1971

Year Book OF ENDOCRINOLOGY

SCHWARTZ

THE YEAR BOOK *of* ENDOCRINOLOGY 1971

EDITED BY

THEODORE B. SCHWARTZ, M.D.

Director, Section of Endocrinology and Metabolism, and Chairman, Department of Internal Medicine, Rush-Presbyterian-St. Luke's Medical Center; Professor and Chairman, Department of Internal Medicine, Rush Medical College

YEAR BOOK MEDICAL PUBLISHERS

INCORPORATED

35 EAST WACKER DRIVE CHICAGO

THE PRACTICAL MEDICINE YEAR BOOKS

Medicine: DAVID E. ROGERS, M.D.; CARL MUSCHENHEIM, M.D.; PAUL HELLER, M.D.; T. JOSEPH REEVES, M.D.; NORTON J. GREENBERGER, M.D.; PHILIP K. BONDY, M.D.; FRANKLIN H. EPSTEIN, M.D.

Surgery: SEYMOUR I. SCHWARTZ, M.D.; JOHN S. NAJARIAN, M.D.; ERLE E. PEACOCK, JR., M.D.; G. TOM SHIRES, M.D.; WILLIAM SILEN, M.D.; FRANK C. SPENCER, M.D.

Anesthesia: JAMES E. ECKENHOFF, M.D.

Drug Therapy: DALE G. FRIEND, M.D.

Obstetrics & Gynecology: J. P. GREENHILL, M.D.

Pediatrics: SYDNEY S. GELLIS, M.D.

Radiology: WALTER M. WHITEHOUSE, M.D.; HOWARD B. LATOURETTE, M.D.

Ophthalmology: WILLIAM F. HUGHES, M.D.

Ear, Nose & Throat: JOHN A. KIRCHNER, M.D.

Neurology & Neurosurgery: RUSSELL N. DE JONG, M.D.; OSCAR SUGAR, M.D.

Psychiatry & Applied Mental Health: FRANCIS J. BRACELAND, DOUGLAS D. BOND, M.D.; M.D.; DANIEL X. FREEDMAN, M.D.; ARNOLD J. FRIEDHOFF, M.D.; LAWRENCE C. KOLB, M.D.; REGINALD S. LOURIE, M.D.

Dermatology: FREDERICK D. MALKINSON, M.D.; RODGER W. PEARSON, M.D.

Urology: JOHN T. GRAYHACK, M.D.

Orthopedics & Traumatic Surgery: H. HERMAN YOUNG, M.D.

Plastic & Reconstructive Surgery: NEAL OWENS, M.D.; KATHRYN STEPHENSON, M.D.

Endocrinology: THEODORE B. SCHWARTZ, M.D.

Pathology & Clinical Pathology: WILLIAM B. WARTMAN, M.D.

Nuclear Medicine: JAMES L. QUINN, III, M.D.

Cancer: RANDOLPH LEE CLARK, M.D.; RUSSELL W. CUMLEY, Ph.D.

Cardiovascular Medicine & Surgery: EUGENE BRAUNWALD, M.D.; W. PROCTOR HARVEY, M.D.; JOHN W. KIRKLIN, M.D.; ALEXANDER S. NADAS, M.D.; OGLESBY PAUL, M.D.; ROBERT W. WILKINS, M.D.; IRVING S. WRIGHT, M.D.

Printed in U.S.A.

Library of Congress Catalog Card Number: 47-1974

There are twenty YEAR BOOKS in various fields of medicine and one in dentistry. Publication of these annual volumes has been continuous since 1900. The YEAR BOOKS make available in detailed abstract form the working essence of the cream of recent international medicoscientific literature. Selection of the material is made by distinguished editors who critically review each year more than 500,000 articles published in the world's foremost journals.

TABLE OF CONTENTS

The material covered in this volume represents literature reviewed up to January, 1971.

THE YEAR BOOK *of* ENDOCRINOLOGY 1971

EDITED BY

THEODORE B. SCHWARTZ, M.D.

