

CR 151715

SUMMARY REPORT

1. ZERO GRAVITY AND CARDIOVASCULAR HOMEOSTASIS

Principal Investigator:	Edgar Haber, M.D.
Contract No.:	NAS 9-15182
Period of Award:	2/1/77 - 1/31/78

2. The objectives of this study were.

- a) Using a bedrest model to determine the role of the renin-angiotensin-aldosterone system in the cardiovascular deconditioning of space flight and in the severe electrolyte disorders seen with prolonged weightlessness.
- b) To determine if the cardiovascular deconditioning and electrolyte abnormalities associated with space flight can be prevented by pharmacologic interventions involving the renin-angiotensin-aldosterone system.

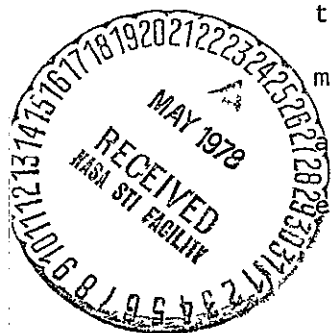
3. SUMMARY REPORT

Because of unanticipated scheduling delays at the N.A.S.A. bedrest facility, it was not possible to begin clinical studies during the first year of this project. During the project period some modifications were introduced into the protocol in order to incorporate non-invasive techniques of assessing cardiac function (echocardiography) and arrangements were made with the Squibb Company to make available the orally active dipeptide converting-enzyme inhibitor for bedrest studies. However, during the delay in the initiation of clinical studies, we elected

N78-22705

Unclas
16645
G3/52

(NASA-CR-151715) ZERO GRAVITY AND
CARDIOVASCULAR HOMEOSTASIS. THE
RELATIONSHIP BETWEEN ENDOGENOUS
HYPERPROLACTINEMIA AND PLASMA ALDOSTERONE
Summary Report, 1 (Massachusetts General



to investigate two aspects of the proposed study in order to gain new insights into the mechanism of the electrolyte abnormalities of spaceflight.

a) Spaceflight and prolonged bedrest are associated with naturesis and kaliuresis; any attempt to explain or present this abnormality in electrolyte metabolism must take into consideration all factors known to influence naturesis. Recently, a role for the pituitary hormone prolactin in the regulation of electrolyte excretion and its control of aldosterone has been suggested (1-7). While some opposing data are available (8-10) to demonstrate that acute endogenous hyperprolactinemia does not alter electrolyte metabolism, the issue remained unresolved. Because of the possibility that hyperprolactinemia might play a role in the hyperaldosteronism of bedrest and spaceflight, we investigated the effect of endogenously-produced hyperprolactinemia on the secretion of aldosterone. Thyrotropin releasing hormone (TRH), a known secretagogue of pituitary prolactin, was administered to normal female subjects to induce endogenous hyperprolactinemia. No elevation in plasma aldosterone was seen for one hour following the induction of hyperprolactinemia. Because prehypothyroid women respond to thyrotropin releasing hormone with an exaggerated prolactin response, we administered TRH to a group of these women and followed serum aldosterone concentrations. In spite of hyperprolactinemia no stimulation of aldosterone was observed. Finally a group of patients with pituitary tumors and extremely high serum prolactin concentrations were studied and no evidence for hypersecretion of aldosterone was detected. The details of these studies are included in the accompanying manuscript (in press, Clinical Endocrinology). Thus, it does not appear that endogenous hyperprolactinemia plays an important role in the control of aldosterone secretion and this observation taken together with previously published data (8-10) make it unnecessary to explicitly investigate the

possible role of prolactin in the naturesis of spaceflight.

