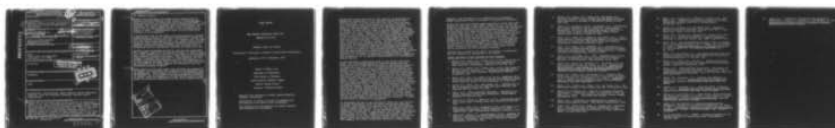


AD-A034 084

LOS ANGELES COUNTY HARBOR GENERAL HOSPITAL TORRANCE CALIF F/G 6/19
CHEMICAL INDEX TO FITNESS (BIOCHEMICAL CORRELATES OF STRESS IN --ETC(U)
DEC 76 R T RUBIN N00014-73-C-0127

UNCLASSIFIED

| OF |
AD
A034084



END

DATE
FILMED
2-77

Unclassified

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

REPORT DOCUMENTATION PAGE

READ INSTRUCTIONS
BEFORE COMPLETING FORM

1. REPORT NUMBER

2. GOVT ACQUISITION NUMBER

3. RECIPIENT'S CATALOG NUMBER

4. TITLE (and Subtitle)

Chemical Index to Fitness (Biochemical
Correlates of Stress in Specialized
Populations).

5. TYPE OF REPORT & PERIOD COVERED

Final Report, (8th year)
Sept 1975-Nov 1976

6. PERFORMING ORG. REPORT NUMBER

7. AUTHOR(s)

Robert T. Rubin M.D.

CONTRACT OR GRANT NUMBER(s)

N00014-73-C-0127

9. PERFORMING ORGANIZATION NAME AND ADDRESS

Office of Naval Research
Biochemistry Branch
Arlington, VA 2221710. PROGRAM ELEMENT, PROJECT, TASK
AREA & WORK UNIT NUMBERS

11. CONTROLLING OFFICE NAME AND ADDRESS

12. REPORT DATE

7 December 1976

13. NUMBER OF PAGES

6 128 p.

14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)

DCAS
11099 South La Cienga Blvd.
Los Angeles, CA 90045

15. SECURITY CLASS. (if this report)

Unclassified

15a. DECLASSIFICATION/DOWNGRADING
SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)

Unlimited

DISTRIBUTION STATEMENT A

Approved for public release;
Distribution Unlimited

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

Unlimited

18. SUPPLEMENTARY NOTES

None

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

Biochemistry, endocrinology, human subjects, stress, pituitary
hormones, sleep and dreaming, biological rhythms, psycho-
pharmacology

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

During the 6th and final year of this contract we published a report on our third neuroendocrine study of sleep, which examined the secretion patterns of the posterior pituitary hormone, anti-diuretic hormone, in normal young adult men. This is the first reported study of the longitudinal secretion patterns of a posterior pituitary hormone in human subjects, and it was found that antidiuretic hormone was secreted episodically, like the anterior pituitary hormones, but with no change in integrated

DD FORM 1473

1 JAN 73

EDITION OF 1 NOV 65 IS OBSOLETE
S/N 0102-014-6601

Unclassified

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

387521

ADA034084

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

plasma levels throughout the night nor any relation of the specific secretory episodes to any stages of sleep. In this study plasma levels of aldosterone and prolactin also were measured, both of which hormones showed increasing blood levels throughout the night, suggesting that these two hormones may play a role in the diminished amount of urine secreted by the kidney at night. A comprehensive report on this sleep study currently is in preparation.

Another project undertaken during the year was the development of a computer program for the variable analysis of scored sleep data, which permits the scoring of sleep stages by user-specified time intervals throughout the night. This program is important because it permits the computation of sleep variables for correlation with physiologic measures such as blood sampling; i.e., if blood samples are taken every 20 minutes, the sleep variables may be scored in 20 minute segments for correlation with the biochemical measures in blood.

Other aspects of this past year's work included the preparation of several invited chapters for textbooks of psychopharmacology and psychiatry. These studies are part of a continuing program of research into the biochemical and psychoendocrine correlates of stress, sleep and dreaming, and other central nervous system states in specialized populations as well as in normal subjects.