Director, Section of Endocrinology and Metabolism, and Chairman, Department of Internal Medicine, Rush-Presbyterian-St. Luke's Medical Center; Professor and Chairman, Department of Internal Medicine, Rush Medical College

YEAR BOOK MEDICAL PUBLISHERS

INCORPORATED

35 EAST WACKER DRIVE CHICAGO

THE PRACTICAL MEDICINE YEAR BOOKS

Medicine: DAVID E. ROGERS, M.D.; CARL MUSCHENHEIM, M.D.; PAUL HELLER, M.D.; T. JOSEPH REEVES, M.D.; NORTON J. GREENBERGER, M.D.; PHILIP K. BONDY, M.D.; FRANKLIN H. EPSTEIN, M.D.

Surgery: SEYMOUR I. SCHWARTZ, M.D.; JOHN S. NAJARIAN, M.D.; ERLE E. PEACOCK, JR., M.D.; G. TOM SHIRES, M.D.; WILLIAM SILEN, M.D.; FRANK C. SPENCER, M.D.

Anesthesia: JAMES E. ECKENHOFF, M.D.

Drug Therapy: DALE G. FRIEND, M.D.

Obstetrics & Gynecology: J. P. GREENHILL, M.D.

Pediatrics: SYDNEY S. GELLIS, M.D.

Radiology: WALTER M. WHITEHOUSE, M.D.; HOWARD B. LATOURETTE, M.D.

Ophthalmology: WILLIAM F. HUGHES, M.D.

Ear, Nose & Throat: JOHN A. KIRCHNER, M.D.

Neurology & Neurosurgery: RUSSELL N. DE JONG, M.D.; OSCAR SUGAR, M.D.

Psychiatry & Applied Mental Health: FRANCIS J. BRACELAND, DOUGLAS D. BOND, M.D.; M.D.; DANIEL X. FREEDMAN, M.D.; ARNOLD J. FRIEDHOFF, M.D.; LAWRENCE C. KOLB, M.D.; REGINALD S. LOURIE, M.D.

Dermatology: FREDERICK D. MALKINSON, M.D.; RODGER W. PEARSON, M.D.

Urology: JOHN T. GRAYHACK, M.D.

Orthopedics & Traumatic Surgery: H. HERMAN YOUNG, M.D.

Plastic & Reconstructive Surgery: NEAL OWENS, M.D.; KATHRYN STEPHENSON, M.D.

Endocrinology: THEODORE B. SCHWARTZ, M.D.

Pathology & Clinical Pathology: WILLIAM B. WARTMAN, M.D.

Nuclear Medicine: JAMES L. QUINN, III, M.D.

Cancer: RANDOLPH LEE CLARK, M.D.; RUSSELL W. CUMLEY, Ph.D.

Cardiovascular Medicine & Surgery: EUGENE BRAUNWALD, M.D.; W. PROCTOR HARVEY, M.D.; JOHN W. KIRKLIN, M.D.; ALEXANDER S. NADAS, M.D.; OGLESBY PAUL, M.D.; ROBERT W. WILKINS, M.D.; IRVING S. WRIGHT, M.D.

Printed in U.S.A.

Library of Congress Catalog Card Number: 47-1974

There are twenty YEAR BOOKS in various fields of medicine and one in dentistry. Publication of these annual volumes has been continuous since 1900. The YEAR BOOKS make available in detailed abstract form the working essence of the cream of recent international medicoscientific literature. Selection of the material is made by distinguished editors who critically review each year more than 500,000 articles published in the world's foremost journals.

TABLE OF CONTENTS

The material covered in this volume represents literature reviewed up to January, 1971.

INTRODUCTION

If the reader will turn back to the title page of this volume, he will note some changes in the editor's credentials. Note, too, which function leads the list, but don't mention it to our new Deans. They hold the view, in general, that wearing more than one academic hat detracts and distracts. Your editor believes (with a shaky sort of certainty) that his case may be exceptional. Still, he recognizes that some accommodations must be made. In this case, the accommodation took the form of enlisting the aid of two bright associates, Drs. Will G. Ryan and Frank O. Becker, to complete this edition of the YEAR BOOK OF ENDOCRINOLOGY. Both, in the increasingly dim past, had training in endocrinology and metabolism under the editor's direction. He finds it embarrassingly difficult to tell them anything that they don't already know. Indeed, in acknowledging an introduction to one of them, a colleague (a friend?) commented, "Oh yes, you're Ted Schwartz's brains!"

