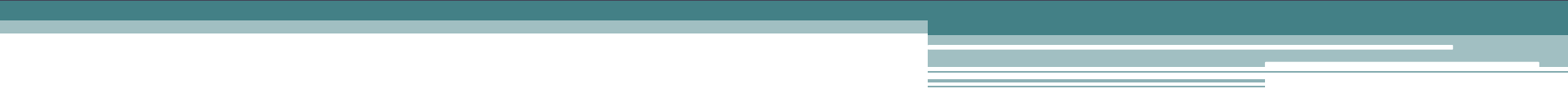


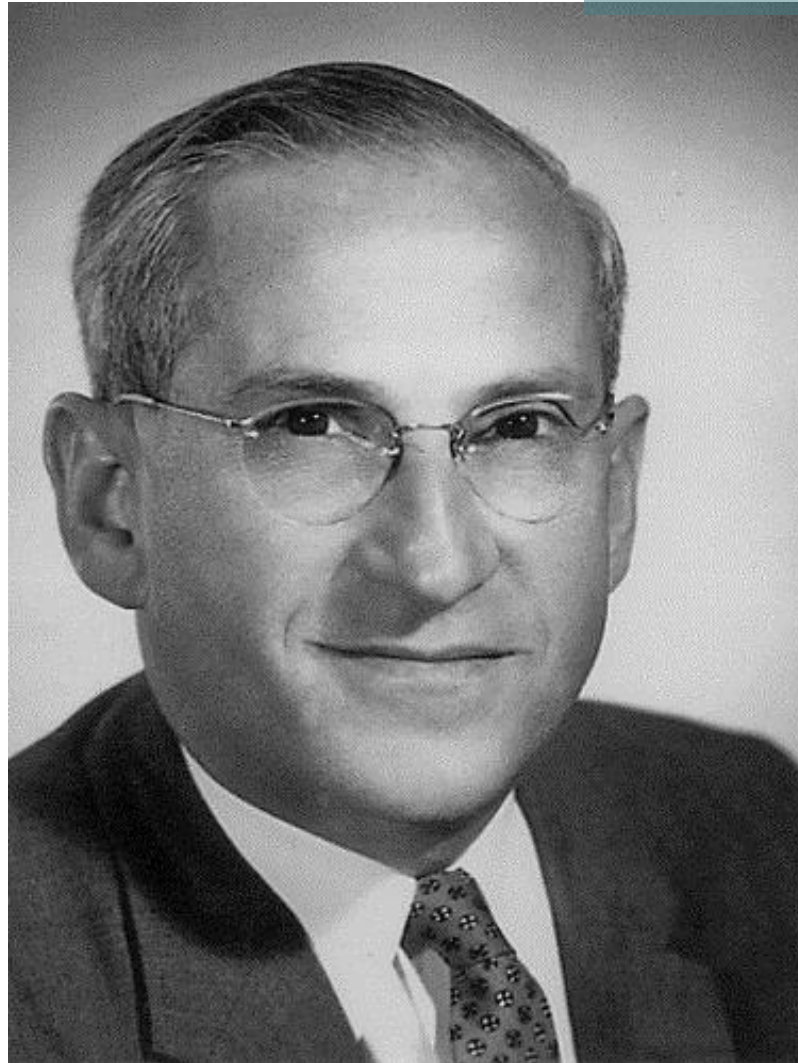
The Beginning of Translational Research in NICHD's Intramural Program: Effects on Women's and Children's Health



Lynn Loriaux, M.D., Ph.D.

Conflicts of Interest:
None

In 1971, the Endocrinology branch of the NCI moved, en bloc, into NICHD. This included all laboratory and office space, and the 12-E ward of building 10. Scientifically, the “prime movers” of the move were three: Roy Hertz, Griff Ross, and Mort Lipsett.



Roy Hertz, 1909-2002

Roy Hertz

Roy Hertz was born in Cleveland, Ohio, June 19, 1909. He was the fourth of seven children. His father was a pawnbroker.

The family, first generation Americans, valued education over most things, and all of the children went to college. Hertz went to the University of Wisconsin, majoring in comparative literature. He re-evaluated this major after earning a “C” in “Latin poetry.” He turned to biology, ultimately earning a PhD with Frederick Hisaw, one of the leading endocrinologists of his day.

Hertz’s assignment was to sort out the role of the pituitary gland in ovulation. He showed that ovulation depended on the sequential effects of FSH and LH on the ovary. To do this, he developed the “parabiotic technique,” a tool that proved critical to unraveling the humeral nature of pituitary-gonadal interactions.

