysis by chlorpromazine. Acta endocrinol. 22: 283-2
1956.
202. PAROLI, E., AND MELCHIORRI, P.: Urinary excretion of hydroxysteroids,
ketosteroids and aldosterone in rats during a cycle of treatment w
morphine 202. PAROLI, E., AND MELCHIORRI, P.: Urinary excretion of hydroxysteroids, 17.

ketosteroids and aldosterone in rats during a cycle of treatment with

morphine. Biochem. Pharmacol. 6: 1-17, 1961.

201. PARLMURT of adrenal
-
- morphine. Biochem. Pharmacol. 6: 1-17, 1961.

View of advantative vastalland testical and testical retroids. Biochem. Pharmacol. 6: 18-20, 1961.
 EARLMUTTER, A. F., RAPINO, E., AND SAFFRAN, M.: A semi-automated *in***

pres** Examing the state of the Hypothesis Content Pharmacol. 6: 18-20, 1961.

204. PEARLMUTTER, A. F., RAPINO, E., AND SAFFRAN, M.: A semi-automated in
 vitro assay for CRF: Activities of peptides related to oxytocin and vaso-
- 1336-1339, **1975.** Pressin. Neuroendocrinology 15: 106-119, 1974.

2005. PEARLMUTTER, A. F., RAPINO, E., AND SAFFRAN, M.: The ACTH-releasing

hormone of the hypothalamus requires a co-factor. Endocrinology 97:

1336–1339, 1975.

2006. PENG,
-
-
-
-
- factor(s) using suspensions of isolated pituitary cells. Neuroendocrinology

12: 236-248, 1973.

237. PORTANOVA, R., AND SAYERS, G.: Isolated pituitary cells. Neuroendocrinology

227. PORTANOVA, R., AND SAYERS, G.: Isolate **208. PORTER, J. C., AND JONES, J. C.: Effect of plasma from hypophysial-portal vessel blood on adrenal ascorbic acid. Endocrinology 58: 62-67, 1956.**
209. PORTER, J. C., AND RUMSFELD, H. W.: Effect of lyophilised plasma vessel blood on adrenal ascorbic acid. Endocrinology 58: 62-67, 1956.
209. PORTER, J. C., AND RUMSFELD, H. W.: Effect of lyophilised plasma and plasma fractions from hypophysial-portal vessel blood on adrenal ascorbic acid FIRTER, J. C., AND RUMSFELD, H. W.: Effect of lyophilised plasma a plasma fractions from hypophysial-portal vessel blood on adrenal ascorded. Endocrinology 58: 359-364, 1966.
acid. Endocrinology 58: 359-364, 1965.
from hyp
-
- 210. PORTER, J. C., VANATTA, J. C., AND DILLON, H. T.: Effect of plasma obtained
from hypothalamico-hypophysial portal vessel blood on urinary electro-
lyte excretion by the rat. Fed. Proc. 14: 116, 1955.
211. RAMERE, V. D **of hypothalamic hormones.** Studies on luteinizing hormone-releasing hor-

- EING FACTOR
Crosignani, and L. Martini, pp. 57–74, Academic Press, London, 1977.
APS, D., BARTHE, P. L., AND DESAULLES, P. A.: Plasma and adren*i* **273**
Crosignani, and L. Martini, pp. 57-74, Academic Press, London, 1977.
212. Raps, D., BARTHE, P. L., AND DESAULLES, P. A.: Plasma and adrenal corticosterone levels during the different phases of the sexual cycle in
nor Crosignani, and L. Martini, pp. 57-74, Academic Press, London, 1977.

212. RAPS, D., BARTHE, P. L., AND DESAULLES, P. A.: Plasma and adrenal

corticosterone levels during the different phases of the sexual cycle in

normal 212. RAPS, D., BARTHE, P. L., AND DESAULLES, P. A.: Plasma and adrenal corticosterone levels during the different phases of the sexual cycle in normal female rata. Experientia (Basel) 27: 339-340, 1971.