We hope that you will enjoy this year's YEAR BOOK; you haven't lost an editor, you've gained a "think tank."

THEODORE B. SCHWARTZ

THE HYPOTHALAMUS; THE PINEAL AND ANTERIOR PITUITARY GLANDS

GENERAL

Immunologic Studies of the Snell-Bagg Pituitary Dwarf Mouse. The autosomal recessive dwarf mutant of the Snell-Bagg (SB) strain of mice has shown diminished antibody production against sheep erythrocytes and hypoplasia of lymphoid tissues. Treatment of the dwarf mouse with growth hormone and thyroxine resulted in reconstitution of the immune apparatus. Further immunologic studies were carried out by René J. Duquesnoy, Pitsa K. Kalpaktsoglou and Robert A. Good[1] (Univ. of Minnesota).

(1) Proc. Soc. Exper. Biol. & Med. 133:201-206, January, 1970.

Ten-week-old dwarf SB mice were severely lymphopenic, with normal levels of polymorphonuclear leukocytes. Hemaglutinating antibody titers to both sheep erythrocytes and brucella antigen were significantly lower than in normal SB mice. As shown with qualitative immunoelectrophoresis, the immunoglobulin concentrations of IgG_1, IgG_2, IgM and IgA were similar to those in the normal SB mouse. The graft-vs.-host reactivity of dwarf SB spleen cells was somewhat depressed as indicated by a significantly lower mean spleen index.

The dwarf thymus was atrophic and had a marked loss of lymphocytes in both medulla and cortex. The peripheral lymphoid organs were also small. The average spleen of a 5-6 Gm. dwarf SB mouse contained only about 10,000,000-15,000,000 lymphoid cells, compared with 80,000,000-100,000,000 cells in a 5-6 Gm., 7-day-old normal SB mouse. The peripheral lymphoid tissues showed hypercellularity, particularly in the so-called thymus-dependent areas, i.e., the paracortical or deep cortical regions of lymph nodes and the perifollicular sheaths in the spleen. The lymphoid follicles of the lymph nodes and spleen were small but apparently structurally similar to those of normal SB mice. The number of plasma cells, however, was somewhat decreased. The adrenals of the dwarfs were relatively small. The ratio of cortex to medulla was lower than in normal mice. The cells of the zona fasciculata were eosinophilic, compared with normal, clear, foamy cells.

The results show that the pituitary dwarf SB mouse is immunologically deficient and suggest a selective deficiency of the thymus-dependent lymphoid system, caused by a defective thymotrophic pituitary control.

► [We begin this year with hints of new hormones. The studies recorded here are hardly definitive in providing criteria to characterize a specific thymotrophic factor of the pituitary. Still, it is a real possibility and the medical community has learned to take seriously the work emanating from Doctor Good's laboratory.

If there is a pituitary thymotrophic factor, what in the thymus might it stimulate? Look below.—Ed.]

Reduction in Incidence of Wasting Disease in Neonatally Thymectomized CBA/W Mice by Injection of Thymosin. Most neonatally thymectomized animals develop a fatal syndrome termed "wasting disease," presumably as a consequence of their inability to respond immunologically to pathogenic organisms. A cell-free, partially purified potent lymphocytopoietic substance called thymosin has been isolated from calf thymus and

is present in thymic tissue of a variety of mammals, including man. Yoshitsugu Asanuma, Allan L. Goldstein and Abraham White[2] (Albert Einstein College of Medicine) injected thymosin into mice which had been thymectomized within 24 hours after birth. Thymosin or bovine serum albumin (BSA) was given in a dosage of 0.25 mg. protein three times a week in the first week after thymectomy, and 0.5 mg. protein three times per week for the next 8 weeks. The mice in the BSA- and saline-treated groups began to show typical symptoms of wasting at about 4 weeks of age; death generally occurred 1-2 weeks later. The thymosin-treated group had a significantly higher frequency of survival (61%) than did the saline- (21%) and BSA-treated (9%) groups. A slight restoration in the absolute blood lymphocyte counts in the thymosin-treated group was also observed, although there was little change in body weight or evidence of lymphoid tissue regeneration.