ACCESSION FOR

DTIC

DIC

UNCLASSIFIED

JUSTIFICATION

BY _____ **DATE** _____

SUBMITTING AGENCY

FILE NO. _____ **AVAIL.** _____

REMARKS:

APPROVED BY: _____

SECURITY CLASSIFICATION OF THIS PAGE(When Data Entered)

FINAL REPORT

ONR CONTRACT NR108-912; NR202-004

(N00014-73-C-0127)

Chemical Index to Fitness

(Biochemical Correlates of Stress in Specialized Populations)

September, 1975 to November, 1976

Robert T. Rubin, M.D.

Department of Psychiatry

UCLA School of Medicine

Harbor General Hospital Campus

1000 W. Carson Street

Torrance, California 90509

Contract work performed at Harbor General Hospital,
Torrance, California.

Reproduction in whole or in part is permitted for
any purpose of the United States Government.

This document has been approved for public release;
its distribution is unlimited.

During the 6th and final year of this contract we published the preliminary communication on the nocturnal secretion of antidiuretic hormone in normal young adult men (22), which was part of a large sleep study investigating the nocturnal secretion patterns of hormones influencing water and electrolyte balance. Using the same experimental design as in our other sleep studies, we sampled 8 normal subjects every 20 minutes throughout the night and assayed the blood samples for antidiuretic hormone, aldosterone, prolactin, and sodium. Whereas the levels of antidiuretic hormone did not increase during the night, both aldosterone and prolactin levels did increase during the hours of sleep, suggesting that these two hormones may play a role in the diminished amount of urine secreted by the kidney at night. The major report on this sleep study has been submitted for publication. We are pursuing the control of antidiuretic hormone by performing neuropharmacologic studies to elucidate which CNS neurotransmitter systems are involved in the control of this posterior pituitary hormone; a report has been submitted for publication which shows that CNS dopamine blockade with haloperidol results in increased plasma prolactin levels but has no effect on antidiuretic hormone levels, suggesting that dopamine is not an important neurotransmitter in antidiuretic hormone control.

We also performed a replication study of our initial work which showed that neuropharmacologically increased plasma prolactin levels result in a dose-related increase in testosterone secretion in normal adult men (20, 21). The second study utilized normal subjects on 4 separate test days, which were saline control, haloperidol-induced increased prolactin levels, intravenous infusion of human luteinizing hormone, and increased prolactin levels along with infused luteinizing hormone. This study not only replicated the first study but also examined the possibility of acute synergistic effects between prolactin and luteinizing hormone on testosterone secretion. Compared to saline control, testosterone secretion was again increased following the haloperidol-induced increases in plasma prolactin levels. Following the intravenous infusion of luteinizing hormone, testosterone levels were clearly increased, but were not further increased when prolactin levels were stimulated along with the infused luteinizing hormone. Therefore, while the first study was replicated in that increased prolactin levels alone resulted in a higher plasma testosterone level than saline control, no synergism was demonstrated between increased prolactin and luteinizing hormone levels on testosterone secretion. A report on this study is currently in preparation.

To investigate the day to day variability within the same subjects in plasma testosterone levels and urine testosterone secretion, 3 subjects were studied on 6 separate days each, by blood sampling every 30 minutes between 0900 and 1700, and by complete urine collections during this period. It was demonstrated that there was a coefficient of variation of approximately 25% in plasma testosterone levels across the 6 days. Whereas urine testosterone levels did not correlate at all with plasma testosterone levels, urine testosterone levels did correlate extremely highly with urine volume. This suggests that urine testosterone excretion is highly volume

dependent, and therefore is not a substitute for integrated plasma testosterone levels in studies of testosterone secretion.

During this past year several papers appeared in print which were in press at the time of last year's report (20, 21, 22, 24, 26). Other work undertaken during this past year includes the preparation of two invited chapters on psychoneuroendocrinology (30, 32) and the development of a computer program for the variable analysis of scored sleep data (31). This computer program permits the user to specify the length of the time interval in minutes for which sleep stage data will be compiled throughout the night. This program is very useful for the correlation of sleep staging with biochemical and physiological measures; e.g., if blood sampling is done every 20 minutes throughout the night, the program user can specify the scoring of sleep stage variables by 20 minute epochs throughout the night, so that the sleep stage measures can be correlated with the biochemical measures.