213. REDGATE, E. S
- 213. **REDGATE, E. S.: ACTH release** evoked by electrical stimulation of brain stem and limbic system sites in the cat: The absence of ACTH release upon infundibular area stimulation Centrophin-releasing activity in steroid **blocked mice. Acts and implies evoked by electrical stimulation of brain** stem and limbic system sites in the cat: The absence of ACTH release upon infundibular area stimulation. Endocrinology 86: 806–823, 1970.
 214. R
-
- 190. MEARTN, J. W., TANTONGCO, M. S., CRABBÉ, J., BAYLES, T. B., AND NELSON, and its central nervous regulation. Hospital (Rio de Janeiro) 2: 221-224,

190. MEARTN, J. W., TANTONGCO, M. S., CRABBÉ, J., BAYLES, T. B., AND N and its central nervous regulation. Endocrinology 86: 806-823, 1970.

RRUP, C.: The determination of corticotrophin-releasing activity in steroid-

blocked mice. Acta endocrinol. 46: 71-79, 1964.

ETTENE, K., AND SCHULZ, F **216.** RETIENE, K., AND SCHULZ, F.: Circadian rhythmicity of hypothalamic CRH and its central nervous regulation. Hospital (Rio de Janeiro) 2: 221-224, 1970.

216. ROYCE, P. C., AND SAYERS, G.: Purification of hypothalamic **releasing factor. Procedure and its central neurons regulation. Hospital (Rio de Janeiro) 2: 221-22

1970.**
 **Roc. B. C., AND SAYERS, G.: Purification of hypothalamic corticotroph

releasing factor. Proc. Soc. Exp. Biol.**
	-
	- 1970.
 216. Rovce, P. C., AND SAYERS, G.: Purification of hypothalamic corticotrophin
 releasing factor. Proc. Soc. Exp. Biol. Med. 103: 447-452, 1960.
 217. Rum, K., AND STEINER, F. A.: Steroid-sensitive single neuro active extract of beef hypothalamus. Arch. Biochem. Biophys. Science 156: 667-669, 1967.

	218. RUMSFELD, H. W., AND PORTER, J. C.: ACTH-releasing activity in an acetone extract of beef hypothalamus. Arch. Biochem. Biophys.
	-
	-
	-
	- 218. RUMSFELD, H. W., AND PORTER, J. C.: ACTH-releasing activity in an acctone extract of beef hypothalamus. Arch. Biochem. Biophys. 82: 473-476, 1959.
219. RUMSFELD, W., AND PORTER, J. C.: ACTH-releasing activity of bovi Inhibition by dexamethasone of the *in tuto* pituitary response to cortico-
trophin releasing factor (CRF). Endocrimology 85: 512-521, 1969.
221. SADOW, J., AND TROMAS P.: An *in virro* bio-assay for corticotrophin releasi
	-
	-
	- physiol. (London) **368:** 9-10P, 1976.

	222. SAFFRAN, M., AND SAFFRAN, J.: Adenohypophysis and the adrenal cortex.

	Annu. Rev. Physiol. **21:** 403-444, 1959.

	223. SAFFRAN, M., AND SCHALLY, A. V.: Release of corticotrophin b **corticotrophin** from the adenohypophysis by a neurohypophysis by a neurohypophysis by a neurohypophysis factor.
 Solution factor of corticotrophin by anterior pituitary tissue in vitro. Can. J. Biochem. Physiol. 33: 408 reserving and *by a nitrogen* mustard. Britannian S24. SAFFRAN, M., SCHALLY, A. V., AND BENFEY, B. G.: Stimulation of the release of corticotropin from the adenohypophysis by a neurohypophysial factor. Endocrinology 57: 43
	- Endocrinology 57: 439-444, 1955.

	225. SAFFRAN, M., AND Voor, M.: Depletion of pituitary corticotrophin by

	reserpine and by a nitrogen mustard. Brit. J. Pharmacol. Chemother. 15:

	226. SAMPSON, P. A., WINSTONE, N. E., AND surface and by a nitrogen mustard. Brit. J. Pharmacol. Chemother. 15:
165-169, 1960.
226. SAMPSON, P. A., WINSTONE, N. E., AND BROOKE, B. N.: Adrenal function in
surgical patients after steroid therapy. Lancet 2: 321-325,
	-
	- **for the preparation of isolated rat adrenal cells: A sensitive, and for the preparation of isolated rat adrenal cells: A sensitive, accurate and for the areparation of isolated rat adrenal cells: A sensitive, accurate and** 228. Rourse in the state of the forest in the effect of a-methods of the prior in the state of the effect of the effect of the effect of the effect of a-methods of a-methods of a-methods of a-methods fit. AL, AND The meth
	-
	- secretion. Neurendocrinology 18: 272-276, 1975.
CAPAGNINI, U., AND PREZIOSI, P.: Role of brain noradrenaline in the tonic
regulation of hypothalamic hypophyseal adrenal axis. Progr. Brain Res. 229. SCAPAGNINI, **U., AND PREZIOSI,** P.: Role of brain noradrenaline in the tonic regulation of hypothalamic hypothalamic hypothalamic hypothalamic hypothesis.
Progression of the effect of a-methyl-p-tyrosine on ACTH
exercetion. Neurendocrinology 18: 272-276, 1975.
The ananomic hypothalamic hypophyseal
	-
- 368, 1962.