Failing to find a steady research job, Hertz enrolled in the University of Wisconsin Medical School. He graduated in 3 years, did a rotating internship, and joined the United States Public Health Service. The UPS sent Hertz to Johns Hopkins to earn an MPH degree.

Hertz was then assigned to the Physiology division of the newly created National Institute of Health in 1944. He was soon made Chief of the NCI Endocrinology section, and then Chief of the Endocrinology Branch in 1953.



Charles Meredith

4/4/01

DEAR LYNN:

HONORED TO BE ASKED FOR
MY PHOTO AT 34 YEARS OF AGE.

BOTH OF THESE NURSES MARRIED
DOCTORS AND PROBABLY LIVED UNHAPPILY
EVER AFTER.

NOW IN MY 91ST YEAR I DON'T
FEEL A DAY OLDER - JUST CENTURIES!

MY BELOVED WIFE IS NOW IMMOBILIZED
AND DEMENTED WITH ALZHEIMER'S AND PARKINSON'S.

WOULD LIKE TO TALK WITH YOU
BY PHONE ONE OF THESE DAYS:

1-301-373-5544.

ALWAYS GRATEFUL TO YOU FOR MY
PROMOTION TO SCIENTIST EMERITUS, N.I.H.

Roy

ROY HERTZ
M.D. Ph.D. 1984

DR. Sc. (Hon.)



Min Chiu Li

Hertz was given an 18-bed facility in the newly opened Clinical Center. He needed a clinician to help him run the unit. Min Chiu Li was recruited from Sloan Kettering to do the job.

After being at the NIH only one month, a young woman with choriocarcinoma was admitted to Hertz's service. Hertz was interested in the rare phenomenon of spontaneous regression of the tumor, and simply measured hCG levels on these patients over long periods of time. This young woman promptly died of a cerebral hemorrhage.

Li was upset. He believed some therapy should be explored in these patients. He told Hertz of his experience at Sloan-Kettering with a patient who had melanoma.

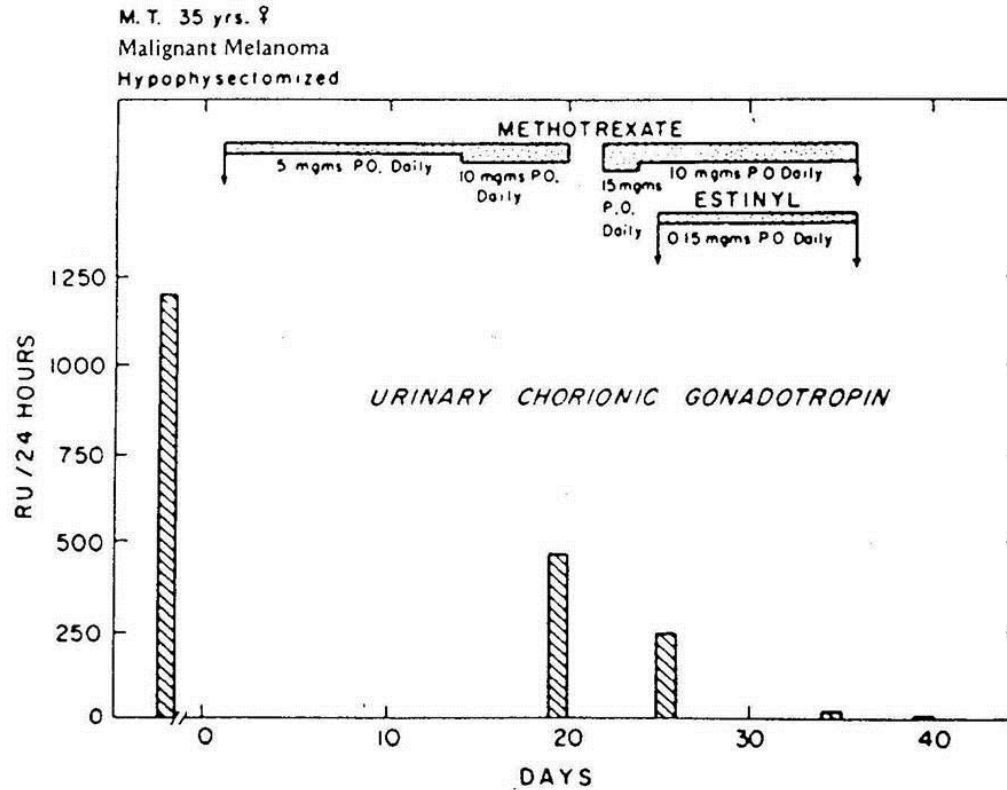


Fig. 1. Effect of methotrexate on urinary gonadotropin excretion in a patient with malignant melanoma. (From Li, M. C., in discussion, Hertz, R., et al.: Chemotherapy of choriocarcinoma and related trophoblastic tumors in women, Ann. N. Y. Acad. Sci. 80:280, 1959.)

