The Historical Foundations of the Linear Non-Threshold (LNT) Dose Response Model for Cancer Risk Assessment

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HOW LNT WAS BORN AND SUSTAINED

A Story of Mistakes, Deceptions, and Failed Public Policy

THE KEY PLAYERS

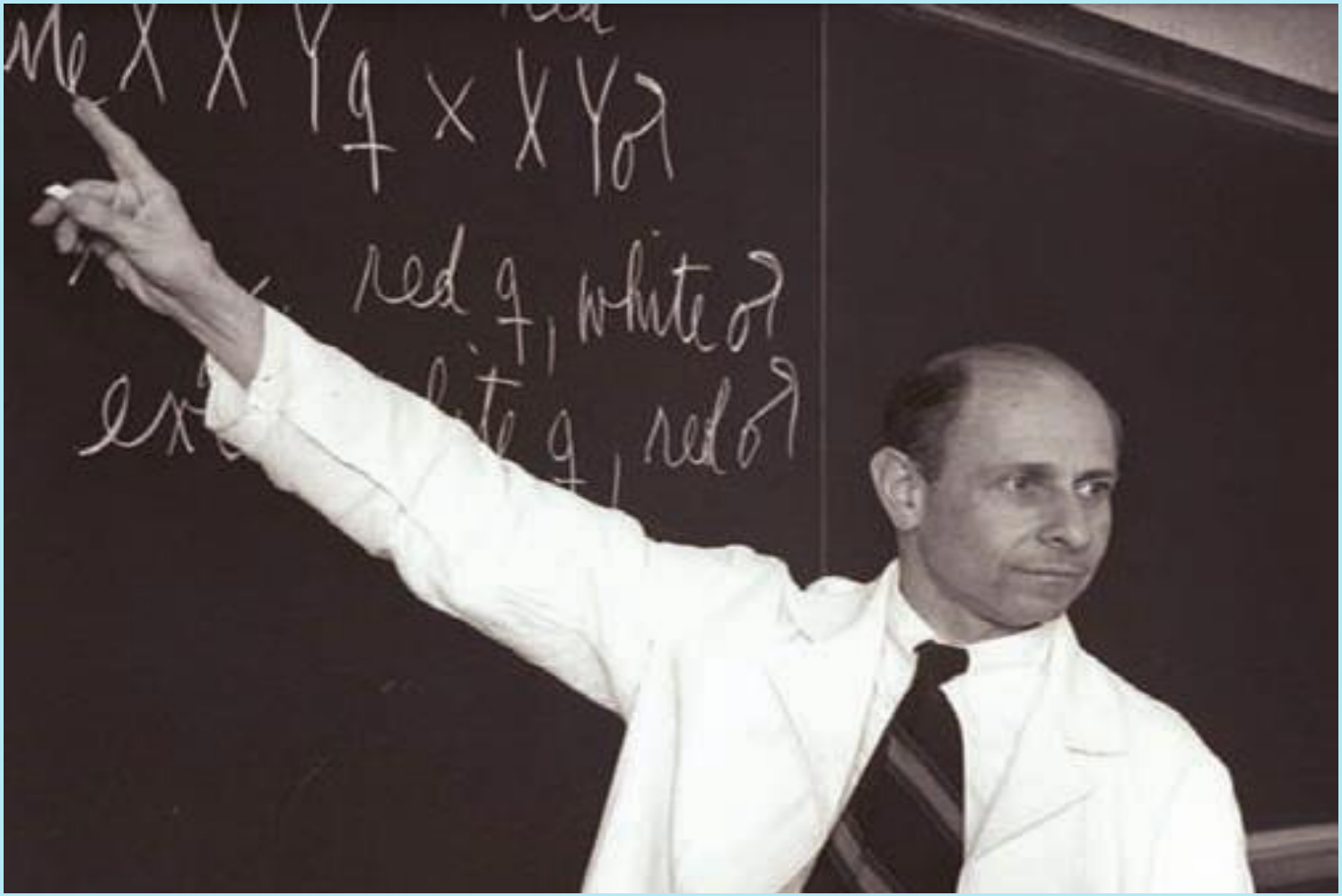
Hermann Muller
Curt Stern
Ernst Caspari
Delta Uphoff
Jim Crow
Warren Weaver
George Beadle
William Russell
Lewis J. Stadler

Barbara McClintock
Vladimir Timofeeff-Ressovsky
Max Delbruck
Edgar Altenburg
Edward B. Lewis
John Gofman