When thymosin was administered at twice the above dosage, the growth rate of neonatally thymectomized mice was significantly increased. There was a significant increase in survival. The mean absolute lymphocyte count in peripheral blood of thymosin-treated mice was about double that of the saline- and BSA-treated groups.

Histologic examination of the tissues of the saline- and BSA-treated mice revealed a large decrease in the number of small lymphocytes present and a striking lack of follicular and germinal center development in lymph nodes and spleen. The gross and histologic findings in lymphoid tissues from neonatally thymectomized mice treated with thymosin were widely variable. Pathologic changes in the tissues of the small number of thymosin-treated mice in which wasting developed were similar to those in the saline- or BSA-treated groups. However, most lymphoid tissues in the thymosin-treated groups were more normal in appearance. The number of small lymphocytes was markedly increased, although the extent of restoration was not complete.

These findings indicate that the protection afforded by the intact thymus resides at least in part in a cell-free component. It is suggested that maturation and proliferation of immunologically competent cells involved in the homograft response require only the endocrine influence of the thymus. In contrast,

(2) Endocrinology 86:600-610, March, 1970.

immunologic maturation of cells involved in humoral antibody production requires both thymosin and/or other humoral factors and stem cells and the in situ environment of the thymus.

► [Again, we have no direct evidence that thymosin is secreted or that there is any control of its secretion. Still, taken together with the preceding article, one can already begin to think in terms of a pituitary-thymus axis complete with negative feedback. And, that's not all. Below is other evidence of metabolic activity of thymus extract.—Ed.]

Action of Thymic Extract "B" on Activity of Glucose-6-Phosphatase and Lactic Acid was studied by Isabela Potop, Elena Juvină and Georgeta Mreană[3] (Bucharest). Adult male mice were given injections of various doses of thymic extract "B" and biochemical measurements were made 2, 6, 12, 24 and 48 hours later. During the first 6 hours, administration of 2 ml. of extract "B" produced significant decrease in activity of glucose-6-phosphatase in the liver. Activity of this enzyme then progressively increased until 12 hours, when it was maximal. After 12 hours, activity decreased until 24 hours, when it returned to its normal value. The concentration of lactic acid in the liver decreased progressively beginning 2 hours after administration of thymic extract until 12 hours, when there was maximal decrease compared with nontreated controls. These results showed that thymic extract in a dose of 2 ml. has a short-term effect on the parameters studied. It increases activity of glucose-6-phosphatase and in parallel fashion decreases concentration of lactic acid.

A dose of 1 ml. of thymic extract produced a 28% increase in glucose-6-phosphatase, compared with a 47% increase when 2 ml. extract was administered. The concentration of lactic acid in the liver decreased by 1.6% with a dose of 0.5 ml. extract, by 12% with a dose of 1 ml. and by 22% with a dose of 2 ml. Thus the effect of thymic extract depends on the dose administered.

These results suggest the possibility of investigation of the action of the thymus by measurements of glucose-6-phosphatase activity and lactic acid concentration in the liver.

► [It is perhaps a strain to include this article with the preceding 2. I have no notion as to how closely related thymosin is to thymic extract B. Neither is it at all clear what the hepatic enzyme and lactic acid concentration changes have to do with the action of a thymic hormone. The results suggest that somehow this extract might increase gluconeogenesis. Does this extract provoke hyperglycemia?—Ed.]

Study of Prolactin-Like Activity in Individual Human Pituitary Glands. Patricia M. Nicholson[4] analyzed crude extracts of

(3) Rev. roumaine endocrinol. 7:49-54, 1970.
(4) J. Endocrinol. 48:639-647, December, 1970.

individual human pituitaries by polyacrylamide disk gel electrophoresis. The glands were collected at autopsy from pregnant women; women 1-56 days post partum; women who had recently undergone abortion; nonpregnant, non-lactating women aged 48-56 years; and men aged 42-87. The prolactin activity of individual anterior pituitary homogenates was determined by a modification of the local method of pigeon crop sac assay.