Although this contract is now ended, the reports in preparation will be submitted for publication in the future.

PAPERS PUBLISHED TO DATE SUPPORTED BY THIS CONTRACT:

1. Miller, R.G., Rubin, R.T., Clark, B.R., et al: The Stress of Aircraft Carrier Landings I. Corticosteroid Responses in Naval Aviators, Psychosomatic Medicine 32:581-588, 1970.
2. Rubin, R.T., Miller, R.G., Clark, B.R., et al: The Stress of Aircraft Carrier Landings II. 3-methoxy-4-hydroxyphenylglycol Excretion in Naval Aviators, Psychosomatic Medicine 32:589-597, 1970.
3. Rubin, R.T., Zir, L.M., Smith, R.A., et al: Experience With the Vankirk-Sassin Technique for Serial Blood Sampling During Sleep, American Journal of EEG Technology, 11:17-18, 1971.
4. Clark, B.R., Rubin, R.T., and Poland, R.E.: Modification of New Fluorometric Method for Serum and Urine Cortisol, Biochemical Medicine 5:177-179, 1971.
5. Rubin, R.T.: Urine Creatinine Excretion: Variability and Volume Dependency During Sleep Deprivation, Psychosomatic Medicine, 33:536-543, 1971.
6. Rubin, R.T., Kales, A., Adler, R., et al: Gonadotropin Secretion During Sleep in Normal Adult Men, Science 175:196-198, 1972.
7. Rahe, R.H., Rubin, R.T., Gunderson, E.K.E., and Arthur, R.J.: Psychological Correlates of Serum Cholesterol in Man: A Longitudinal Study, Psychosomatic Medicine, 33:399-410, 1971.
8. Rahe, R.H., Rubin, R.T., and Gunderson, E.K.E.: Measures of Subjects' Motivation and Affect Correlated with Their Serum Uric Acid, Cholesterol, and Cortisol, Archives of General Psychiatry, 26:357-359, 1972.

9. Poland, R.E., Rubin, R.T., Clark, B.R., and Gouin, P.R.: Circadian Patterns of Urine 17-OHCS and VMA Excretion During Sleep Deprivation, *Diseases of the Nervous System*, 33:456-458, 1972.
10. Rubin, R.T., Gunderson, E.K.E., and Arthur, R.J.: Life Stress and Illness Patterns in the U.S. Navy VI. Environmental, Demographic, and Prior Life Change Variables in Relation to Illness Onset in Naval Aviators During a Combat Cruise, *Psychosomatic Medicine*, 34:533-547, 1972.
11. Rubin, R.T., Gouin, P.R., Kales, A., and Odell, W.D.: Luteinizing Hormone, Follicle Stimulating Hormone, and Growth Hormone Secretion in Normal Adult Men During Sleep and Dreaming, *Psychosomatic Medicine*, 35:309-321, 1973.
12. Rubin, R.T., Gouin, P.R., Arenander, A.T., and Poland, R.E.: Human Growth Hormone Release During Sleep Following Prolonged Flurazepam Administration, *Research Communications in Chemical Pathology and Pharmacology*, 6:331-334, 1973.
13. Gouin, P.R., and Rubin, R.T.: RISC: Radioimmunoassay Standard Curve Determination and Dose Interpolation (Computer Programs in Endocrinology), *Endocrinology*, 93:60, 1973.
14. Rubin, R.T., Kales, A., and Odell, W.: Secretion of LH and FSH During Sleep in Man, in Lissak, K. (ed.): Hormones and Brain Function: Proceedings of the Second Congress of the International Society for Psychoneuroendocrinology 1971, Akademiai Kiado, Budapest, 1973, pp. 521-526.
15. Rubin, R.T., Gouin, P.R., and Poland, R.E.: Biogenic Amine Metabolism and Neuroendocrine Function in Affective Disorders, in de la Fuente, R., and Weisman, M.N., (eds.): Psychiatry: Proc. V. World Congress Psychiatry, 1971, Excerpta Medica, Amsterdam, 1973, pp. 1036-1039.
16. Rubin, R.T., Poland, R.E., Rubin, L.E., and Gouin, P.R.: The Neuroendocrinology of Human Sleep, *Life Sci.* 14:1041-1052, 1974.
17. Rubin, R.T. and Rahe, R.H.: Navy Men in Severely Stressful Environments: Biochemical Studies, in Gunderson, E.K.E. and Rahe, R.H., (eds.): Life Stress and Illness, Charles Thomas, Springfield, 1974.
18. Rubin, R.T.: Biochemical and Neuroendocrine Responses to Severe Psychological Stress: Some General Observations, *ibid.*
19. Rubin, R.T., Gouin, P.R., Lubin, A., Poland, R.E., and Pirke, K.M.: Nocturnal Increase of Plasma Testosterone in Men: Relation to Gonadotropins and Prolactin, *J. Clin. Endocrinol. Metab.*, 40:1027-1033, 1975.