Li believed that choriocarcinoma might respond to methotrexate. A “non-sequitur” to be sure.

Two months later, another young woman was referred. Before any therapy could be given, she developed a large hemo-pneumo-thorax, and appeared to be dying. Li gave her 10 mg methotrexate IV. She survived the night, and another 50 mg was given.

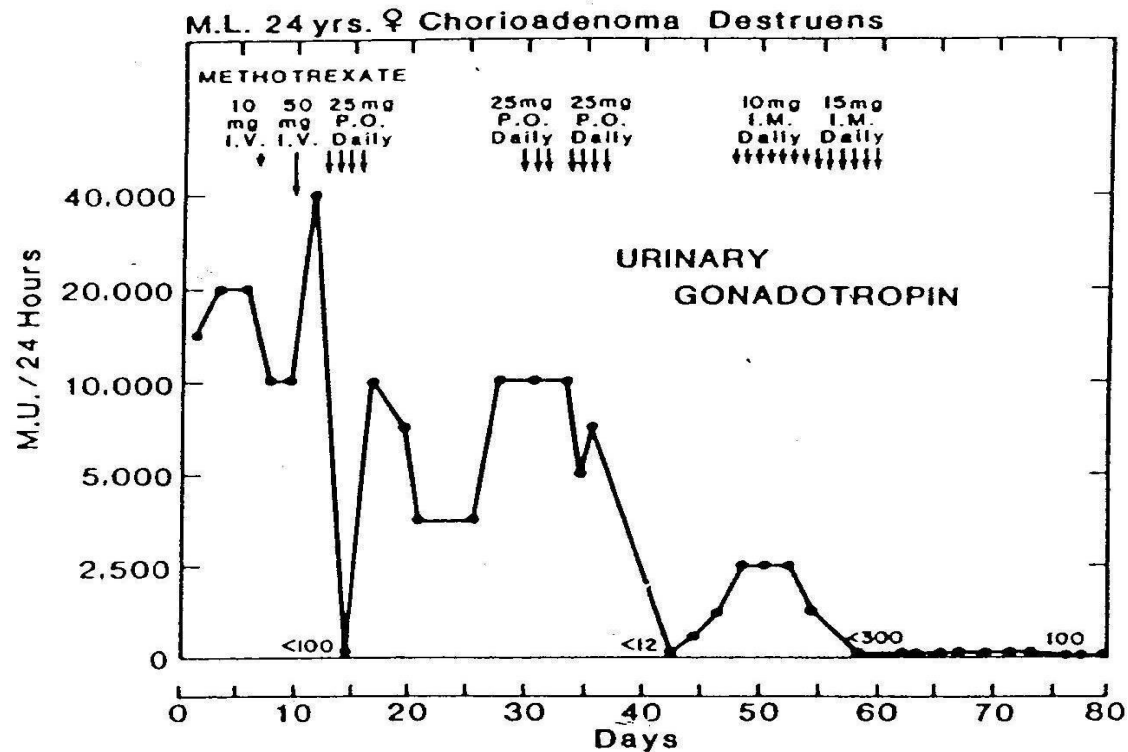


Fig. 2. Effect of methotrexate on urinary gonadotropin excretion in a patient with metastatic uterine chorioadenoma. (From Li, M. C., Hertz, R., and Spencer, D. B.: Effect of methotrexate therapy upon choriocarcinoma and chorioadenoma, Proc. Soc. Exp. Biol. Med. 93:361, 1956, published by Academic Press, Inc.)