b) Prolonged inhibition of converting-enzyme by either the continuous administration of nonapeptide or dipeptide (oral) converting-enzyme inhibitor will play a role in our proposed studies of bedrest and spaceflight. While awaiting availability of space at the N.A.S.A. bedrest facility, we undertook to begin an investigation of the effects of prolonged administration of nonapeptide inhibitor to man (Re, Escourrou, Talamo, and Haber - manuscript in preparation). A 28-year old, severely hypertensive male was studied on the metabolic ward of the Massachusetts General Hospital after withdrawal of antihypertensive medication. Nonapeptide converting-enzyme inhibitor was administered intravenously on an intermittent basis as needed for blood pressure control over a three-day period. Diastolic blood pressure, although not normalized, was consistently reduced by 30mm Hg. The patient suffered no ill effects from his therapy. Following the initial injections of CEI, plasma renin increased (from about 2.0 ng/ml/hr to 12.0 ng/ml/hr), but by the end of the therapy period no such brisk response occurred, suggesting possible "exhaustion" of renin release. No tachyphylaxis secondary to hyperreninemia was observed. Plasma bradykinin was determined before and after CEI administration (doses of CEI ranged from 0.25 mg/kg to 1 mg/kg). No increase in bradykinin was observed (values were 0.25 ng/ml before CEI and <0.35 ng/ml following most injections of CEI). Thus, CEI can produce inhibition of converting enzyme and lowering of blood pressure without hyperbradykininemia, thus pointing out that CEI is potentially a "cleaner" blocking agent than previously thought (11). Significant naturesis was not consistently observed in this patient, but it must be remembered that this patient was not continuously infused with the drug.

Thus, this study provided considerable insight into the effects of long-term CEI administration in man and provides the background for future continuous infusion experiments.

Along with the above study, we undertook the perfection of a radioimmunoassay for angiotensin II and the development of new antisera for the accurate measurements of this compound. We now have a working radioimmunoassay with detection limit of about 12 pg/ml and we are continuing development of newer assays. This is important to the monitoring of Angiotensin II levels in clinical studies of spaceflight, especially (though not exclusively) those involved with the administration of CEI.

Thus, we have made considerable progress in the last year, and it is clear that the next reasonable step in our research would be a study of continuous CEI administration to normal volunteers in order to assess its effects on renal function. This could be done at the M.G.H. and would not require use of the N.A.S.A. bedrest facility.

REFERENCES

1. Horrobin, D.F.: in Prolactin, Eden Press, Montreal p. 100-101, 1975
2. Horrobin, D.F., Burstyn, P.G., Lloyd, I.J., Durkin, N., Lipton, A. and Muiruri, K.L.: Actions of prolactin on human renal function. Lancet 2:352-354, 1971.
3. Horrobin, D.F., Mañku, M.S., and Robertshaw, D.: Water losing action of antidiuretic hormone in the presence of excess cortisol: restoration of normal action by prolactin or by oxytocin. J. Endocrinology 58:135-136, 1973.
4. Locket, M.F.: A comparison of the direct renal actions of pituitary growth and lactogenic hormones in rats. J. Physiology 180:147-156, 1965.
5. Locket, M.F. and Nail, B.: A comparative study of the renal actions of growth and lactogenic hormones in rats. J. Physiology 180:147-156, 1965.
6. Buckman, M.T. and Peak, G.T.: Osmolar control of prolactin secretion in man. Science 181:755-757, 1973.
7. Edwards, C.R.W., Maill, P.A., Hanker, J.P., Thorner, M.O., Al-Dujaili, E.A.S. and Besser, G.M.: Inhibitors of the plasma-aldosterone response to furosemide by bromocriptine. Lancet 2:903-904, 1975.
8. Gomez-Sanchez, C., Holland, O.B., Higgins, J.R., Kem, D.C. and Kaplan, N.M.: Circadian rhythms of serum renin activity and serum corticosterone, prolactin, and aldosterone concentrations in the male rat on normal and low-sodium diets. Endocrinology 99: 567-572, 1976.
9. Baumann, G. and Loriaux, D.L.: The effect of endogenous prolactin on renal salt and water excretion and adrenal function in man. J. Clin Endocrinology and Metabolism 43:643-649, 1976.
10. Baumann, G., Mayrneck, S.P., Winters, S.J. and Loriaux, D.L.: The effect of osmotic stimuli on prolactin secretion and renal water excretion in normal man and in chronic hyperprolactinemia. J. Clin. Endocrinology and Metabolism 44:199-202, 1977.
11. Williams, G.H. and Hollenberg, N.K.: Accentuated vascular and endocrine response to SQ 20881 in hypertension. N. Engl. J. Med. 297:184-188, 1977.