229. SCAPAGNINI, U., AND PREZIOSI, P.: Role of brain noradrenaline in the tonic regulation of stress-induced adrenal ascorbic regulation of hypothalamic hypophyseal adrenal axis. Progr. Brain Res.

229. SCAPAGN Becretion. Neurendocrinology 18: 272-276, 1975.

229. SCAPAGNINI, U., AND PREZIOSI, P.: Role of brain noradrenaline in the tonic

regulation of hypothalamic hypophyseal adrenal axis. Progr. Brain Res.

39: 171-184, 1973.
 factors in rats. Eur. J. Pharmacol. 11: 266-268, 1970.

231. SCHALLY, A. V., ANDERBON, R. N., LIPSCOMB, H. S., LONG, J. M., AND GUILLEMIN, R.: Evidence for the existence of two corticotrophin-releasing factors, alpha and
	-
	- **OULLEMIN, R. Evidence for the existence of two corticotrophin-releasing**
factors, alpha and beta. Nature (London) 189: 1192-1193, 1960.
232. SCHALLY, A. V., AND BOWERS, C. Y.: Corticotrophin-releasing factor and
other hyp morphine. Amer. J. Physiol. 209: 1169-1174, 1965. 234. SCHALLY, A. V., CAND BOWERS, C. Y.: Corticotrophin-releasing factor and other hypothalamic peptides. Metabolism 13: 1190-1205, 1964.
233. SCHALLY, A. V., CARTER, W. H. 233. SCHALLY, A. V., CARTER, W. H., HEARN, I. C., AND BOWERS, C. Y.: Determination of CRF activity in rats treated with monase, dexamethasone and
morphine. Amer. J. Physiol. 200: 1169-1174, 1965.
234. SCHALLY, A. V., LIFEC
	-
	-
	- 236. SCHALLY, A. V., LIPSCOMB, H. S., LONG, J. M., DEAR, W. E., AND GUILLEMIN,

	R.: Chromatography and hormonal activities of dog hypothalamus. En-

	decrinology 70: 478-480, 1962.

	236. SCHALLY, A. V., SAFFRAN, M., AND ZIM
	-
	- uretic hormone and the secretion of ACTH following cold stress. Endo-
crinology 62: 278-282, 1958.
238. SEDEN, G., AND BRODISH, A.: Improved parameters of pituitary incubation
for the assay of corticotrophin-releasing fact
	-
	-
	- 240. SELYE, H.: Hormones and resistance. J. Pharm. Sci. 60: 1-28, 1971.
241. SEVY, R. W., OHLER, E. A., AND WEINER, A.: Effect of chlorpromazine on
stress-induced adrenal ascorbic acid depletion. Endocrinology 61: 45-51
24
	- **EVALUATION CONSUMER, A. AND WEINER, A.: Effect of chlorpromazinstress-induced adrenal ascorbic acid depletion. Endocrinology 61: 41
1957.
MON, M. L., AND GEORGE, R.: Diurnal variations in plasma corticoste
and growth horm** stress-induced adrenal ascorbic acid depletion. Endocrinology 61: 45-51,
1957.
242. Show, M. L., AND GEORGE, R.: Diurnal variations in plasma corticosterone
and growth hormone as correlated with regional variations in nore

spet $\, \mathbb G \,$

ARMACOLO

- 17: 125-138, 1975.
 269. TULLNER, W., AND HERTZ, R.: Suppression of corticosteroid production in
 269. TULLNER, W., AND HERTZ, R.: Suppression of corticosteroid production in the dog by monase. Proc. Soc. Exp. Biol. Med
- 243. SIMON, M., GEORGE, R., AND GARCIA, J.: Chronic morphine effects on regional brain amines, growth hormone and corticosterone. Eur. J. Pharmacol. 34: 27-38, 1975.
244. SIRETT, N. E., AND GIBBS, F. B.: Dexamethasone supp
- release: Effect of the interval between steroid administration and the application of stimuli known to release ACTH. Endocrinology 85: 355-359, 1969.
RETRI, N. E., AND PURVES, H. D.: The effect of corticotrophin-releasing
 grafts. Proc. Univ. Otago Med. Sch. 48: 50-52, 1970.