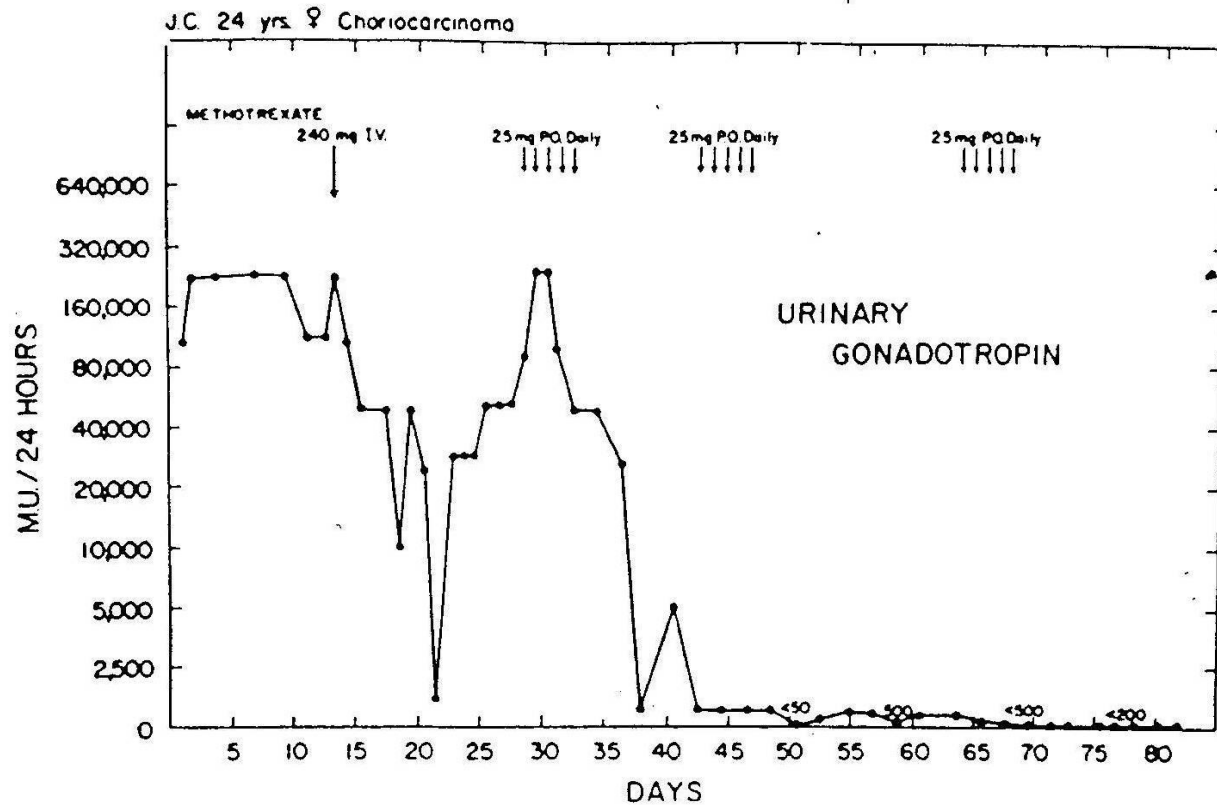


Fig. 4. Effect of methotrexate on urinary gonadotropin excretion in a patient with metastatic uterine choriocarcinoma. (From Li, M. C., Hertz, R., and Bergenstal, D. M.: Therapy of choriocarcinoma and related trophoblastic tumors with folic acid and purine antagonists, *N. Engl. J. Med.* 259:66, 1958, published by the New England Journal of Medicine.)

| | |
|-------------|--|
| 1965 – 1966 | Scientific Director NICHD |
| 1967 – 1969 | Chief, Reproductive Research Branch |
| 1969 – 1972 | Associate Director, Population Council, Rockefeller University |
| 1973 – 1989 | Professor of Pharmacology, George Washington University |
| 1987 – 2002 | Adjunct Scientist, NIH |

Awards include:

| | |
|------|---------------------------------------|
| 1972 | The National Academy of Sciences |
| 1972 | The Lasker Award |
| 1996 | The Koch Award, The Endocrine Society |



Lasker Awardees - 1972

Top row: Emil Freireich, Vince DeVita, Jr., V. Anomah Ngu, Donald Pinkel

Middle row: Min Chiu Li, Eugene Van Scott, James Holland, John Ziegler, Joseph Burchenal, Denis Burkitt, Paul Carbone

Bottom row: Isaac Djerassi, Emil Frei, III, (Mary Lasker, Sidney Farber, Alice Fordyce), C. Gordon Zubrod, Roy Hertz

Three other things:

1. Hertz R. Biotin and the avidin-biotin complex. *Physiol Rev* 1946 Oct;26(4):479-94.
2. Hertz R, Tullner W, Raffelt E. Progestational activity of orally administered 17 alpha-ethinyl-19-nortestosterone. *Endocrinology*. 1954 Feb;54(2):228-30.
3. Pincus G, Roch J, Garcia CR. Effects of certain 19-nor steroids upon reproductive processes. *Ann NY Acad Sci* 1958 Jul;71(5):677-90.