The Relationship Between Endogenous
Hyperprolactinemia and Plasma Aldosterone

Richard N. Re, Ione A. Kourides,
Albert C. Wehl, and Farahe Maloof

From the Cardiac and Thyroid Units
Department of Medicine
Massachusetts General Hospital, Boston, Massachusetts 02114
and Harvard Medical School, Boston, Massachusetts 02115

Running Title: Effect of Prolactin on Aldosterone

This work was supported by USPHS grants CA-18280, AM-16791, AM-04501,
and by National Aeronautics and Space Administration Contract NAS9-15182

Requests for reprints should be addressed to:
Richard N. Re, Massachusetts General Hospital, Boston, Massachusetts 02114

SUMMARY

It has been suggested that prolactin is a regulator of aldosterone secretion. In order to test this hypothesis, we measured prolactin, thyrotropin and aldosterone by radioimmunoassay and plasma renin activity by the radioimmunoassay of angiotensin I in 8 normal women before and after the intravenous injection of 200 µg of thyrotropin releasing hormone. Prolactin increased from 4.4 ± 1.1 ng/ml (mean \pm SE) to a peak of 27.4 ± 3.8 ($p < 0.005$) at 15 minutes following thyrotropin releasing hormone. Plasma renin activity was not different from control levels (1.0 ± 0.2 ng/ml/hr) during the first hour following the administration of thyrotropin releasing hormone, nor did the plasma aldosterone concentration differ significantly from the control levels (39 ± 7 pg/ml) during this period. However, with upright posture, an increase in aldosterone (from 31 ± 3 pg/ml at 1 hr to 68 ± 9 at 2 hrs, $p < 0.005$) and in plasma renin activity (from 0.9 ± 0.2 ng/ml/hr at 1 hr to 2.0 ± 0.5 at 2 hrs, $p < 0.05$) was noted, demonstrating a normal capacity to secrete aldosterone in these subjects.

Similarly, no change in aldosterone was seen in 9 patients with primary hypothyroidism given thyrotropin releasing hormone, despite the fact that the increase in prolactin was greater than normal. Chronic hyperprolactinemia was not associated with hyperaldosteronism in 6 patients with pituitary tumor. These data demonstrate that acutely or chronically elevated serum prolactin levels do not result in increased plasma aldosterone levels in humans.

INTRODUCTION

Prolactin has been demonstrated to have a sodium retaining action in marine teleosts, and there are data to suggest that in mammals it also plays a role in sodium homeostasis and osmoregulation (Locket & Nail, 1965; Locket, 1965; Horrobin *et al.*, 1973, Relkin & Adachi, 1973; Buckman & Peake, 1973, Buckman *et al.*, 1976, Horrobin *et al.*, 1971). Recently attention has been focused on the possibility that prolactin stimulates secretion of aldosterone by the adrenal cortex (Beck *et al.*, 1964; Horrobin, 1975; Edwards *et al.*, 1975). Baumann and Loriaux (1976), however, have reported that elevations in endogenous prolactin in normal men induced by thyrotropin releasing hormone were not associated with increased plasma aldosterone, cortisol, or renal electrolyte excretion, and similar results were obtained by Ogiwara *et al.*, 1977, using metoclopramide to stimulate prolactin secretion in normal men.

We have investigated the effect of elevations in serum prolactin induced by thyrotropin releasing hormone on the control of aldosterone secretion in normal women and in women with primary hypothyroidism, whose thyrotropin releasing hormone-stimulated prolactin levels are supranormal. We have also studied the effect of chronically elevated prolactin levels in patients with a pituitary tumor.

**ORIGINAL PAGE IS
OF POOR QUALITY**

MATERIALS AND METHODS

Subjects: Light normal women (euthyroid with normal menstrual cycles and on no medications) between 21 and 29 years of age were injected with 200 µg of thyrotropin releasing hormone intravenously at 8 A.M. while supine. Patients remained supine for one hour and engaged in *ad libitum* activity thereafter. Blood was obtained at various time intervals before and for three hours after thyrotropin releasing hormone injection (200 µg i.v.) and assayed for aldosterone, plasma renin activity, thyroid stimulating hormone, prolactin, thyroxine (T_4), free thyroxine (FT_4) and triiodothyronine (T_3).

