

CREATING SCIENCE THAT MATTERS

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Environmental influences on Child Health Outcomes (ECHO)

April 19, 2023



INSIGHTS FROM HALF A CENTURY* IN THE TRENCHES

- My first published contribution, an abstract of a talk at the American Thoracic Society, was published in 1972.





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I'll return to lessons learned from
that first scientific experience later
in this talk

SCIENCE THAT MATTERS

Important biomedical research is recognized by its **impact** on health.

And the examples I will provide today are not necessarily marked by scientific brilliance or by having advanced a new methodology.

They are marked by having **created a measurable difference in health or survival.**



TO CREATE SCIENCE THAT MATTERS

We must avoid some behaviors that **get in the way** of impactful science.

I will suggest some approaches to scientific research that have been shown, based on examples from the history of medicine and public health, **to be useful**.

We'll see how some of these lessons might **be applied to ECHO** studies.



SOME BEHAVIORS AND IDEAS THAT GET IN THE WAY OF CREATING SCIENCE THAT MATTERS



TRYING TO ACHIEVE PERFECTION



John Snow once wrote in a paper on the possible nutritional origins of rickets:

*“The subject is capable of being decided by an exact numerical investigation, but I have thought it better to publish my inquiry in its present **imperfect** state, than to wait till I should be able to make such a complete research as I could wish, more especially as, by directing the attention of the profession to the question, it may be earlier decided.”*

Snow, J: On the adulteration of bread as a cause of rickets. Lancet 1857; July 4, p 4-5.



THE INTERNAL VOICE THAT IS HARD TO SHAKE

- BUILT-IN ASSUMPTIONS
 - AUTHORITY
 - CONVENTION
 - POPULARITY



- Conventional wisdom for decades was that premature babies should be kept warm, but not too warm, since cold was a stimulus to breathing.
- Holt's Pediatric textbook of 1945 recommended an ambient temperature for premature babies "*in the range of 80°-85°.*" Virtually all authorities recommended this range.
- But William Silverman and his colleagues undertook a randomized trial in premature newborns of two thermal environments: 83°-85° vs. 88°-90°.



THE INFLUENCE OF THE THERMAL ENVIRONMENT UPON THE SURVIVAL OF NEWLY BORN PREMATURE INFANTS

**By William A. Silverman, M.D., John W. Fertig, Ph.D.,
and Agnes P. Berger, Ph.D.**

*Babies Hospital, Department of Pediatrics, College of Physicians and Surgeons, and
School of Public Health and Administrative Medicine, Columbia University*

Death rate of premature infants at two ambient temperatures

83°-85°	88°-90°	RR of dying
29/91	15/91	0.52 (p <.05)



THE TYRANNY OF THE P VALUE

FAILURE TO ACHIEVE A P-VALUE OF $<.05$ DOES
NOT MEAN “NO EFFECT”



EVIDENCE FAVORING THE USE OF ANTICOAGULANTS IN THE HOSPITAL PHASE OF ACUTE MYOCARDIAL INFARCTION

THOMAS C. CHALMERS, M.D., RAYMOND J. MATTA, M.D., HARRY SMITH, JR., PH.D.,
AND ANNE-MARIE KUNZLER, M.A.

Abstract Since the last comprehensive review of anticoagulation in acute myocardial infarction four additional randomized control trials have been reported. The overwhelming majority of all trials favored anticoagulation. Rates of thromboembolism were higher in the control, and hemorrhagic complications in the anticoagulated group. Pooling of all randomized control trials gives mean case fatality rates of 19.6 per cent for the control and 15.4 per cent for the anticoagulated group, a relative reduction of 21 per cent

($P < 0.05$ or < 0.001 , depending on the analytic method). Five of six randomized control trials reported "no effect" because the difference favoring anticoagulation was not statistically significant. However, sample sizes in these "negative" papers were too small to protect against missing a 21 per cent reduction in true case fatality rate due to anticoagulation ($\beta > 0.10$). All patients who present no specific contraindication should receive anticoagulants during hospitalization for infarction. (N Engl J Med 297:1091-1096, 1977)



IGNORING THE SOCIAL ENVIRONMENT





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THE NEXT SLIDE SHOWS MORTALITY
BY SOCIAL CLASS, SEX, AND AGE
AMONG MORE THAN 1,000 PEOPLE

What cause of death could this be?

	Men	Women	Children	Total
1 st class	118/175 67%	6/144 4%	1/6 17%	125/325 38%
2 nd class	154/168 92%	13/93 14%	0/24 0%	167/285 59%
3 rd class	387/462 84%	89/165 54%	52/79 66%	528/706 75%
Total	659/805 82%	108/402 26%	53/109 49%	820/1,316 63%

IGNORING BIOLOGY

Thinking that only statistical issues matter



IGNORING BIOLOGY IN ASSESSING EVIDENCE

GRADE criteria, COCHRANE and PRISMA guidelines, and the CONSORT checklist for evaluating studies pay virtually no attention to the underlying biologic rationale of the trial, focusing intently on design, measurement, and analysis issues.

This can allow the results of trials with serious problems in the nature, timing, and dosage of the intervention and the appropriateness of the study population to be highly rated as long as they were conducted according to accepted practice.

The concept of biological plausibility - built into all guidelines for establishing causal inference in epidemiology - is absent from these widely used protocols for the evaluation of scientific evidence.