Griff T. Ross, M.D., Ph.D.
1920-1985

Griff was born in Mount Enterprise, East Texas. (He thought of East Texas as different from the larger entity. He called it the land of tall pines, red dirt, hook worm, and pellagra.) He came from Calvinist stock. He went to Stephen F. Austin State Teachers College and, in 1942, to the University of Texas Medical Branch in Galveston. He entered private practice in his hometown, the fourth generation of his family to do so.

He was drafted into the Air Force with the Korean War and spent two years as a general medical officer in England. When the war was over, Griff took a “Fellowship” in Internal Medicine at the “Mayo Brothers” clinic. Working with Al Albert, he developed a bioassay for urinary gonadotropins. This was the perfect tool for following the treatment response of patients with choriocarcinoma.

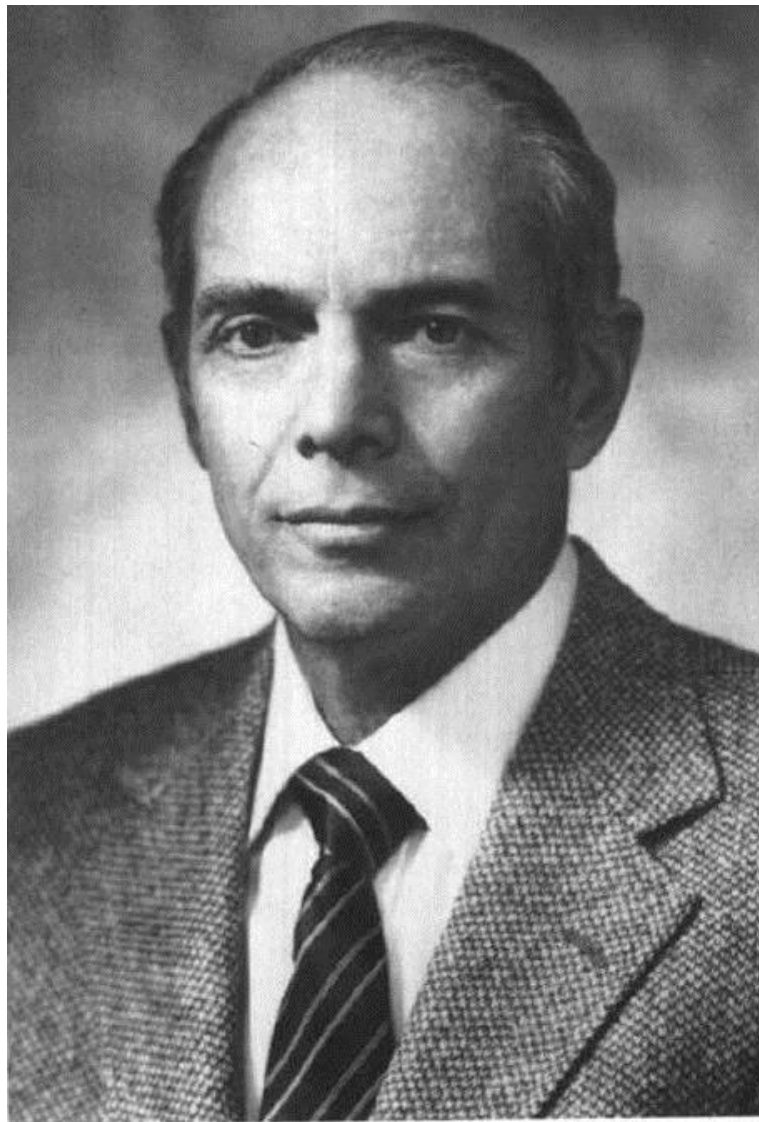
Roy Hertz needed someone to continue the choriocarcinoma initiative, and Griff was hired as an NIH Medical Officer in 1960. His first assignment was to improve the urinary assay for hCG.

Griff's method consisted of the Kaolin-acetone precipitation of a 24-hour urine collection, followed by graded twice-a-day injections of the extract into immature female mice. The mice were sacrificed on the 4th day. The uteri were dissected free and weighed.

It was an accurate and precise assay, but exceedingly labor intensive; 500 mice twice a week; 50,000 mouse uteri per annum. There had to be a better way!