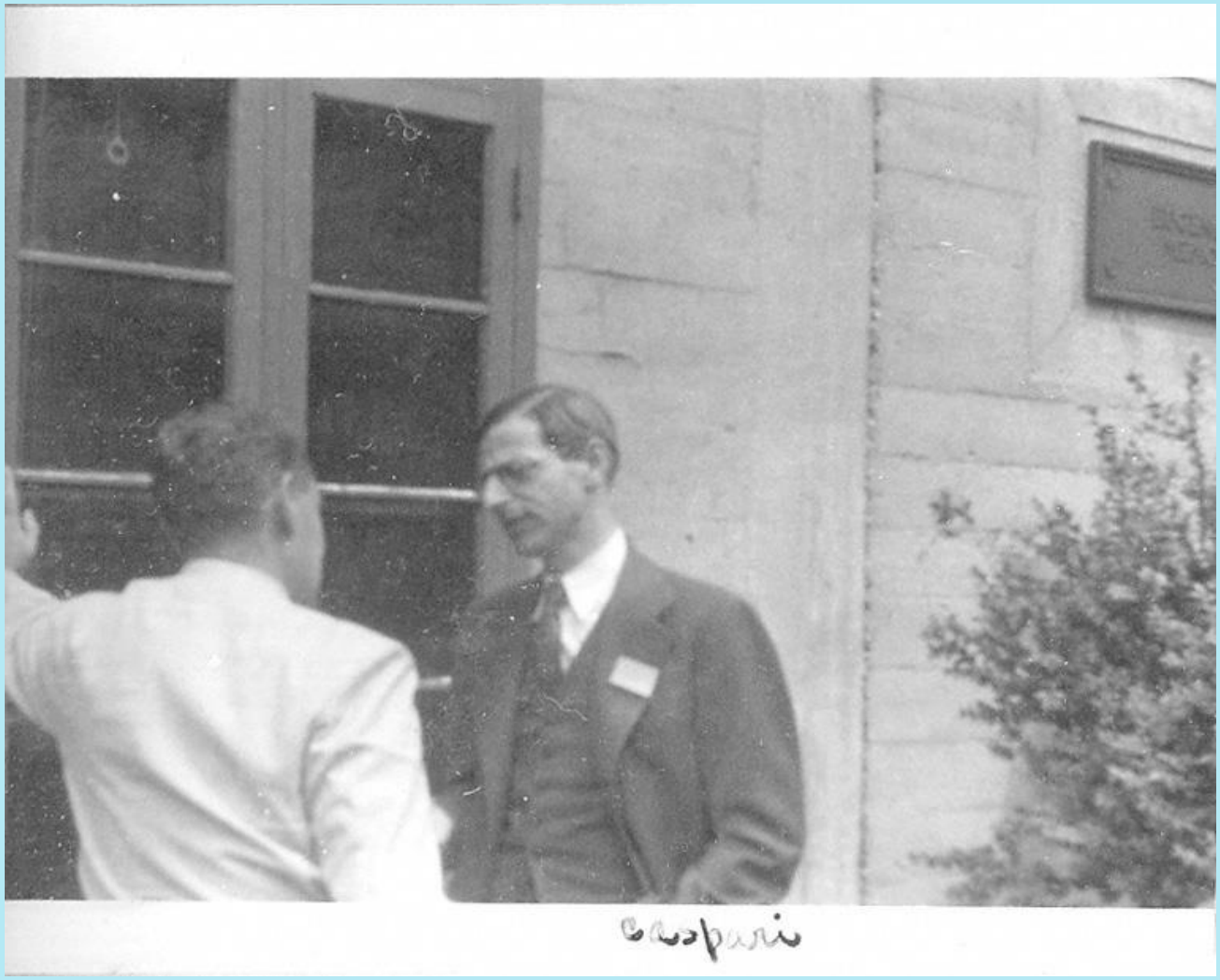
Hermann Muller

Hermann Muller

Curt Stern



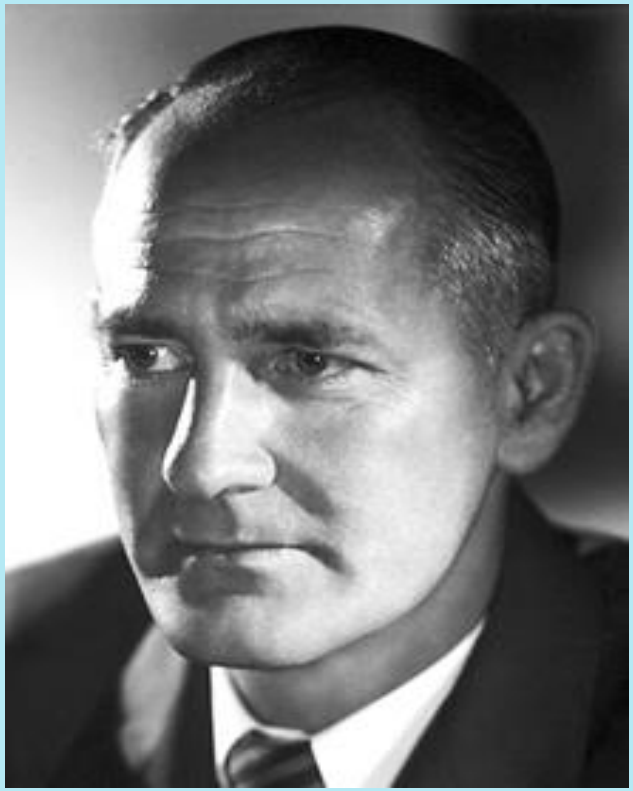
Ernst Caspari



Delta Uphoff

Warren Weaver

George W. Beadle



William L. Russell

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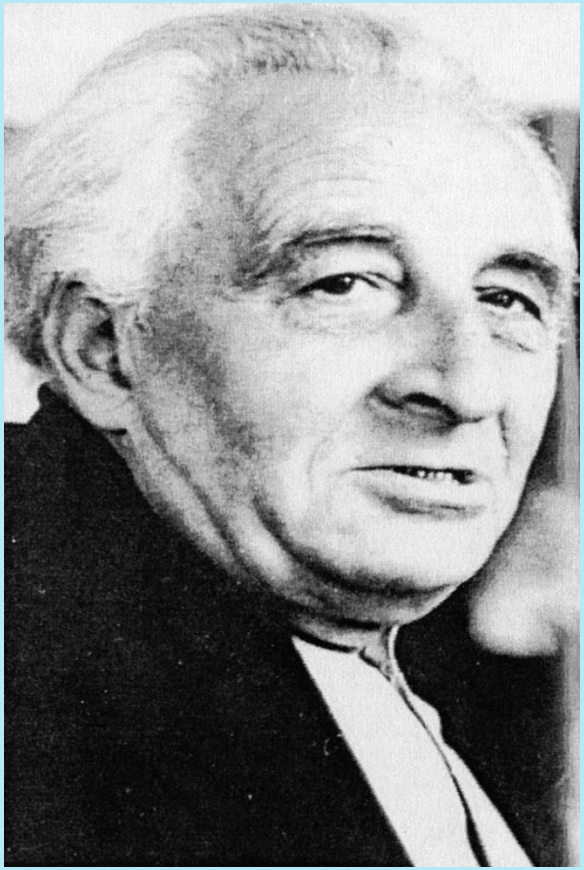
Lewis J. Stadler