Similar studies were performed in 9 women (30—56 years old) with untreated primary hypothyroidism (including 4 women with galactorrhea), and in 4 women and 2 men (25—69 years old) with a proven pituitary tumor and chronically elevated prolactin. Clinical information regarding the patients with pituitary tumors is provided in Table I; only one patient with pituitary tumor required glucocorticoid replacement. The 2 premenopausal women with a pituitary tumor had galactorrhea. All patients were studied on an *ad libitum* diet.

Laboratory Studies: Plasma renin activity was measured by the method of Haber *et al.* (1969) (normal < 0.1—4.7 ng/ml/hr). Plasma aldosterone was determined by a sensitive radioimmunoassay which does not require preliminary chromatography (Poulsen *et al.*, 1974) (normal = 15—270 pg/ml). Thyroid stimulating hormone was determined by radioimmunoassay (Ridgway *et al.*, 1973) (normal < 0.5—3.2 µU/ml). Prolactin was measured by a homologous radioimmunoassay (Gautvik *et al.*, 1974, Kourides *et al.*, 1976) (normal < 2—12 ng/ml). T_4 (normal = 4—11 µg/dl) and FT_4 (normal = 0.8—2.4 ng/dl) were determined by competitive protein binding assay and equilibrium dialysis respectively (Ridgway *et al.*, 1973). T_3 was determined (normal = 70—170 ng/dl) by

radioimmunoassay (Gautvik *et al.*, 1974).

Analysis of Data: Data for each group were analyzed by paired Student's t-test. Comparisons between groups were performed by Student's t-test or one-way analysis of variance as appropriate.

RESULTS

Normal Subjects: Normal subjects had a mean serum T_4 of 6.4 ± 0.5 $\mu\text{g/dl}$ (mean \pm SE), FT_4 of 1.2 ± 0.1 ng/dl , T_3 of 81 ± 4 ng/dl , and thyroid stimulating hormone of 1.6 ± 0.3 $\mu\text{U/ml}$. Mean prolactin increased from 4.4 ± 1.1 ng/ml before thyrotropin releasing hormone to a peak of 27 ± 3.8 at 15 minutes following thyrotropin releasing hormone ($p < 0.005$). However, plasma renin activity before thyrotropin releasing hormone, 1.0 ± 0.2 ng/ml/hr and maximal plasma renin activity during the first hour after thyrotropin releasing hormone, 1.0 ± 0.3 ng/ml/hr , were not different. Similarly, plasma aldosterone before thyrotropin releasing hormone, 39 ± 7 pg/ml , and maximal plasma aldosterone during the first hour after thyrotropin releasing hormone, 39 ± 6 pg/ml (Figure 1) were not different. However, with the assumption of upright posture (between hours 1 and 2 of this study), increases in plasma renin activity (0.9 ± 0.2 ng/ml/hr at one hour to 2.0 ± 0.5 ng/ml/hr at two hours, $p < 0.05$) and in plasma aldosterone (from 31 ± 3 pg/ml at one hour to 68 ± 9 at two hours, $p < 0.005$) were noted, indicating a normal capacity to secrete aldosterone in these subjects.

Prolactin hyperresponders: The 9 patients with primary hypothyroidism had a mean T_4 of 1.4 ± 0.4 $\mu\text{g/dl}$, FT_4 of 0.3 ± 0.1 ng/dl , T_3 of 43 ± 9 ng/dl , and thyroid stimulating hormone of 119 ± 19 $\mu\text{U/ml}$. Following thyrotropin releasing hormone, prolactin increased from a mean of 13 ± 1.9 ng/dl to 132 ± 12 ng/dl at 15 minutes ($p < 0.001$) and to 88 ± 17 ng/dl at 60 minutes ($p < 0.001$). The prolactin levels in these patients were significantly greater than those in the normals at 15 minutes ($p < 0.001$). Plasma aldosterone was 49 ± 11 pg/ml before thyrotropin releasing hormone and was not significantly increased at 15 minutes (43 ± 10 pg/ml) or at 60 minutes (60 ± 13 pg/ml) (Figure 2). In addition, when one-way analysis of variance was carried out,

there was no significant difference among the zero time, 15 minute, or 60 minute aldosterone values. Mean basal aldosterone concentration in the hypothyroid patients was also not significantly different from that of normals.