It was not possible to detect a protein band characteristic of pregnancy or lactation that might be ascribed to prolactin, even when high concentrations of the extracts were applied to the gels. However, certain differences in width and staining intensity of the human growth hormone (HGH) bands were observed between pituitaries from different categories. The HGH bands were prominent in the glands from aborted women and in the pregnancy group. After parturition, the bands were less prominent, but they tended to increase as the postpartum period increased. The reduction in the HGH band after parturition supports the possibility that HGH may act as a lactogenic hormone. The HGH bands of pituitaries from nonpregnant, nonlactating women and from men were of similar width and staining intensity and increased with the age of the donor to become as prominent as the HGH bands in the glands from aborted women.

In the pigeon crop assay, the anterior pituitaries from pregnant and parturient women had no higher activity than did glands in the other categories. This appears to be contrary to what might be expected if appreciable amounts of prolactin are produced only during pregnancy and lactation. However, HGH makes a considerable contribution to the activity observed by this method, which may therefore prove unsuitable to detect the separate contribution made by prolactin. The combined effects of clinical treatment, stress and postmortem changes may also have reduced pituitary prolactin to undetectable levels. These results do not provide any evidence for the existence of a human pituitary prolactin distinct from growth hormone.

► [In this and the 7 following articles we have this year's first "instant symposium."

Just as there seems to be difficulty in separating growth hormone from thymotrophic factor (see the first article in this chapter), for a long time there has been an ongoing debate as to whether the prolactin activity is separable from pituitary growth hormone activity. The present author cautiously concludes that her studies permit her to adduce no evidence that these are separable. Other workers, however, have other conclusions (see below).—Ed.]

Secretion of Prolactin and Growth Hormone by Cultures of Adult Simian Pituitaries. Cornelia P. Channing, M. Taylor, E. Knobil, C. S. Nicoll and C. W. Nichols, Jr.[5] cultured explants of rhesus monkey pituitaries and estimated the secretion of growth hormone (by a radioimmunoassay) and prolactin (by the local pigeon crop sac assay) after various periods to determine if a differential secretion of the two hormones would be demonstrated.

In each experiment there was a variable decline in the secretion rate of both hormones with time, but the rate of decline of growth hormone secretion was always greater than that of prolactin. This was reflected in the ratio of medium prolactin concentration to growth hormone concentration, which increased as culture time progressed in each experiment.

The results suggest that growth hormone and prolactin activities secreted by the monkey pituitary reside in separate molecules. Other physiologic observations in primates support the concept that they are separate hormones. However, it is conceivable that growth hormone and prolactin activities reside in the same molecule with a ratio of about 2-4 mU. prolactin to 1 μg. growth hormone and that, with the passage of time in culture, a conformational change could occur in the molecule, with a resultant loss in immunoreactivity and an increase in the ratio of prolactin to growth hormone.

► [Here the authors cautiously conclude that prolactin and growth hormone activities could be separable in Rhesus monkeys. What about man? Look below.—Ed.]

Normal Lactation and Blood Growth Hormone Studies. W. N. Spellacy, W. C. Buhi and S. A. Birk[6] (Univ. of Miami) measured plasma human growth hormone (HGH) by a radioimmunoassay method in 26 lactating women successfully nursing their infants and 35 control nonlactating women, all of whom were at least 6 weeks post partum. The two groups were similar with regard to mean age, postpartum interval, weight and parity. Plasma HGH was measured under controlled conditions both in a fasting resting state and during an insulin-induced hypoglycemic episode.

There was no significant difference between the blood glucose values of the two groups during fasting or after insulin injection. The hypoglycemic challenge produced a rise in the blood HGH levels in all subjects studied. The mean total HGH value

(5) Proc. Soc. Exper. Biol. & Med. 135:540-542, November, 1970.
(6) Am. J. Obst. & Gynec. 107:244-248, May 15, 1970.

for the control group was 110 mμg./ml. per 3 hours and for the lactating group, 141 mμg./ml. per 3 hours; these values are not significantly different. The ratio of the peak value to the basal HGH value was also not significantly different in the two groups.