246. SIRETT, N. E., AND PURVES, H. D.: The effect of corticotrophin-releasing

stimuli and injections of stalk median eminence extracts on plasma corticotrophic

grafts **factor tested by** assumed by a state and the minence extracts on plasma corticosterone levels in hypophysectomized rats with multiple ectopic pituitary grafts. Proc. Univ. Otago Med. Sch. 48: 50-52, 1970.
RETT, N. E., AND
- process of the Med. Sch. 48: 50-52, 1970.

246. SIRETT, N. E., AND PURVES, H. D.: The stability of corticotrophin-releasing

factor tested by assay in hypophysectomized rats with multiple ectopic

pituitary grafia. Proc. U FACT, N. E., AND PURVES, H. D.: The stability of corticotrophin-releasing factor tested by assay in hypophysectomized rats with multiple ectopic pituitary grafts. Proc. Univ. Otago Med. Sch. 48: 52-54, 1970.
RETT, N. E., A
- From the tector of the process in hypophysectomized rats with multiple ectopic pituitary grafts. Proc. Univ. Otago Med. Sch. 48: 52-54, 1970.

247. SIRETT, N. E., AND
- (CRF) in ACTH primed 'grafted' rats Neuroendocrinology 10: 83-93, 1972.
 **249. SIRETT, N. E., AND PURVES, H. D.: The assay of corticotrophin-releasing factor

248. SIRETT, N. E., AND PURVES, H. D.: Assay of corticotrophin**
- **factor in** ACTH primed 'grafted' rats. Neuroendocrinology 10: 83-93, 1972.
 infractor in ACTH primed 'grafted' rats. Neuroendocrinology 10: 83-93, 1977.
 infractor in ACTH primed 'grafted' rats. *In* Brain-Pituitary 1972.

249. SIRETT, N. E., AND PURVES, H. D.: The assay of corticotrophin-releasing

factor in ACTH primed 'grafted' rats. In Brain-Pituitary-Adrenal Inter-

relationships, ed. by A. Brodish and E. S. Redgate, pp. 78–98, K
-
-
-
- relationships, ed. by A. Brodish and E. S. Redgate, pp. 78-98, Karger,

Basel, 1973.

250. SLUSHER, M. A., AND HYDE, J. E.: Effect of limbic stimulation on release of

corticosteroids into the adrenal venous effluent of th **EXECUTE:** ACTED SOFTING THE SECTION OF THE SECTION OF THE SECTION OF THE SECTION OF THE SUPPRESSURE THE SUPPRESSURE THE SAMELIK, P. G.: Relation between blood level of corticoids and their inhibiting effect on the hypophy
- 253. SMELLE, P. G.: Relation between blood level of corticoids and their inhibiting
effect on the hypophyseal stress response. Proc. Soc. Exp. Biol. Med. 113:
616-619, 1963.
254. SMELLE, P. G., AND SAWYER, C. H.: Effects o
-
- the brain stem or pituitary gland on the adrenal response to stress in the

255. Surres, R. L., MAICKEL, R. P., AND BRODER, B. B.: ACTH-hypersecretion

induced by phenothiazine tranquillizers. J. Pharmacol. Exp. Ther. 139: nduced by phenothiarine tranquillizers. J. Pharmacol. Exp. Ther. 189:

185-190, 1963.

256. SOFRONIEW, M. V., WEINDL, A., AND WETZSTEIN, R.: Immunoperoxidase

266. SOFRONIEW, M. V., WEINDL, A., AND WETZSTEIN, R.: Immunoper
-
-
-
- of drug tolerance. J. Pharmacol. Exp. Ther. 107: 12-23, 1953.
259. SUZUEI, T., ABE, K., AND HIROSE, T.: Adrenal cortical secretion in response to pilocarpine in dogs with hypothalamic lesions. Neuroendocrinology 17:
26. SU 261. SUZUKI, T., IKEDA, H., NARITA, S., SHIBATA, **0., Was, S., AND EGASHIRA, K.:** Adrenal cortical secretion in response **to nicotine in conscious** and
- adrenocortical secretory responses to cyanide and pilocarpine in
hypothalamic lesions. Neuroendocrinology 19: 269-276, 1975.