Chronic Prolactin Hypersecreters: In the 6 patients with a pituitary tumor and chronic hyperprolactinemia, mean serum T_4 was 7.3 ± 1.9 $\mu\text{g/dl}$, FT_4 was 1.9 ± 0.6 ng/dl , T_3 was 148 ± 41 ng/dl , and thyroid stimulating hormone was 3.2 ± 2.2 $\mu\text{U/ml}$. Thyrotropin releasing hormone infusion resulted in small increases in prolactin (Table II) which were not statistically significant. Mean basal plasma aldosterone (62 ± 18 pg/ml) in these patients was not significantly different from that of normals, and no significant increase in plasma aldosterone occurred following thyrotropin releasing hormone.

DISCUSSION

Prolactin has been demonstrated to play an osmoregulatory role in fish (Ensor & Ball, 1972). Although the action of this hormone in mammals seems predominantly related to breast development, data exist to suggest that it also plays a role in sodium retention and osmoregulation (Locket & Nail, 1965; Locket, 1965; Horrobin *et al.*, 1973; Relkin & Adachi, 1973; Buckman & Peake, 1973; Buckman *et al.*, 1976; Horrobin *et al.*, 1971; Buckman *et al.*, 1973). While it has been suggested that prolactin may directly act on the kidney to promote sodium reabsorption (Locket, 1965; Horrobin *et al.*, 1971), recent studies have focused on the possibility that prolactin stimulates adrenal secretion of aldosterone. Increased urinary excretion of aldosterone has been reported in man following the administration of ovine prolactin (Beck *et al.*, 1964). However, when endogenous prolactin was transiently increased in normal men by the administration of thyrotropin releasing hormone, no change in plasma aldosterone or urinary electrolytes was found (Baumann & Loriaux, 1976). It is possible that vasopressin contamination of the ovine prolactin used in the earlier studies may account for the reported differences in electrolyte excretion. A correlation between the diurnal rhythms of aldosterone and prolactin has been reported in man (Horrobin, 1975), but a recent study failed to demonstrate this correlation in rats (Gomez-Sanchez *et al.*, 1976). Finally, bromergocryptine, an inhibitor of pituitary prolactin secretion, has been shown to block the normal increase in plasma aldosterone seen following furosemide administration in man, without an inhibition of renin stimulation (Edwards *et al.*, 1975). While a direct suppressive effect of bromergocryptine on the secretion of aldosterone by the adrenal could not be excluded, the data raised the possibility that bromergocryptine-mediated suppression of pituitary prolactin secretion led to the absence of an aldosterone response to elevated plasma renin activity.

ORIGINAL PAGE IS
OF POOR QUALITY

We have increased endogenous prolactin levels in normal women by the administration of thyrotropin releasing hormone, but no change in plasma renin activity or plasma aldosterone followed the increase in prolactin. These data concur with those reported only for normal men by Baumann & Loriaux (1976). In order to determine whether greater elevations in endogenous prolactin might stimulate aldosterone secretion, we extended these investigations by for the first time studying plasma aldosterone concentrations in hypothyroid patients who were prolactin hyperresponders to thyrotropin releasing hormone. Acute supranormal elevation in prolactin was associated with only a small rise in plasma aldosterone at 60 minutes, which was not statistically significant. Additionally, we studied patients with chronically increased prolactin due to pituitary tumor and found their plasma aldosterone to not be significantly different from that of our 8 normal subjects, and to be within the normal range for aldosterone in our laboratory. In these patients with severe chronic hyperprolactinemia, thyrotropin releasing hormone infusion resulted in no change in plasma aldosterone and little further increase in prolactin. Hormonal deficiencies in the pituitary tumor patients were varied, ranging from virtually normal pituitary function (patient M.N.) to deficiencies of adrenocorticotropin and thyrotropin (patient S.G.). Thus it is highly unlikely that the deficiency of any particular pituitary hormone masked a stimulatory effect of prolactin on aldosterone. It is thus reasonable to infer from absence of hyperaldosteronism in our patients with pituitary tumor and hyperprolactinemia that chronic elevation of prolactin has little effect on plasma aldosterone.