Griff Ross and Bill O'Dell were pioneers in the development of antibodies for the radioimmunoassay of gonadotropins. Among their better antisera was B-1 (bunny one). The B-1 RIA had a high degree of cross-reactivity between hCG and hLH. The B-1 antibody permitted the first detailed studies of the menstrual cycle, pregnancy, and hCG-producing neoplasms.

Subjects with low hCG titers, however, could not be separated from patients excreting detectable levels of hLH. Ross and Vaitukaitis began to develop an ultra-specific hCG assay based on the unique 31 amino acid carboxy-terminal peptide (CTP) of the hCG β -subunit. These antisera recognized only hCG and were made available to anybody who wanted them. This antibody, enzyme linked and immobilized on a solid phase, led to the early pregnancy test that has played such an important role in family planning.



Mortimer B. Lipsett, M.D.
1921-1985

Mort Lipsett was born in New York City. He was a gifted student, destined for advanced study, and had been accepted into the Bronx High School for Science when his family moved to San Francisco. He completed high school there and graduated from the University of California (Berkeley) with a major in Chemistry.

His education was interrupted by the Second World War. He served as a medic with the 10th Mountain Division. In the Italian campaign he was decorated twice for valor in combat. With the cessation of hostilities, he enrolled in the University of Southern California School of Medicine.

After an internship at the Los Angeles County Hospital and a residency in medicine at the Sawtelle VA Hospital, he returned to New York as an endocrine fellow with Olof Pearson at the Sloan-Kettering Institute. Mort then moved to the National Institutes of Health in 1957 to work with Roy Hertz.

Except for a two-year period as Director of the Northeast Ohio Cancer Center and a sabbatical year at the Karolinska Institute, he spent his professional life at the NIH.

Mort was a steroidologist. He clarified the pathophysiology of the adrenal insufficiency syndromes while he was in New York. He established the beginnings of “steroid” dynamics and compartmental analysis at the NIH, and clarified much of the pathophysiology of the androgen excess syndromes in women.

Mort's great contribution to the program, however, was his administrative genius. He became Chief of the Endocrinology Branch of the National Cancer Institute in 1962 and then moved to the NICHD in 1970 as Associate Scientific Director. He became Director of the Clinical Center in 1976 and Director of NICHD in 1980. In 1984 he was appointed Director of NIADDK and held this post until his death. He is the only person ever to have held three directorships at the NIH.

Mort never misrepresented his position. He was generous with neither compliment nor criticism, but if you pushed the point, you could get his view of you. You could not get his view of another. Gossip, back room politics, and hidden agendas were simply foreign to his nature. Flattery was anathema to the extent that it was difficult to thank him, even in circumstances where the appropriateness of this simple gesture was apparent to all.

These three men collaborated in the cure of choriocarcinoma, a common and uniformly fatal cancer of women, found the first orally active progestin which led to the oral contraceptive, and laid the groundwork for the early pregnancy test as we know it today. They built the foundation for what is now called the “metabolic” syndrome.

The “Secret”

1. They were smart and creative.
2. They had the pick of the litter when it came to trainees and fellows.
3. They had a secure salary – failure was an acknowledged part of the scientific process.
4. They were in the lab and on the ward every day.
5. Their research questions were guided by the human condition. Experiments of nature. Bedside to bench.

What is next?

“It is just as hard to solve an unimportant problem as it is to solve an important problem.”