Barbara McClintock

Nikolay Timofeeff-Ressovsky



Max Delbruck

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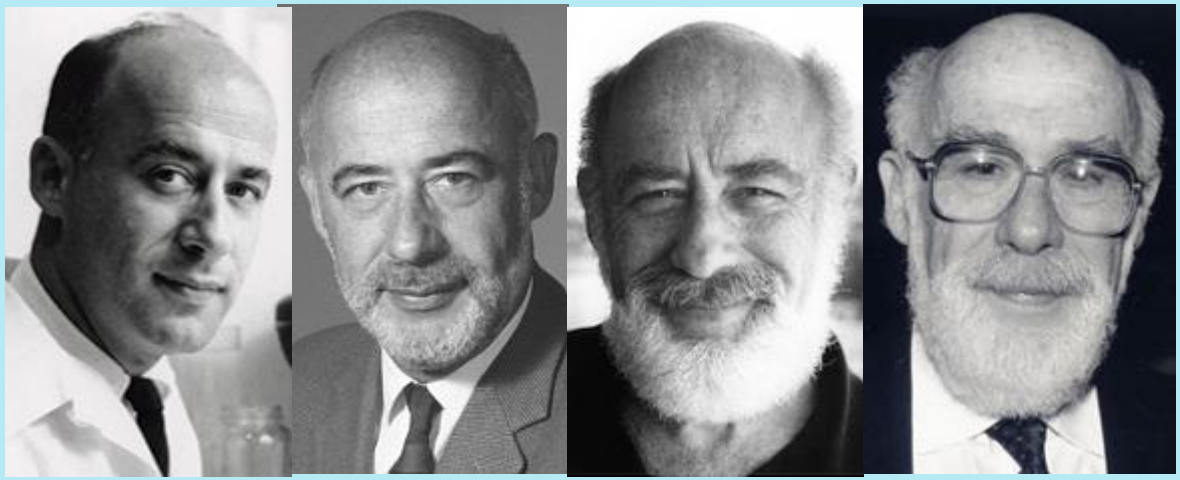
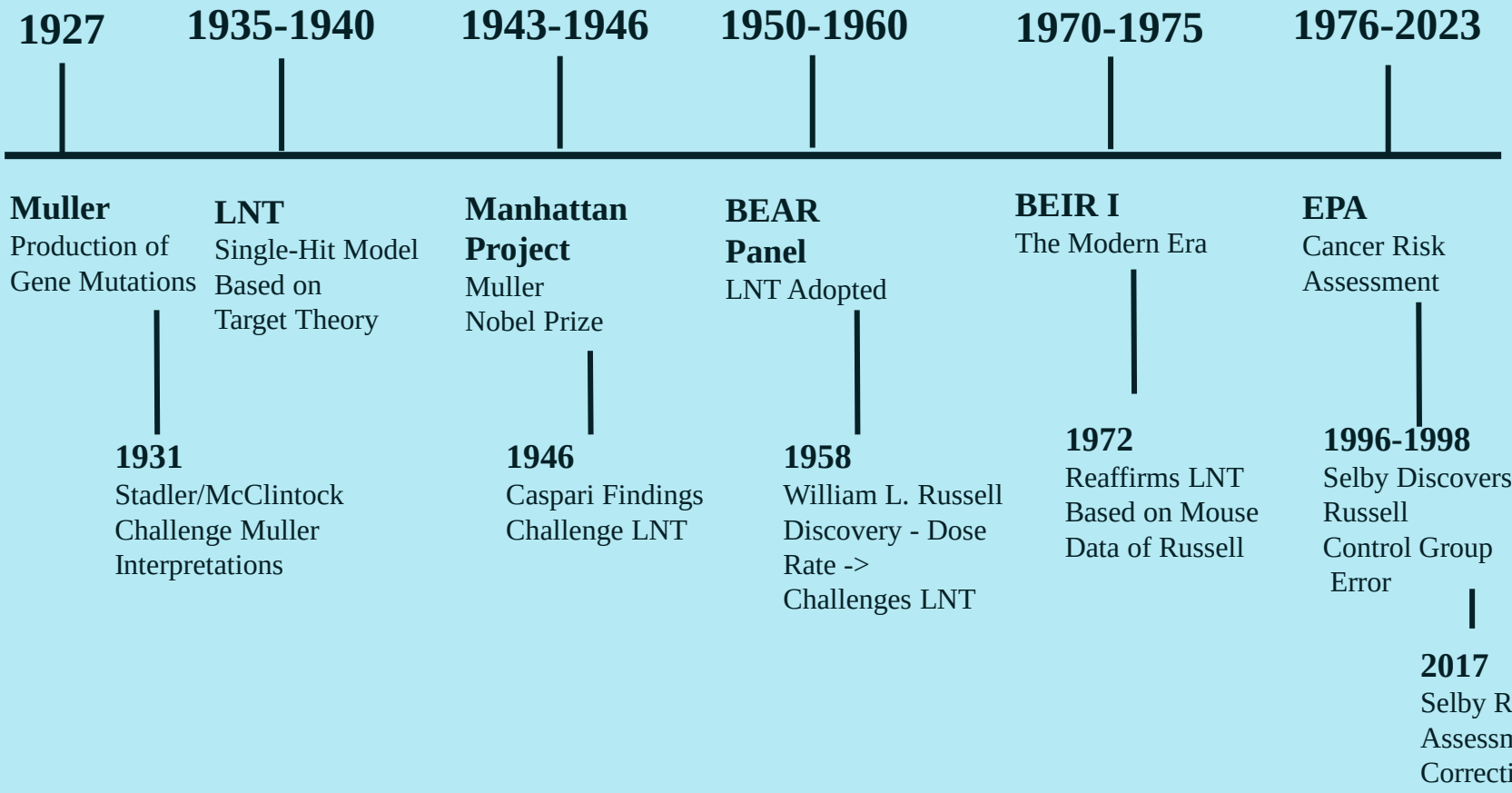