These results demonstrate that the amount of HGH in women during the hypoglycemic test is not altered by lactation. It is uncertain whether the primate growth hormone and prolactin represent 1 or 2 separate hormones. That HGH does not seem to be related to occurrence of normal lactation suggests that a separate anterior pituitary hormone (prolactin?) does exist in primates.

► [Here is indirect evidence for a distinct functional separation of growth hormone and prolactin. Is better evidence available? Look ahead.—Ed.]

Prolactin: Evidence That It Is Separate from Growth Hormone in Human Blood. Andrew G. Frantz and David L. Kleinberg[7] (Columbia Univ.) devised a highly specific bioassay for prolactin which depends on ability of prolactin to cause differentiation and milk secretion of mouse breast tissue in organ culture and used this assay to measure prolactin concentration in circulating plasma in various conditions.

Prolactin activity was undetectable (less than 15 ng./ml.) under resting conditions in the blood of all 4 normal men and 19 of 20 normal women. When tested after insulin-induced hypoglycemia, however, all 10 normal women and 4 normal men had elevated prolactin activity (15-50 ng./ml. ovine equivalents). Growth hormone concentrations as measured by radioimmunoassay, initially less than 15 ng./ml. in all subjects except 1 woman, rose after administration of insulin to peaks of 17-50 ng./ml.

In 16 acromegalic patients, all with elevated plasma growth hormone levels (13-180 ng./ml.), prolactin activity was detectable in all, with concentrations of 15-400 ng./ml. ovine equivalents. Prolactin activity was also detected in subjects whose growth hormone levels had been elevated after exercise, administration of estrogen and administration of arginine; in every situation in which immunoassayable growth hormone was 15 ng./ml. or greater, prolactin activity was also detectable.

High concentrations of circulating prolactin (15-130 ng./ml.), with normal or low concentrations of growth hormone (less than 0.3-5 ng./ml.) were found in 10 lactating patients at 1-6

(7) Science 170:745-747, Nov. 13, 1970.

days post partum, in 7 women with galactorrhea of varying etiology and in 4 endocrinologically normal men and women receiving chlorpromazine or imipramine in high doses. A potent antiserum to human growth hormone was completely ineffective in neutralizing the growth hormone activity in any of these patients; however, when added to normal human serum, the antiserum completely neutralized prolactin activity. It is concluded that, in the plasma of these patients, there is a prolactin molecule different from human growth hormone.

In the normal subjects whose prolactin and growth hormone were simultaneously elevated after administration of insulin, prolactin activity was largely but not always entirely neutralized by antiserum to human growth hormone. It is suggested that circulating growth hormone has an intrinsic lactogenicity. Persistence of some prolactin effect after exposure to antiserum suggests that prolactin is released in some individuals concomitantly with growth hormone after induction of hypoglycemia with insulin. The high ratio of prolactin activity to growth hormone encountered in some patients with acromegaly suggests that prolactin as well as growth hormone may be secreted in this condition.

► [The authors' conclusions are plausible but a little worrisome. They use a new bioassay for the measurement of prolactin and conclude that the activity measured is different from immunoassayable growth hormone because of differing ratios of the two substances under different circumstances. One wonders whether ratios of bioassayable and immunoassayable activities can provide quantitative differences which justify *qualitative* differences in conclusions. The notion that growth hormone has intrinsic galactogenicity finds a parallel in the relationship between ACTH and melanocyte-stimulating hormone. ACTH has clear-cut intrinsic MSH activity but the converse is not true.

In the following article, we get on to radioimmunoassays of prolactin.—Ed.]

Serum and Pituitary Prolactin Levels before, during and after Puberty in Female Rats was measured by J. L. Voogt, C. L. Chen and J. Meites[8] (Michigan State Univ.) with the use of a radioimmunoassay.

Serum prolactin levels were uniformly low (13-21 mμg./ml.) from age 21 to 36 days (Fig. 1). There was twice as much serum prolactin in the 36-day rats with ballooned uteri as in rats of similar age with nonballooned uteri. Increased estrogen secretion by ovaries of the former rats is believed to account for the increased serum prolactin in these rats. A sharp three- to fourfold increase in serum prolactin was noted on the day of

(8) Am. J. Physiol. 218:396-399, February, 1970.