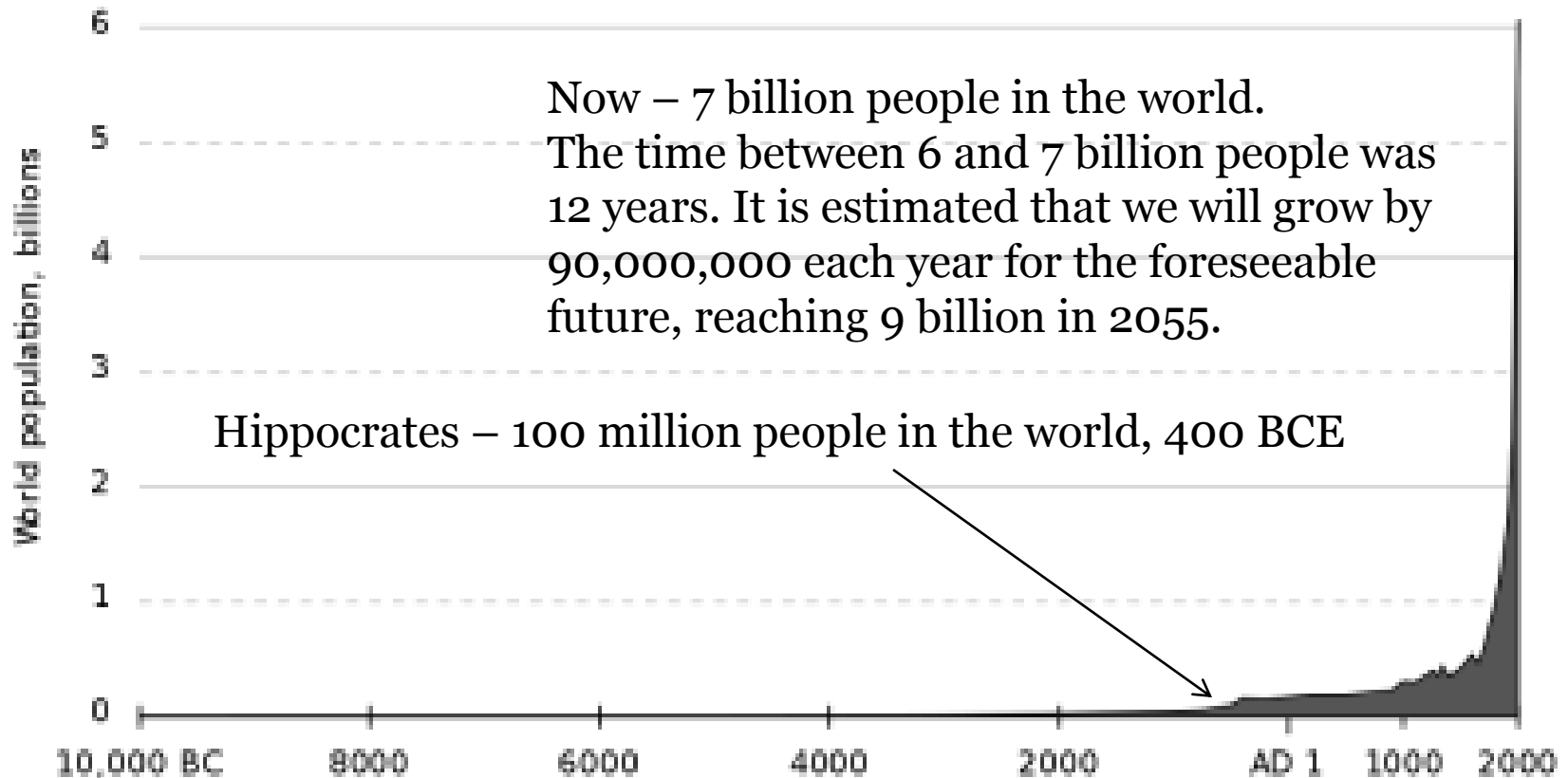
Julius Axelrod

NIH – 1949-2004

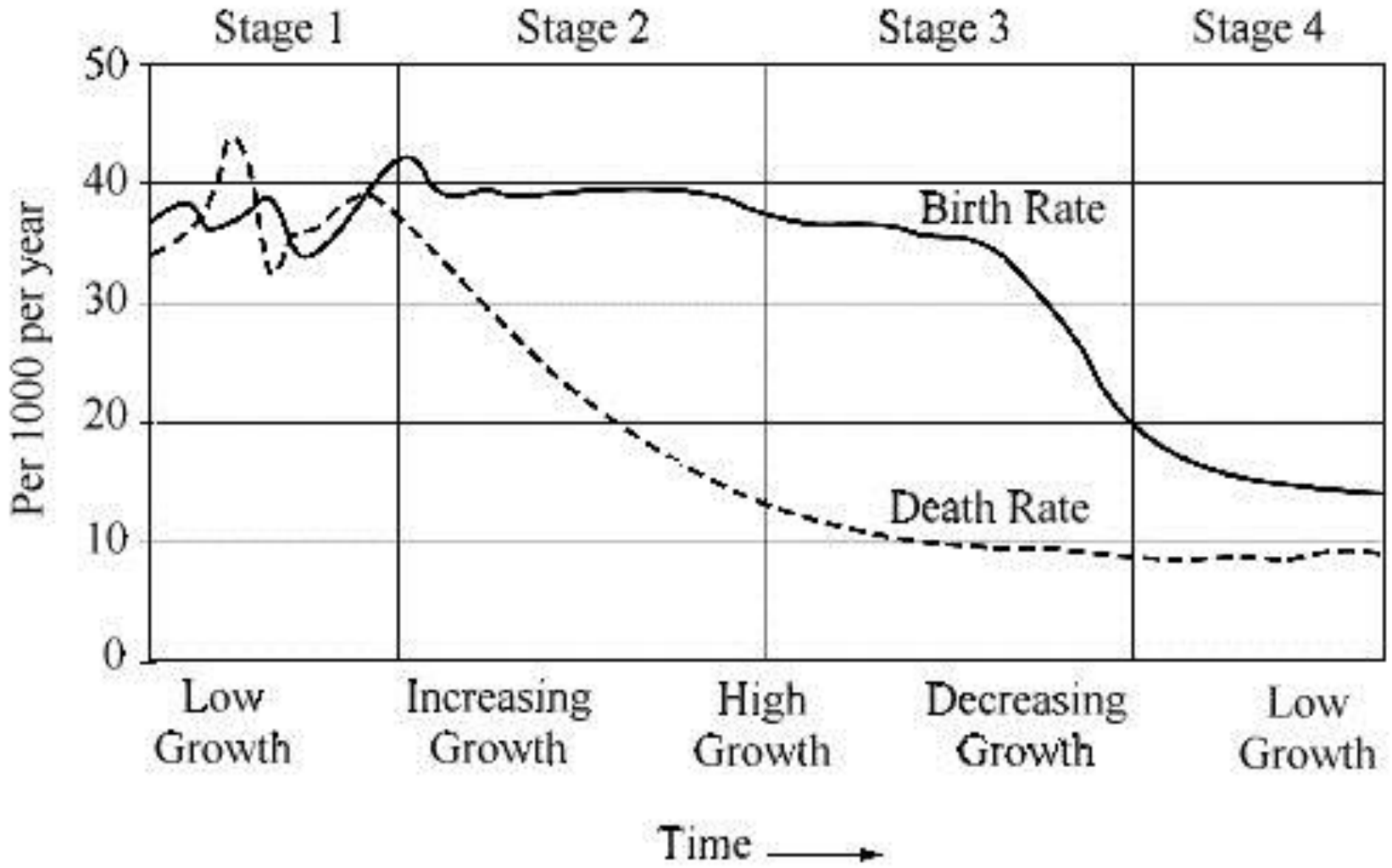
Nobel Prize – 1970

Catecholamines, synthesis,
secretion and reuptake





Most authorities believe that the “carrying capacity” of the planet is somewhere between 10 and 12 billion people. At that time, wars will be fought over a glass of clean water.



The answer is contraception.

Highly effective contraceptives have been available for some time, but they fail to the degree that compliance is incomplete.

The contraceptive for this challenge must be:

1. Low cost (free)
2. Accessible (wide distribution)
3. Acceptable (when does life begin?)
4. Safe (breast cancer, DVT)
5. Reversible
6. And, make women feel better by taking it and for taking it.

“Life is short; art is long; opportunity fugitive; experience delusive; judgment difficult. It is the duty of the physician **not only to do that which immediately belongs to him, but likewise to secure the cooperation of the sick, of those who are in attendance, and of all the external agents.**”

-Hippocrates, The Aphorisms
Section 1, #1

Criticism

A through Z. The author is aware that there has been a goodly sprinkling of metaphysics among this recording of some experimental facts: He is very well aware that the deductions will not stand the test of time. He does hope, however, that thoughts will be stimulated by this presentation – if not by truths, why then by errors: *Apologiae* are there none.

Fuller Albright
Harvey Lecture
Series 38, p123, 1942-3

Resources

1. Yarris JP, Hunter AJ. Roy Hertz, M.D. (1909-2002): The cure of choriocarcinoma and its impact on the development of chemotherapy for cancer. *Gynecol Oncol.* 2003 May;89(2):193-8.
2. Loriaux L. Remembrance: Mort and Griff. *Endocrinology.* 1992 Jul;131(1):1-3.
3. Loriaux DL. In memoriam: Mortimer B. Lipsett, M.D. *Endocrinology* 1987 Feb;120(2):841-3.
4. Vaitukaitis J. In memoriam: Griff T. Ross, M.D., Ph.D. *Journal of Clinical Endocrinology and Metabolism.* 1986;63:1250-51.
5. World Population to 2300. United Nations, Department of Economic and Social Affairs/Population Division. New York, 2004.