LINEAR NON-THRESHOLD (LNT)
Key Events/Periods -Timeline



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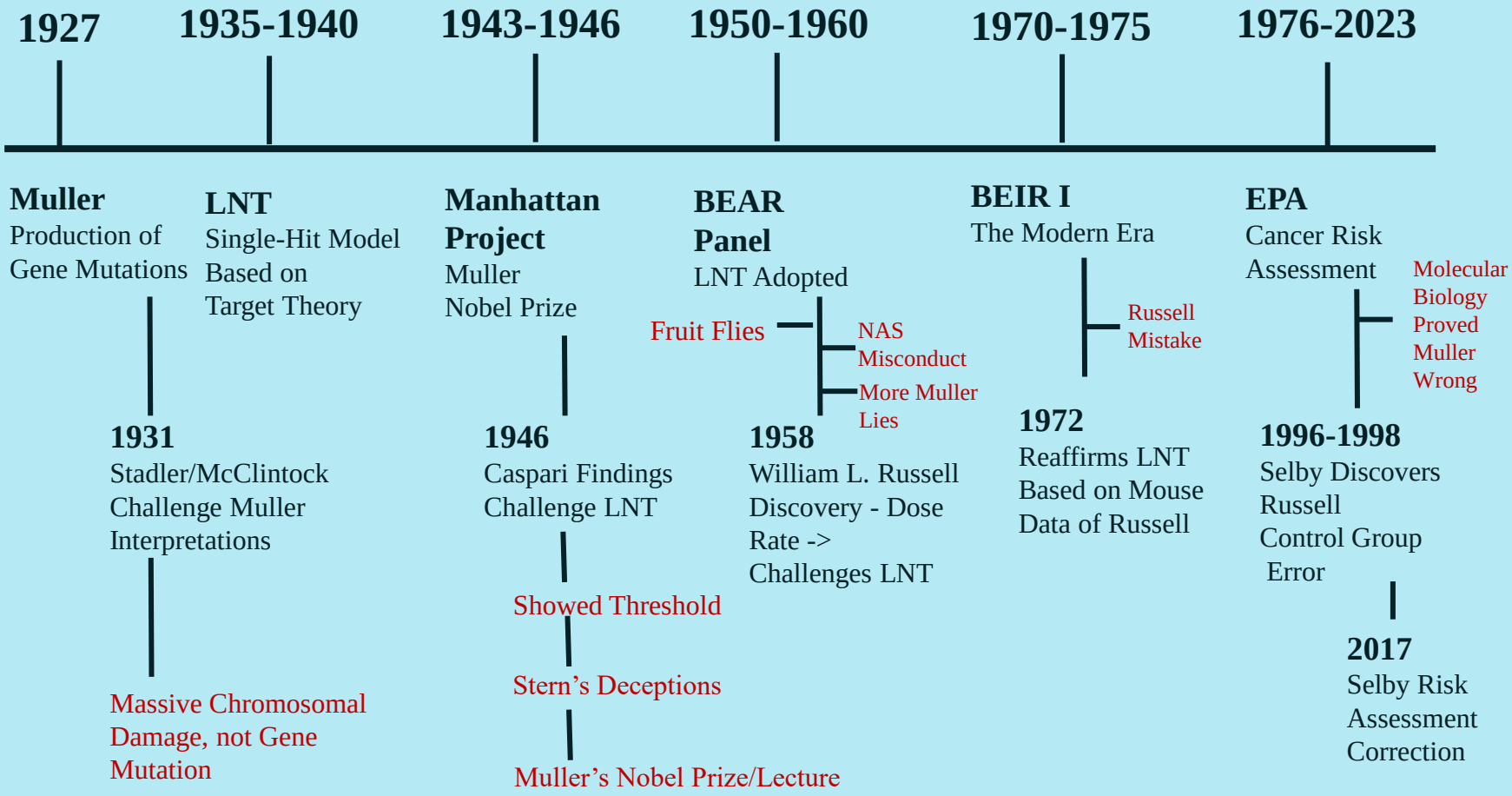


RISK ASSESSMENT'S "ORIGINAL SIN"

Muller's First Big Mistake: Two Parts

- Getting the Concept of Evolution Wrong
- Integrated Mistake into Risk Assessment

THE BIG MISTAKE: HOW IT HAPPENED

- Very Few Visual Mutations in Fruit Flies:
  - 400 mutations/20-25 million flies
- Seemed impossible to induce mutations
- Conclusion: Genome is extremely stable

THE MUTATION QUEST

"…In the course of this work, animals and plants have been drugged, poisoned, intoxicated, etherized, illuminated, kept in darkness, half smothered, painted inside and out, whorled round and round, shaken violently, vaccinated, mutilated, educated and treated with everything except affection, from generation to generation. But their genes seem to remain oblivious, and they could not be distracted into making an obvious mistake……" Muller, 1929

MUTATION AND EVOLUTION

- 1927-Muller eventually induces “gene mutations” from very high doses of X-rays.
- 1929-Muller writes that he has “found at least one of the natural causes of mutations, and hence of evolution”…..indicating that background radiation was a cause of evolution.
- The only way he could make that claim was to assert linearity at low doses even though he exposed his flies to ionizing radiation at a rate of 100 million-fold greater than background.
- For Muller: natural mutations, through scattered and very infrequent, were sufficient… with natural selection taking control, deciding the fate of the organism/species

THE MISTAKES

Mistake # 1:

- The genome is highly unstable, vast numbers of mutations occur each second of the day in each cell but get repaired.

- Repair is so rapid one can’t tell that there was a mutation.

THE MISTAKES

Mistake # 2:

- Muller only offered one hypothesis—background radiation induces mutations-no repair-natural selection operates. He needed to propose several competing hypotheses but failed to do so.

- The field eventually adopted his LNT view.

DID MULLER INDUCE GENE MUTATION?

- NO!!
- He induced mostly massive gene deletions.
- Many notable geneticists disputed Muller on this topic, showing significant limitations in his argument and data.
- Muller was eventually proven wrong with modern nucleotides measurement techniques.
- His great “gene mutation” discovery wasn’t so great.

MULLER GENE MUTATION PAPER

- Science Paper: No data provided

- How Does Muller Get his Paper in Science: New Evidence Suggesting Quid Pro Quo with Science owner and editor.

MULLER GENE MUTATION PAPER

- Conference Proceedings Paper: Never Peer-reviewed.
- Muller Avoids Peer Review, escapes criticisms, never cites others claiming gene mutation prior to his work.
- Altenburg: “Hermann, did you just blow holes in the chromosomes?”
- Can’t support his gene mutation claim.

MULLER'S ADVOCACY OF LNT

- Muller advocated the LNT dose response model for ionizing radiation and mutation; two independent student projects using extremely high doses supported this view. (His own research had not supported linearity.)

- In 1930, Muller created the term "Proportionality Dose Response" and soon transformed this into a "PROPORTIONALITY RULE".

- This phrasing dominated mutation literature during the 1930s.