JEURI, T., IEEDA, H., NARITA, S., SHIBATA, O., WAEI, S., AND E.

K.: Adrenal cortical secretor i
- Myochalamic lesions. Neuroendocrinology 19: 269-276, 1975.

26. SUZUKI, T., IKEDA, H., NARITA, S., SHIBATA, O., WAKI, S., AND EGASHIRA,

K.: Adrenal cortical secretion in response to nicotine in conscious and

anaesthetise 263. TACHAMONTE, A., TAGLIAMONTE, P., CORSINI, G. U., MERUE, G. P., AND GESSA, G. L.: Decreased conversion of tyrosine to catecholamines in the brain of rate treated with p-chlorophenylalanine. J. Pharm. Pharmacol.
263. TA **OF DESA, G. L.: Decreased conversion of tyrosine to catecholamines in the brain of rats treated with p-chlorophenylalanine. J. Pharm. Pharmacol.**
263. TAKEBE, K., SAKAKURA, M., HORIUCHI, Y., AND MASHIMO, K.: Persistence
- 263. TAKEBE, K., SAKAKURA, M., HORIUCHI, Y., AND MASHIMO, K.: Persistence of diurnal periodicity of CRF activity in adrenalectomized and hypophy-
269. Sections are active and simple *in vitro* assay for corticotropin-rel
-
- of diurnal periodicity of CRF activity in adrenalectomized and hypophy-
of diurnal periodicity of CRF activity in adrenalectomized and hypophy-
sectomized rats. Endocrinol. Jap. 18: 451-455, 1971.
284. TAKEBE, K., YASUDA, 266. TANNENBAUM, G. S.: Growth hormone, insulin and glucose dynamics in 29 normal rats possively immunized with antiserum to somatostatin. *In* Endocrinology 1960, p. 790, Australian Academy of Science, Melbourne, 29
1960.
- Endocrinology 1980, p. 790, Australian Academy of Science, Melbourne,
266. TELEODY, G., AND KOVACS, G. L.: Role of monoamines in mediating the
action of ACTH, vasopressin and oxytocin. In Central Nervous System
266. TELEOD
- hypophysia-adrenal **system.** *In* Brain-Pituitary-Adrenal Interrelation- A. Barbaau, J. R. Ducharme, and J. G. Rochefort, pp. 189-206, Raven
Press, New York, 1979.
267. TELEON, G., AND VERMES, I.: The role of serotonin in the regulation of the hypophysis-advenal system. In Brain-Pituitary-Adven
-
- 269. TULLNER, W., **AND HERTZ, R.: Suppression of corticoateroid production in**
-
- regional brain aromas, growth **hormonic and cortical brain aromas, growth aromas, Growth Law Loon, G. R., HILGER, L., KING, A. B., BORYCZKA, A. T., AND GANONG, release: Effect of the interval between steroid administration**
- GHAM

269. TULLNER, W., AND HERTZ, R.: Suppression of corticosteroid production in

the dog by monase. Proc. Soc. Exp. Biol. Med. 116: 837-840, 1964.