20. Rubin, R.T., Poland, R.E., O'Connor, D., Gouin, P.R., and Tower, B.B.: Selective Neuroendocrine Effects of Low-Dose Haloperidol in Normal Adult Men, *Psychopharmacol.* 47:135-140, 1976.
21. Rubin, R.T., Poland, R.E., and Tower, B.B.: Prolactin-Related Testosterone Secretion in Normal Adult Men, *J Clin. Endocrinol. Metab.* 42:112-116, 1976.
22. Rubin, R.T., Poland, R.E., Ravessoud, F., Gouin, P.R., and Tower, B.B.: Antidiuretic Hormone: Episodic Nocturnal Secretion in Adult Men, *Endocr. Res. Comm.* 2:459-469, 1975.
23. Rubin, R.T.: Sleep-Endocrinology Studies in Man, in Gispen, W.H., van Wimersma Greidanus, Tj. B., Bohus, B., and de Wied, D., (eds.): Hormones, Homeostasis, and the Brain, Progress in Brain Research, Vol. 42, Elsevier, Amsterdam, 1975, pp. 73-80.
24. Rubin, R.T. and Poland, R.E.: Synchronies Between Sleep and Endocrine Rhythms in Man and Their Statistical Evaluations, *Psychoneuroendocrinol.* 1:281-290, 1976.
25. Chang, P.C., Rubin, R.T., and Yu, M.: Optimal Statistical Design of Radioimmunoassays and Competitive Protein-Binding Assays, *Endocrinol.* 96:973-981, 1975.
26. Rubin, R.T.: Mind-Brain-Body Interaction: Elucidation of Psychosomatic Intervening Variables, in Pasnau, R., (ed.): Consultation-Liaison Psychiatry, Grune and Stratton, New York, 1975, pp. 73-85.
27. Rubin, R.T. and Sassin, J.F.: Hormones and Behavior, in Jarvik, M.E., (ed.): Psychopharmacology for Primary Care Physicians, Appleton-Century-Crofts, New York, 1975, in press.
28. Sassin, J.F. and Rubin, R.T.: Drugs and Sleep, in Jarvik, M.E., (ed.): Psychopharmacology for Primary Care Physicians, Appleton-Century-Crofts, New York, 1975, in press.
29. Rubin, R.T. and Poland, R.E.: Human Sleep: Basic Mechanisms and Pathologic Patterns, in Frazer, A. and Winokur, A. (eds.): Introduction to Clinical Neuropsychopharmacology, Spectrum Publications, New York, in press.
30. Rubin, R.T. and Kendler, K.: Psychoneuroendocrinology: Fundamental Concepts and Correlates in Depression, in Usdin, G. (ed.): Depression: Clinical, Biological and Psychological Perspectives, Proceed. 1976 Meeting Amer. Coll. Psychiat., in press.
31. Yu, M. and Rubin, R.T.: VARSLP: A Computer Program for the Variable Analysis of Scored Sleep Data, *Psychophysiol.* 13:273, 1976.

32. Rubin, R.T.: Strategies of Neuroendocrine Research in Psychiatry, in Usdin, E., Hamburg, D., and Barchas, J. (eds.): Neuroregulators and Hypotheses of Psychiatric Disorders, Oxford Press, New York, in press.