EVOLUTIONARY THEORY AND LNT

- Proportionality Rule/LNT was born out of a need to explain evolution.
- Evolution was the cardinal belief.
- Muller concluded that LNT must be the fundamental dose response for radiation-induced mutation.
- For Muller the only way that evolution could work was via gene mutation from background radiation …that required linearity at low dose and no repair…..thus, the birth of LNT-The Original Sin

LINKING MECHANISM TO MODEL

1935 – Timofeeff-Ressovsky, Zimmer, and Delbruck

- Single-hit mechanism based on target theory.
- Accounted for linear response based on gene target.
- The Model: wrong from the start, being based on Muller's incorrect "gene mutation" conclusion.
- Assumed no genetic damage repair

MULLER SET BACKS

- 1930-1940
- Evidence mounted that Muller had induce massive deletions….not gene mutations.
- Muller could never counter the challenge that he "confused an observation with a mechanism."

MUTATION:
TOTAL DOSE VS DOSE RATE

- Since he was losing the gene mutation argument, Muller undertook an experimental initiative to test his gene mutation explanation and LNT.

- University of Edinburgh…1938-1939.

Muller's Recovery: MUTATION AND DOSE RATE

- Muller's student demonstrated that X-ray-induced mutation in the mature spermatozoa of the fruit fly appeared independent of dose rate.

- These findings supported the hypothesis that X-ray-induced mutations were irreparable and cumulative.

MUTATION AND DOSE RATE

- Total dose, therefore, rather than dose rate was the best predictor of genetic damage, supporting LNT.

- This study had important experimental limitations, some very serious and needed replication.

NEW CONCERNS RAISED

- Flaws Hidden and Missed - never revealed

- A few examples:
  - piloted strain tested not used; multiple genetic sub-strains used at the same time; changed strain and diet midway through; failed to report data that did not support hypothesis; poor temperature control and system failures;

NEW CONCERNS RAISED

- Never reported location of gamma source….If located near controls then high exposure to controls (24 r) even with lead shielding likely occurred with no treatment effect……

MANHATTAN PROJECT/GENETIC DAMAGE COMPONENT

Goal: understand the nature of the dose response in the low dose zone for germ cell mutation.

- Experiments would test dose rate vs cumulative dose for risk assessment purposes.

- Use of Mouse Model – Dr. Donald R. Charles

- Use of Drosophila (Fruit Fly) – Dr. Curt Stern

MANHATTAN PROJECT/GENETIC DAMAGE COMPONENT

Results and Issues

- Charles's Research – 400,000 mice, no meaningful publications.

- Stern's Research – Highly significant; findings affected scientific beliefs and national policy on dose response.

STERN'S RESEARCH

- Acute Exposure Data – Warren Spencer and Curt Stern indicated a linear dose response and were widely accepted.

- Weaknesses of the Spencer/Stern findings were never acknowledged nor recognized.
  - Poor temperature control
  - Inconsistent instrument calibration
  - Poor matching of control and treatment experimental days
  - Combining of treatments with the same total dose but different dose rates
  - Lack of data adjustment for genetic lethal linkages
  - Improper statistical analysis at low dose

STERN'S RESEARCH

- Chronic Exposure Data (dose rate 1/13,000 of the lowest dose used by Spencer/Stern) (100,000 fold greater than background) – Ernst Caspari and Curt Stern supported a threshold dose response and challenged the belief that mutation damage was due to total dose and independent of dose rate.

- The chronic findings posed a serious challenge to the LNT concept.

STERN – THRESHOLD CONTROVERSY

Stern challenged Caspari over control group validity.

- Documentation in literature supported Caspari controls

- Stern backed down

STERN – THRESHOLD CONTROVERSY

Stern's New Strategy:

- Create discussion that discounts Caspari findings
- Stern suppressed the significance of the threshold findings by demanding in the discussion of their paper that the data not be accepted until it could be determined why the response was not linear (i.e. disagreed with Spencer's findings; published the paper in his own journal (Genetics) without independent peer-review).

STERN – THRESHOLD CONTROVERSY

- Did Muller see the Caspari findings prior to his Nobel Prize lecture?

- Yes, November 6, 1946 letter and Muller's answer to Stern's November 12, 1946 letter.

MULLER'S NOBEL PRIZE LECTURE

- Muller used his Nobel Prize lecture to demand the rejection of the long-standing threshold dose response model for genomic mutation.

- Muller: LNT should replace the threshold model.

MULLER'S NOBEL PRIZE LECTURE

- This lecture received enormous publicity and influenced regulators, the media, and the scientific community on public health concerns with ionizing radiation even at very low doses.

MULLER'S NOBEL PRIZE LECTURE

- Prior to his Nobel Prize lecture, Muller knew of the threshold supportive study by Caspari and Stern (November 12, 1946 letter). It was the strongest study to date with the lowest dose rate tested.

- Muller recognized the challenge to LNT and strongly supported study replication.

- Muller found no technical issues with this paper. Letter exchanges indicate that Muller's views were similar five weeks before and five weeks after his Nobel lecture (January 14, 1947 letter).

MULLER'S NOBEL PRIZE LECTURE

- Following the internal review by Muller of the Caspari and Stern paper, the threshold conclusion was dropped and Muller's name was added to the acknowledgements.

REPLICATING CASPARI

- Replication studies of Uphoff, as directed by Stern, were problematic because of extremely low control group values, making the data “un-interpretable”.

- This happened on several occasions. Stern acknowledged this issue in a classified publication for the Atomic Energy Commission.

- Stern blamed low controls of Uphoff’s replication study on “investigator bias”.

STERN AFFIRMS LNT

- Stern published a meta-analysis of the five Manhattan project experiments in Science. He now used the un-interpretable data (Uphoff), treating it as normal, while reviving his unsupported criticism of the Caspari study. Such changes led to a linear interpretation.

- The meta-analysis was a one-page report/table. He promised to provide all methodological details and data in a subsequent report and never did.

CASPARI'S FINDINGS MARGINALIZED

- The Caspari threshold study was marginalized based upon "rumors" that its control group was aberrantly high and that its findings were unreliable.

CASPARI'S FINDINGS MARGINALIZED

- The Caspari controls: Stern claimed that Caspari's control group values were aberrantly high. However, the literature and unpublished data by Muller supported Caspari.

- The basis of these conclusions are found in letters, cables, and manuscripts of Stern and Muller.

MULLER'S DECEIT

- In the early 1950s, Muller repeatedly and inexplicably challenged the Caspari findings claiming in writing that his control group values were aberrantly high. Yet, the data of Muller both before and after the Caspari paper fully supported the Caspari interpretation.