270. UNGAR, F.: In vitro studies of adrenal-pituitary circadian rhythms Neuroendocnnology **8:** 257-272, 1971. 272. VAN LOON, G. R., SCAPAGNINI, U., COHEN, R., AND GANONG, W. F.: Effect of intraventricular administration of adrenergic drugs on the adrenal venous 17-hydroxycorticosteroid response to surgical stress in the dog. Neuro
	- Venous 17-hydroxycorticosteroid response to surgical stress in the dog.
Neuroendocrinology 8: 257-272, 1971.
AN PEENAN, P. F. D., AND WAY, E. L.: The effect of certain central nervous
system depressants on pituitary-adrena
	- 273. VAN PEENAN, P. F. D., AND WAY, E. L.: The effect of certain central nervous
system depressants on pituitary-adrenal activating agents. J. Pharmacol.
Exp. Ther. 126: 261-267, 1957.
274. VAN WHEREMA GREIDANUS, T. B., DO
	-
	- 275. VELLUCCI, S. V.: The effects of reserpine on hypothalamo-pituitary adren-
coortical function. Gen. Pharmacol. 9: 275-285, 1978.
276. VERMES, I., AND TELEGDY, G.: Effect of intraventricular injection and
intrahypothala 275. VELLUCCI, S. V.: The effects of reserptine on hypothalamo-pituitary adren-
ocortical function. Gen. Pharmacol. 9: 275-285, 1978.
276. VERMES, I., AND TELEGDY, G.: Effect of intraventricular injection and
intrahypothal
	- intrahypothalamic implantation of serotonin on the hypothalamohypo-
physeal-adrenal system in the rat. Acta physiol. acad. sci. hung. 42: 49-
59, 1972.
Recent De. **Recent De. Proposition** of hypothalamo-pituitary-adrenal For 1972.

	196, 1972.

	ERMES, I., AND TELEGDY, G.: The role

	the regulation of hypothalamo-pituitan

	velopments of Neurobiology in Hungar

	56, Akademia Kiadó, Budapest, 1976.

	ERNIKOS-DANELLIS, J.: Effect of acu 277. VERMES, I., AND TELEODY, G.: The role of serotoninergic transmission in the regulation of hypothalamo-pituitary-adrenal function. In Recent Developments of Neurobiology in Hungary, vol. V, ed. by K. Lissák, pp. 25-56, the regulation of hypothalamo-pituitary-adrenal function. In Recent Developments of Neurobiology in Hungary, vol. V, ed. by K. Lissák, pp. 25-56, Akademia Kiadó, Budapest, 1976.
278. VERNIKOS-DANELLIS, J.: Effect of acute
	-
	- 279. VERNIKOS-DANELLIS, J.: Estimation of corticotropin-releasing activity of rat
hypothalamus and neurohypophysis before and after stress. Endocrinol-
	- 56, Akademia Kiadó, Budapest, 1976.

	278. VERNIKOS-DANELLIS, J.: Effect of acute stress on the pituitary gland:

	Changes in blood and pituitary ACTH concentrations. Endocrinology 72:

	279. VERNIKOS-DANELLIS, J.: Effect of
	-
	- 282. VERNIKOS-DANELLIS, J., BERGER, P., AND BARCHAS, J. D.: Brain serotonin
	- **281. VERNIKOS-DANELLIS, J.; Effect of rat median eminence extracts on pituitary ACTH content in normal and adrenalectomized rats. Endocrinology 76: 282. VERNIKOS-DANELLIS, J., BERGER, P., AND BARCHAS, J. D.: Brain seroton**
- mours. Endocrinology **36:** 345-350, 1967.

258. Suva, C-Y, WAY, E. L., AND SCOTT, K. G.: Studies on the relationship of the

269. Suva, C-Y, WAY, E. L., AND SCOTT, K. G.: Studies on the relationship of the

269. Surges in 282. VERNIKOS-DANELLIS, J., BERGER, P., AND BARCHAS, J. D.: Brain serotonin
283. VERNIKOS-DANELLIS, J., BERGER, P., AND BARCHAS, J. D.: Brain serotonin
283. VERNIKOS-DANELLIS, J., AND TRIGG, L. N.: Feedback mechanisms regu 284. WATERFIELD, A. A., LORD, J. A. H., HUGHES, J., AND KOSTERLITZ, H.
Differences in the inhibitory effects of normorphine and opioid pept
on the responses of the vasa deferentia of two strains of mice. Eur
Pharmacol. 47:
	- Differences in the inhibitory effects of normorphine and opioid peptides
on the responses of the vasa deferentia of two strains of mice. Eur. J.
Pharmacol. 47: 249-250, 1978.
285. WELCH, A. S., AND WELCH, B. L. Effect of s reserving to the ACTH secretion in response to stressful stimulate one of the stress in grouped and isolated mice. Biochem. Pharmacol. 17: 699-706,
1968.
286. WELLS, H., BRIGGS, F. N., AND MUNSON, P. L.: The inhibitory eff
	- ELLS, H., BRIGGS, F. N., AND MUNSON, P. L.: The inhibitory effect of reserpine on ACTH secretion in response to stressful stimuli. Endocrinology 59: 571-579, 1956.
ESTERMANN, E. O., MAICEEL, R. P., AND BRODIE, B. B.: On th
	-
	- reserpine on ACTH secretion in response to stressful stimuli. Endocrinology 59: 571-579, 1956.
287. WESTRMANN, E. O., MAICKEL, R. P., AND BRODIE, B. B.: On the mechanism
of pituitary-adrenal stimulation by reserpine. J. Ph 288. DE WIED, D.: The effect of autonomic blockade on the release of corticotro-
phin from the hypophysis, as induced by a hypothalamic extract. Acta
endocrinol. 24: 200-208, 1957.
289. DE WIED, D.: An assay of corticotrop
	-
	- 290. DR WIED, D.: Corticotrophin releasing factor (CRF): evaluation of assays. In
290. DR WIED, D.: Corticotrophin releasing factor (CRF): evaluation of assays. In
251. 28 of Animal Origin, ed. by A. Leonardi, pp. 3-12, Fe
	-
	-
	- Milano, 1967.