Our data demonstrate that under the conditions of this study, neither transient nor chronic increases in endogenous prolactin lead to significant increases in plasma aldosterone. These findings, taken with the demonstration

ORIGINAL PAGE IS
OF POOR QUALITY

that chronic hyperprolactinemia does not alter renal electrolyte handling (Baumann *et al.*, 1977), strongly suggest that prolactin does not play an important osmoregulatory role in humans.

Table 1 Clinical Characteristics of Patients with Pituitary Tumors

Patient	Age	Sex	Abnormalities
K.S.	61 y.o.	male	elevated prolactin and α -subunit of thyrotropin
L.O.	25 y.o.	female	amenorrhea, galactorrhea, primary hypothyroidism (but chronically euthyroid on replacement), elevated thyrotropin, prolactin
S.G.	69 y.o.	female	premature menopause with low gonadotropins; elevated prolactin without galactorrhea; elevated secretion of α -subunit of thyrotropin; hypoadrenal and hypothyroid. Replacement therapy with 5 mg prednisone, 0.15 mg L-Thyroxine; clinically euthyroid
H.G.	38 y.o.	male	acromegalic with increased growth hormone, increased prolactin, increased thyrotropin, hyperthyroid
N.F.	59 y.o.	female	elevated prolactin without galactorrhea; suprasellar extension of tumor; premature menopause with low gonadotropins; hypothyroid with elevated thyrotropin
M.H.	25 y.o.	female	oligomenorrhea with elevated prolactin; normal growth hormone and cortisol response to insulin tolerance test; normal thyrotropin response to thyrotropin releasing hormone

Table II Studies in 6 Hyperprolactinemic Patients
with a Pituitary Tumor

A.

Patient	Basal Prolactin (ng/ml)	Maximal Prolactin (ng/ml) following TRH (200 µg iv)
S.G.	11,900	12,300
N.F.	4,490	4,940
K.S.	4,200	4,320
L.O.	479	559
M.G.	74	96
M.H.	62	98

B.

Mean Plasma Aldosterone \pm 1SE
Following TRH Infusion in the Same 6 Patients

Time (min)	0	5	15	30	60
Plasma Aldosterone (pg/ml) mean	62.0	60.5*	61.2*	52.5*	74.2*
\pm 1SE	18.1	17.9	25.6	16.6	16

*not significantly different from 0 time value

LEGENDS TO FIGURES

Fig. 1. Serum prolactin, aldosterone and plasma renin activity (mean \pm 1SE) in 8 normal subjects following the administration of 200 μ g thyrotropin releasing hormone i.v. Subjects were supine until 60 minutes after thyrotropin releasing hormone injection.

Fig. 2. Serum prolactin and aldosterone (mean \pm 1SE) in 9 hypothyroid women following the administration of 200 μ g thyrotropin releasing hormone i.v. The prolactin response of the normal subjects is shown on this figure as the shaded area.

ACKNOWLEDGMENTS

The authors wish to acknowledge the technical support of Ms. Linda Lorenz, Ms. Sharon Schwartz, Ms. Virginia Lucas and Mr. Joseph Torano, and the secretarial assistance of Ms. Ruth DiBlasi. We would like to thank Dr. Brian Mordica of Abbott Laboratories for providing the thyrotropin releasing hormone.