- Why would Muller make such knowingly false comments repeatedly? Robley Evans Paper favors Caspari

UPHOFF RESEARCH IN PERSPECTIVE

- The two key Uphoff/Stern chronic experiments: the data have never been published and the data have been missing for 70 years.

- No information exists on the two chronic studies of Uphoff/Stern beyond the one-page summary.

- Based on the study design information, it has been recently shown that the studies included two simultaneous variables and could not test the total dose/dose rate hypothesis. The study is fundamentally flawed even if the data are found.

LNT ACCEPTANCE

- Stern published a highly acclaimed genetics textbook with multiple editions, from 1950 onward.
- He claimed that the data of Uphoff and Spencer provided the basis for a linearity interpretation, ignoring Caspari's findings.

BEAR I GENETICS PANEL

1956 – Recommended the adoption of the LNT model for ionizing radiation induced genomic mutation, rejecting the threshold model.

- Selected only those Geneticists with a strong record of supporting LNT.
- Adopted the LNT belief at the start of their meeting; no possibility of alternative dose response models.

BEAR I GENETICS PANEL

1956 – Recommended the adoption of the LNT model for ionizing radiation induced genomic mutation, rejecting the threshold model.

- The Genetics Panel failed to assess the scientific basis for the LNT but adopted it based on an assumption that it was true.
- This conclusion is supported by Genetics Panel transcripts and other source material.
- The Panel decision not to provide documentation was accepted by the President of the NAS.

BEAR I AND ATOMIC BOMB RESULTS

- NAS BEAR I Genetics Panel decided not to assess 10 year study of genetic damage in children of Atomic Bomb survivors, using only fruit fly and mouse data.
- Study directed by Panel member, Jim Neel.
- Neel secretly gives report to British Genetics Panel.
- The Neel study has a major impact on the British Report.

BEAR I GENETICS PANEL

Scientific Misconduct: Falsification

- Estimations of genetic risk
  - Misrepresented the number of geneticists providing estimates.
  - Misrepresented the range of variability and uncertainty amongst estimates.
  - Deliberately omitted data since it would affect acceptance of their recommendations.

NAS AND BEAR I DECIEVE AGAIN

- It was recently discovered that the Public Report by the BEAR 1 Genetics Panel was not written, reviewed or approved by the Panel. It was written by an independent third party.
- The NAS leadership nonetheless asserted that it was approved and written by the Panel.
- Panel members asserted that the Report contained serious errors that were never acknowledged or corrected.
- The Panel Membership knew of these actions and never acted to correct the matter.

BEAR I GENETICS PANEL

Significance:

- International Commission for Radiation Protection: lowers occupational exposure standards by 2/3.
- The Federal Radiation Council/Atomic Energy Commission established nuclear power plant emission standards (1961) based on the risk estimates of the Genetics Panel.
- These standards were used by Gofman and Tamplin to estimate cancer risks, creating massive controversy, leading to the establishment of BEIR I, 1970.

BEAR I GENETICS PANEL

Significance:

- Lead President Eisenhower to remove risk assessment from AEC and to create FRC.

- Directly lead to the Ed Lewis influential paper on leukemia and radiation risk assessment.

BEAR I GENETICS PANEL

- Significance:

- This LNT recommendation was soon applied to somatic cells for cancer risk assessment by the NCRPM in 1958 incorrectly assuming that findings with mature spermatozoa could be generalized to all cells.

- Genetics Panel members testified before Congress strongly emphasizing the Spencer and Uphoff findings to support their linearity recommendation.

BEAR I GENETICS PANEL

- Significance:

- Recommendations of the BEAR I Genetics Panel provided the foundation for cancer risk assessment for chemicals and radiation worldwide.

- This is the most significant action in the history of environmental risk assessment.

HISTORICAL ASSESSMENT

- The BEAR I Genetics Panel recommendation was the result of an orchestrated deception by key leaders of the radiation genetics community, Curt Stern, Hermann Muller, and eventually the entire NAS Genetics Panel and the leadership of the Rockefeller Foundation.

HISTORICAL ASSESSMENT

- The principal goal of these individuals was to support the LNT model and advocate its use in risk assessment.

EDWARD B. LEWIS, LEUKEMIA AND LNT

HOW ONE PAPER AND ONE PERSON MADE A DIFFERENCE

WHO WAS EDWARD B. LEWIS?

- A Future Nobel Prize Laureate in 1995.
- In 1957-A young Cal Tech genetics professor, a fruit fly expert.
- No Education in radiation, cancer biology, leukemia, epidemiology, risk assessment and biostatistical modeling at low doses.
- How did he get involved with radiation, leukemia and risk assessment?

LEWIS GETS INSPIRED

- Cal Tech was a center of environmental activism….most notably…Linus Pauling, Alfred Sturtevant and George Beadle.
- Beadle challenged all faculty in his department to try to assess the impact of fallout on humans in July, 1955…
- Lewis was the one who took the challenge….
- This started his efforts that would lead to the 1957 *Science* paper.

DID LEWIS BECOME A SCIENTIFIC STALKING HORSE FOR THE NAS BEAR I GENETICS PANEL

- A 10 year report on genetic damage in offspring of atomic bomb survivors is negative…..reported in early 1956….by James Neel, Panel Member.

- This report was rejected by the Panel since it did not support their LNT paradigm-Neel gave it to British Panel-where it was influential

DID LEWIS BECOME A SCIENTIFIC STALKING HORSE FOR THE NAS BEAR I GENETICS PANEL

- Major public conflict between Muller and Neel in the summer of 1956.

- Muller tried to prevent Neel from publishing his findings in a major WHO document.

DID LEWIS BECOME A SCIENTIFIC STALKING HORSE FOR THE NAS BEAR I GENETICS PANEL

- This caused major problems for the radiation genetics field and many personal/professional disputes.

- Beadle-chair of the Panel- tried to redirect the Panel from this study to the leukemia issue and its relationship to mutation and risk…..re-motivating Lewis

LEWIS FINALIZES PAPER

- Beadle gets Lewis to share draft *Science* paper with Panel in late November, 1956

- Lewis receives comments from Panel members

LEWIS FINALIZES PAPER

- Lewis revises manuscript removing comments that he was unable to prove his low dose LNT leukemia risk assessment

- He ties his mutation mechanism to research in fruit fly mature sperm that were not relevant to somatic cells…later this work was determined to have produced principally major gene deletions….not gene mutations.