	291. Excelsive, etc. by A. Escanda, pp. 6-12, Perro Edizson,

	291. DE WIED, D.: Chlorpromazine and endocrine function. Pharmacol. Rev. 19:

	251-288, 1967.

	292. DE WIED, D.; BOUMAN, P. R., AND SMELIE, P. G.: NOTH from the pituitary gland. Endocrinology 63: 605-613, 1968.

	293. DE WIED, D., SMELIK, P. G., MOLL, J., AND BOUMAN, P. R.: On the mechanisms of ACTH release. In Major Problems in Neuroendocrinology, ed. by E. Bajusz an roechanisms of ACTH release. In Major Problems in Neuroendocrinology,
ed. by E. Bajusz and G. Jasmin, pp. 156-176, Baltimore, Williams &
Willkins, 1964.
294. Wikins, P. K., PEARLMUTTER, A. F., AND MILLER, R. E.: Decreased
	-
	- ILEY, M. K., PEARLMUTTER, A. F., AND MILLER, R. E.: Decreased adrenal sensitivity to ACTH in the vasopressin deficient (Brattleboro) rat. Neurondocrinology 14: 257-270, 1974.
 remondocrinology 14: 257-270, 1974.
 FIEK, roandocrinology 14: 257-270, 1974.
 **YASUDA, THER, U.: Hypothalamo-pituitary-adrenocorticotrophic activity in the pentherbitone/chlorpromazine treated rat. Thesis, University of London, 1978.

	296. YASUDA, N., AND GREER, M**
	-

ARMACOLO

spet

 $\overline{\mathbb{O}}$

- CORTICOTROPHIN RI

factor (CRF) content remains constant despite marked acute or chronic

changes in ACTH secretion. Neuroendocrinology 22: 48-56, 1976.

297. Zmananavava, E., AND CRITCHLOW, V.: Effects of intracerebral de
- changes in ACTH secretion. Neuroendocrinology 22: 48-56, 1976.

297. ZEMMANNN, E., AND CRITCHLOW, V.: Effects of intracerebral dexamethance on pituitary-adrenal function in female rats. Amer. J. Physiol. 217:

392-396, 196
- 299. Z0R, U., KANEKO, **T.,** SCHNEIDER, H. P. **G., MCCANN, S. M.,** LOWE, **I. P.,** BLOOM, G., BORNEIDER, H. P. G., MCCANN, S. M., LOWE, I. P.,
BLOOM, G., BORLAND, B., AND FIELD, J. B.: Stimulation of anterior
pituitary adenylcyclase activity and adenosine 3',5'-cyclic phosphate by
hypothalamic extract an 299. ZOR, U., KANEKO, T., SCHNEIDER, H. P. G., MCCANN, S. M., LOWE, I. P.,
BLOOM, G., BORLAND, B., AND FIELD, J. B.: Stimulation of anterior
pituitary adenylcyclase activity and adenosine 3',5'-cyclic phosphate by
hypothal
- hypothalamic extract and prostaglandin E. Proc. Nat. Acad. Sci. U.S.A.
63: 918-925, 1969.
300. Zsm.LA, G., CHENEY, D. L., RACAGNI, G., AND COSTA, E.: Correlation between
analgesia and the decrease of acetylcholine turnover

PHARMACOLOGICAL REVIEWS