REFERENCES

- BAUHMANN, G. & LORIAUX, D.L. (1976) The effect of endogenous prolactin on renal salt and water excretion and adrenal function in man. *Journal of Clinical Endocrinology and Metabolism*, 43, 643—649.
- BAUHMANN, G., MARYNECK, S.P., WINTERS, S.J. & LORIAUX, D.L. (1977) The effect of osmotic stimuli on prolactin secretion and renal water excretion in normal man and in chronic hyperprolactinemia. *Journal of Clinical Endocrinology and Metabolism*, 44, 199—202.
- BECK, J.C., GONDA, A., HAMID, H.A., MORGEN, R.O., RUBENSTEIN, P. & MCGARRY, E.E. (1964) Some metabolic changes induced by primate growth hormone and purified ovine prolactin. *Metabolism*, 13, 1108—1134.
- BUCKMAN, M.T., KAMINSKY, H., CONWAY, M. & PEAKE, G.T. (1973) Utility of L-dopa and water loading in evaluation of hyperprolactinemia. *Journal of Clinical Endocrinology and Metabolism*, 36, 911—919.
- BUCKMAN, M.T. & PEAKE, G.T. (1973) Osmolar control of prolactin secretion in man. *Science*, 181, 755—757.
- BUCKMAN, M.T., PEAKE, G.T. & ROBERTSON, G. (1976) Hyperprolactinemia influences renal function in man. *Metabolism*, 25, 509—516.
- EDWARDS, C.R.W., HALL, P.A., HANKER, J.P., THORNER, M.O., AL-DUJAILI, E.A.S. & BESSER, G.M. (1975) Inhibitors of the plasma-aldosterone response to furosemide by bromocriptine. *Lancet*, 2, 903—904.
- ENSOR, D.H. & BALL, J.N. (1972) Prolactin and osmoregulation in fishes. *Federation Proceedings*, 31, 1615—1623.
- GAUVIK, K.M., TASHJIAN, A.H., JR., KOURIDES, I.A., WINTRAUB, B.D., GRAEBER, C.T., MALOOF, F., SUZUKI, K. & ZUCKERMAN, J.E. (1974) Thyrotropin-releasing hormone is not the sole physiologic mediator of prolactin release during suckling. *New England Journal of Medicine*, 290, 1162—1165.

- GONLZ-SANCHEZ, C., HOLLAND, O.B., HIGGERS, J R., KIM, D.C. & KAPLAN, N.M. (1976) Circadian rhythms of serum renin activity and serum corticosterone, prolactin, and aldosterone concentrations in the male rat on normal and low-sodium diets. *Endocrinology*, 99, 567—572.
- HABER, E., KOLRNER, T., PAGE, L.B., KLIMAN, B. & PURNODE, A. (1969) Application of a radioimmunoassay for angiotensin I to the physiologic measurements of plasma renin activity in normal human subjects. *Journal of Clinical Endocrinology and Metabolism*, 29, 1349—1355.
- HORROBIN, D.F. (1975) *Prolactin*, pp. 100—101. Eden Press, Montreal.
- HORROBIN, D.F., BURSTYN, P.G., LLOYD, I.J., DURKIN, N., LIPTON, A. & MUIRURI, K.L. (1971) Actions of prolactin on human renal function. *Lancet*, ii, 352—354.
- HORROBIN, D.F., HANKU, M.S. & POBERTSHAW, D. (1973) Water-losing action of antidiuretic hormone in the presence of excess cortisol: restoration of normal action by prolactin or by oxytocin. *Journal of Endocrinology*, 58, 135—136.
- KOURIDES, I.A., WLINTRAUB, B.D., ROSEN, S.W., RIDGWAY, E.C., KLIMAN, B. & HALOOF, F. (1976) Secretion of alpha subunit of glycoprotein hormones by pituitary adenomas. *Journal of Clinical Endocrinology and Metabolism*, 43, 97—106.
- LOCKET, M.I. (1965) A comparison of the direct renal actions of pituitary growth and lactogenic hormones. *Journal of Physiology*, 181, 192—199.
- LOCKET, M.F. & NAIL, B. (1965) A comparative study of the renal actions of growth and lactogenic hormones in rats. *Journal of Physiology*, 180, 147—156.
- OGIHARA, T., MATSUMURA, S., ONISHI, T., MIYAI, K., UOZUMI, T., & KUMALRORO, Y. (1977) Effect of metoclopramide-induced prolactin on aldosterone secretion in normal subjects. *Life Sciences*, 20, 523—
- POULSEN, VITNER, K.W., SANCHO, J. & HABER, E. (1974) A simplified radio-immunoassay for plasma aldosterone employing an antibody of unique specificity.

ORIGINAL PAGE IS
OF POOR QUALITY

Clinical Immunology and Immunopathology, 2, 373—380.

RELKIN, R. & ADACHI, M. (1973) Effects of sodium deprivation on pituitary and plasma prolactin, growth hormone and thyrotropin levels in the rat.

Neuroendocrinology, 11, 240—247.

RIDGWAY, E.C., WEINFRAUB, B.D., CEVALLOS, J.L., RACK, M.C. & MALOOL, F. (1973)

Suppression of pituitary TSH secretion in the patient with a hyperfunctioning thyroid nodule. *Journal of Clinical Investigation*, 52, 2783—2792.