- Panel member Bentley Glass was one of six senior editors at *Science* Panel….

THE KEY LEWIS PAPER

- Published in *Science* Journal- May 17, 1957-strongly advocating LNT for assessing radiation-induced leukemia risks.

- Received strong supportive editorial endorsement-despite the fact that the editor new little at best, concerning the technical aspects of Lewis's paper.

- Lewis gets appointed to NCRPM committee which recommends LNT.

THE KEY LEWIS PAPER

- The paper received great publicity and created the momentum for LNT.
- Paper Discussed on Meet The Press one week later.
- Lewis testified before Congress on June 3, 1957 supporting LNT.
- *Life Magazine* publishes article based on Lewis paper on June 10, 1957, with Lewis picture.

IMPACT OF LEWIS PAPER ON CANCER RISK ASSESSMENT

- Established the LNT concept for Cancer Risk Assessment
- Provided the biostatistical basis for risk estimation
- Applied the LNT model for leukemia

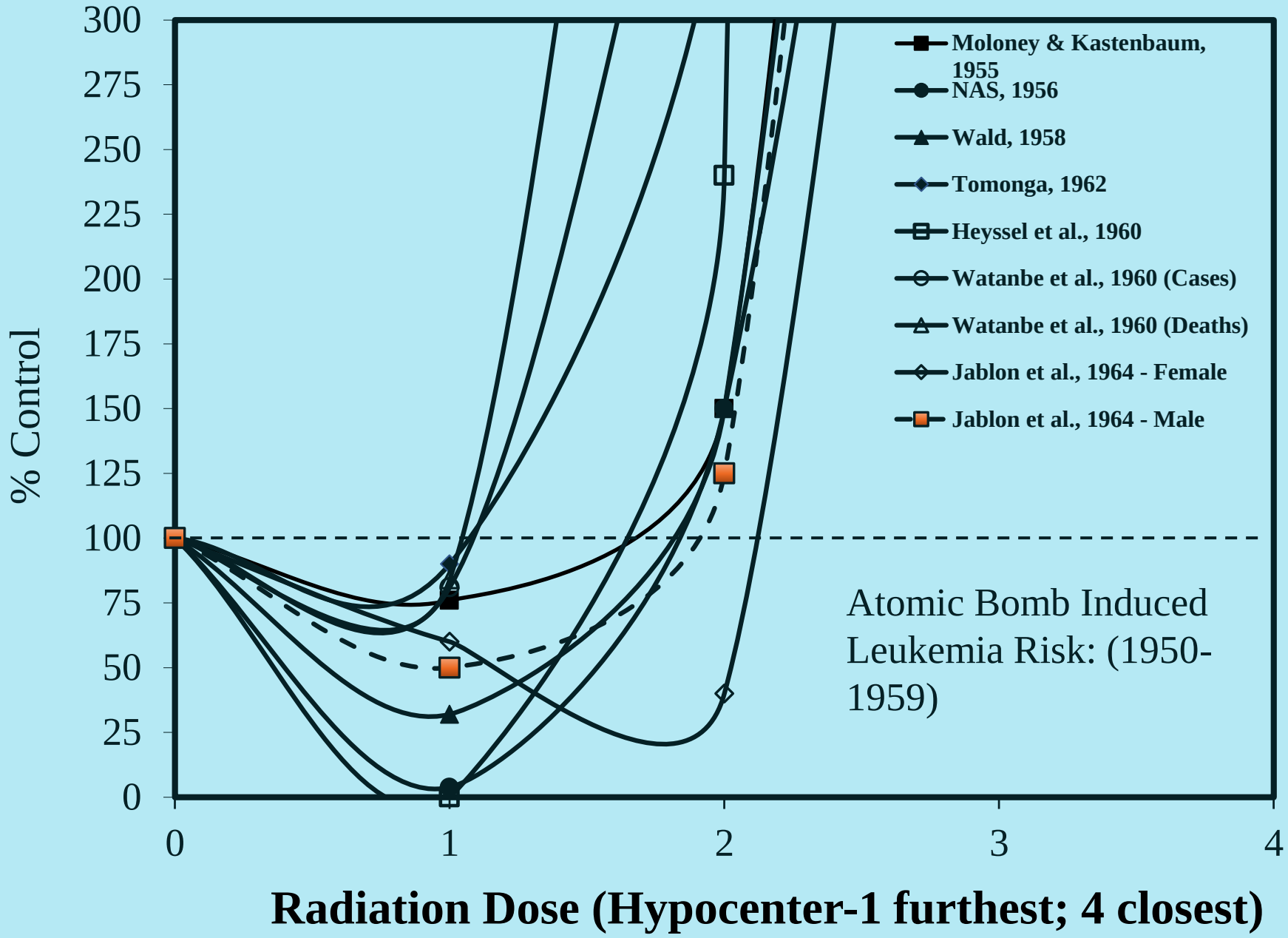
IMPACT OF LEWIS PAPER ON CANCER RISK ASSESSMENT

- Generalized the approach for all types of tumors induced by ionizing radiation and chemical carcinogens

- Impact continued through BEIR I-1972-with Lewis being very influential in the activities of the Committees.

PROBLEMS WITH LEWIS PAPER

- Failed to analyzed the Hiroshima and Nagasaki leukemia data properly.
- Other radiation exposed leukemia population groups used by Lewis had very high doses.


300
275
250
225
200
175
150
125
100
75
50
25
0
% Control
0
1
2
3
4
Radiation Dose (Hypocenter-1 furthest; 4 closest)
Moloney & Kastenbaum, 1955
NAS, 1956
Wald, 1958
Tomonga, 1962
Heyssel et al., 1960
Watanbe et al., 1960 (Cases)
Watanbe et al., 1960 (Deaths)
Jablon et al., 1964 - Female
Jablon et al., 1964 - Male
Atomic Bomb Induced Leukemia Risk: (1950-1959)

PROBLEMS WITH LEWIS PAPER

- Lewis ignored conclusions of study authors that their findings would not provide reliable findings for low dose risk estimates and should not be used to do so.

- Lewis failed to inform the readers of his paper about these judgments.

- Lewis failed to consider reasonable alternative hypotheses for the leukemia findings.

PROBLEMS WITH LEWIS PAPER

- Lewis's use of the mutation data was shown to be incorrect.
- Lewis made multiple unverified exposure assumptions that lacked scientific grounding, being characterized by others as "guesses".

PROBLEMS WITH LEWIS PAPER

- Lewis failed to consider the capacity of multiple other factors that could affect disease incidence, lacking a broader epidemiological perspective.

- The multiple limitations and research transparency failures indicate a high degree of bias.

LEWIS GETS CRITICIZED

- The Lewis paper was strongly criticized by numerous high level scientists in the US and Europe
- Lewis did not rebut the criticisms.
- No member of the radiation genetics community or from the BEAR I Genetics Panel came to the defense of Lewis.

LEWIS IS SUCCESSFUL IN THE END

- Lewis got the members of the NCRPM to adopt the Precautionary Principle for Cancer risk assessment.

- The compromise that Lewis made was to admit that the data were not adequate for him to support his LNT at low dose assertions.

- This type of resolution for low dose cancer risk assessment was later adopted by regulatory agencies, down to the present time.

RUSSELL AND DOSE RATE

- December 1958, Russell et al. report significant dose rate findings in male (spermatogonia) and female (oocytes) mice.
- At low dose rates, X-ray/gamma-ray-induced mutation was significantly decreased compared to the same total dose when given acutely.
- These findings suggested the existence of DNA repair and the possibility of a threshold.

RUSSELL AND DOSE RATE

- Research with female oocytes revealed a threshold effect at low dose rate (i.e., 27,000-fold greater than background radiation).

- Research with male spermatogonia showed a 70% decrease in mutation but did not achieve a threshold.

THE RUSSELL COVER-UP STUDY

- 1959-1960: William Russell and Arthur Upton (former director of NCI and Chairman of BEIR V) suppressed a major negative lifespan and radiation cancer study with mice.

- Russell: "…**it was feared that publication of a negative finding could mislead the public into a false feeling of safety".**

- 1993: Russell and Upton published the findings to win a UK litigation for the defense.

- Russell never shared these findings with BEAR, AEC, FRC, BEIR and others.

NEW CHALLENGE TO LNT

- Endogenous metabolism produces 200 million times more mutagen oxy-radicals than background radiation per unit time.
- DNA repair evolved to correct damage from endogenous metabolism, not background radiation.
- These developments were not cited by the radiation genetics community from 1956 onward.
- Mutations from endogenous metabolism: mechanism for evolution - not background radiation.

BEIR I - 1972

- Genetics Subcommittee rejected the conclusion of the BEAR I Genetics Panel, that mutation rate was independent of dose rate. They accepted the new findings of Russell.

- Genetics Subcommittee retained the LNT recommendation, because the spermatogonia responses had not regressed to control values as was the case with oocytes.

US EPA – 1975/1977

- EPA accepts linearity for ionizing radiation for induced cancer risks based on the recommendation of the BEIR I, 1972 dose rate interpretation.

- The Russell studies became the “homing” principle for the LNT concept.

RUSSELL AND SELBY DEBATE-1996

- Paul Selby revealed an error in Russell's control group mutation rates.

- Russell and Selby corrected the control group values. The correction resulted in the male spermatogonia values of 1972 becoming indistinguishable from control values.

- If correction had been made in 1972, the LNT would not have been supported by the Russell data.

KEY LNT FINDINGS IN PERSPECTIVE

- Muller's Evolution Concept of a highly stable genome and no genetic damage repair is now proven incorrect.
- Muller's Gene Mutation Claim – now proven incorrect
- LNT Single-Hit Model is based on Muller's incorrect interpretations.
- Muller was Deliberately Deceptive in his Nobel Prize Lecture.
- Muller and Stern Misrepresented Manhattan Project findings to promote LNT.

NAS PANELS

BEAR I GENETICS PANEL - 1956

- Misrepresented the scientific record to promote acceptance of LNT and their Public Report was not written or approved by them, and contained serious errors.

BEIR I GENETICS SUBCOMMITTEE - 1972

- Department of Energy Research - >2 million mice
  - Provided new basis for LNT
  - Foundation for EPA LNT
  - Major error discovered – 2 decades later
  - Correction indicates a threshold or hormetic dose response should have been established

WHY LNT SUCCEEDED

- Producing Gene Mutations was a major advance.
- Evolution and mutation concepts overwhelmed the field and became integrated within the LNT model.
- Key studies not peer-reviewed
  - Ray-Chaudhuri
  - Uphoff – never published/data missing
- Manhattan Project → massive project/influence.

WHY LNT SUCCEEDED

- Dropping the A Bomb → frightened the world
- Nobel Prize → created major platform for Muller's ideology
- Cold War → above ground testing of atomic bombs → even more fear
- Rockefeller Foundation/NAS created a separate Genetics Panel and stacked the members with those promoting the LNT ideology.
- NAS (i.e., appeal to its authority) → Ideology – Lies, Deception.
- Russell cover-up, mistakes and dishonesties

HISTORY OF LNT-Bottom Line

- Scientific/toxicology community got the LNT question wrong.
- Self-Interest and scientific misconduct → lead to the LNT.
- All the errors, deceptions and mistakes were given a pass.
- The scientific/toxicology and regulatory communities failed in their oversight, review and leadership.

HISTORY OF LNT-Bottom Line
Role of *Science* Journal

Science published four key papers that were deceptive:

- Muller (1927) without data and peer review;
- Uphoff and Stern, 1949 with no methods, analysis and data and with a fundamentally flawed design;
- BEAR I Genetics Panel, 1956
- Edward B. Lewis, 1957 leukemia and radiation risk assessment.
- ***Science* journal has a major role the acceptance of the incorrect and fraudulent history of LNT.**

FINAL PERSPECTIVES ON LNT

- Entire regulatory programs and public education activities are based upon such deceptive historical practices, involving the NAS, *Science* journal, and prominent leaders in the radiation genetics community.

- The EPA has served as an unwitting vehicle to implement such scientific deceptions due to its failure both to explore the historical foundations of cancer risk assessment, much of which occurred prior to its creation and to take actions to correct the errors once the ramifications were understood.