FAILING TO UNDERSTANDING
WHO YOU ARE FAILING TO STUDY
THE CASE OF DAMAGED WW II AIRCRAFT



The Air Force asked Abraham Wald, a mathematician, which part of planes should be reinforced against enemy fire. They showed him the following diagram summarizing where bullet holes were found in planes returning to base and the number of bullet holes per square foot of the plane.



Plane section	Bullet holes/ft ²
Engine	1.11
Fuel system	1.55
Fuselage	1.73
Rest of plane	1.80





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Wald surprised the Air Force by answering that the areas with the **fewest bullet holes** should be reinforced. Why did Wald say this?

WALD'S INSIGHT

- Wald realized first that damage from gunfire in planes was random as to location and second that he did not know about the most important airplanes of all – **the ones that had been shot down**.
- Since engines and to a lesser extent, fuel systems, had **less damage** in planes returning to base, Wald reasoned that planes shot down would have more **more damage** in those areas.
- Wald thought that returning airplanes were **“healthy survivors”** and that their damage must have been less lethal than the damage to planes that were shot down.



MORAL OF THIS STORY

Consider carefully who your study **leaves out**



A SUMMARY OF SOME THINGS TO AVOID

- Perfectionism
- The powerful voices of authority, convention, and popularity
- Becoming overly enamored of the p value
- Ignoring the social environment
- Ignoring biological realities
- Failing to recognize who you are **not** studying



SOME KEY PRACTICES THAT PROMOTE SCIENCE THAT MATTERS



KNOWING WHAT TO ASK

- Scientific research **never** starts from a blank slate. To undertake useful science it is critically important to know what has been done before.
- By reading carefully in the relevant literature one learns what questions most need asking at this moment.
- The literature can spark an idea that allows you to formulate a key question, the single most important step in science.





Carlos Juan Finlay (1833 – 1915), the great Cuban scientist, was the first to hypothesize that *Aedes aegypti* was the vector of yellow fever. But the tests he made of his hypothesis did not confirm that the Aedes mosquito could transmit yellow fever.



Walter Reed (1851 – 1902) in 1900 successfully produced yellow fever through the bite of an infected mosquito, thus showing how yellow fever (YF) is transmitted and opening the door to prevention.



WHAT DID REED KNOW THAT FINLAY DIDN'T?

- In 1900, Henry Carter wrote a paper titled:
*“A note on the **interval** between infecting and secondary cases of yellow fever from the records of the yellow fever at Orwood and Taylor, Mississippi, in 1898.”*
- Carter found that two to three weeks passed from the time an infected individual came to a town before the second case occurred.
- Reed put this information together with Finlay’s hypothesis and concluded that the agent of yellow fever **had to develop over time inside the mosquito** before the mosquito bite was infective.
- What did Reed do upon reading this paper?



REED CHANGED HIS SCIENTIFIC APPROACH

- Reed abandoned his search for the bacterial cause of YF to focus on the vector, performing human experiments to attempt to transmit YF.
- He kept the mosquitos he had infected (by having them bite a YF patient) **alive for at least two weeks before having them bite the volunteer**, producing experimental YF fever and proving that *Aedes aegypti* was the vector.
- This critical discovery led to *Aedes* control measures that nearly eradicated YF in Havana.
 - Annual deaths from yellow fever in Havana 1891-1900 - **563**
 - Annual deaths from yellow fever in Havana 1901-1910 - **44**



NOT IGNORING, BUT PURSUING THE
FINDING THAT DOESN'T FIT WITH
WHAT YOU KNOW



In 1970, a group of Boston gynecologists published a fairly standard case series describing vaginal cancer.

*“Data from 68 cases of primary carcinoma of the vagina are analyzed in detail. The tumors tend to occur **beyond the fifth decade of life.**”*

Herbst, AL, Green, TH, Ulfelder, H: Primary carcinoma of the vagina. An analysis of 68 cases. Am J Obstet Gynec 1970; 106;210-218 (Jan 28)



BUT 3 MONTHS LATER THE TEAM SAW SOMETHING COMPLETELY UNEXPECTED

“Seven cases of adenocarcinoma of the vagina occurring in young women 15 to 22 years of age are reported.”

These cases stood out because the authors had just studied this cancer and knew that it was a disease of older women. Thus the cases in young women came as a great surprise.

Herbst, AL, Scully, RE: Adenocarcinoma of the vagina in adolescence. A report of 7 cases including 6 clear-cell carcinomas. Cancer 1970; 25:745-57 (April)



HERBST WONDERED WHAT TO DO NEXT

- As legend has it, Herbst was discussing the problem of these surprising cases in young women in an elevator at the Massachusetts General Hospital.
- Overhearing the conversation, a neurologist named David Poskanzer with an MPH in epidemiology, said, “you need to do a case-control study.”



THIS WAS THE FINDING OF THE CASE-CONTROL STUDY

Pregnancy use of Diethyl Stilbestrol (DES)	Clear Cell Vaginal Adenocarcinoma	Matched control
YES	7	0
NO	1	32
	8	32

SOURCE: Herbst AL, Ulfelder H, Poskanzer D:
NEJM 1971; 285; 16 (April), 878

FDA ruled that DES is contraindicated in pregnancy in November 1971.



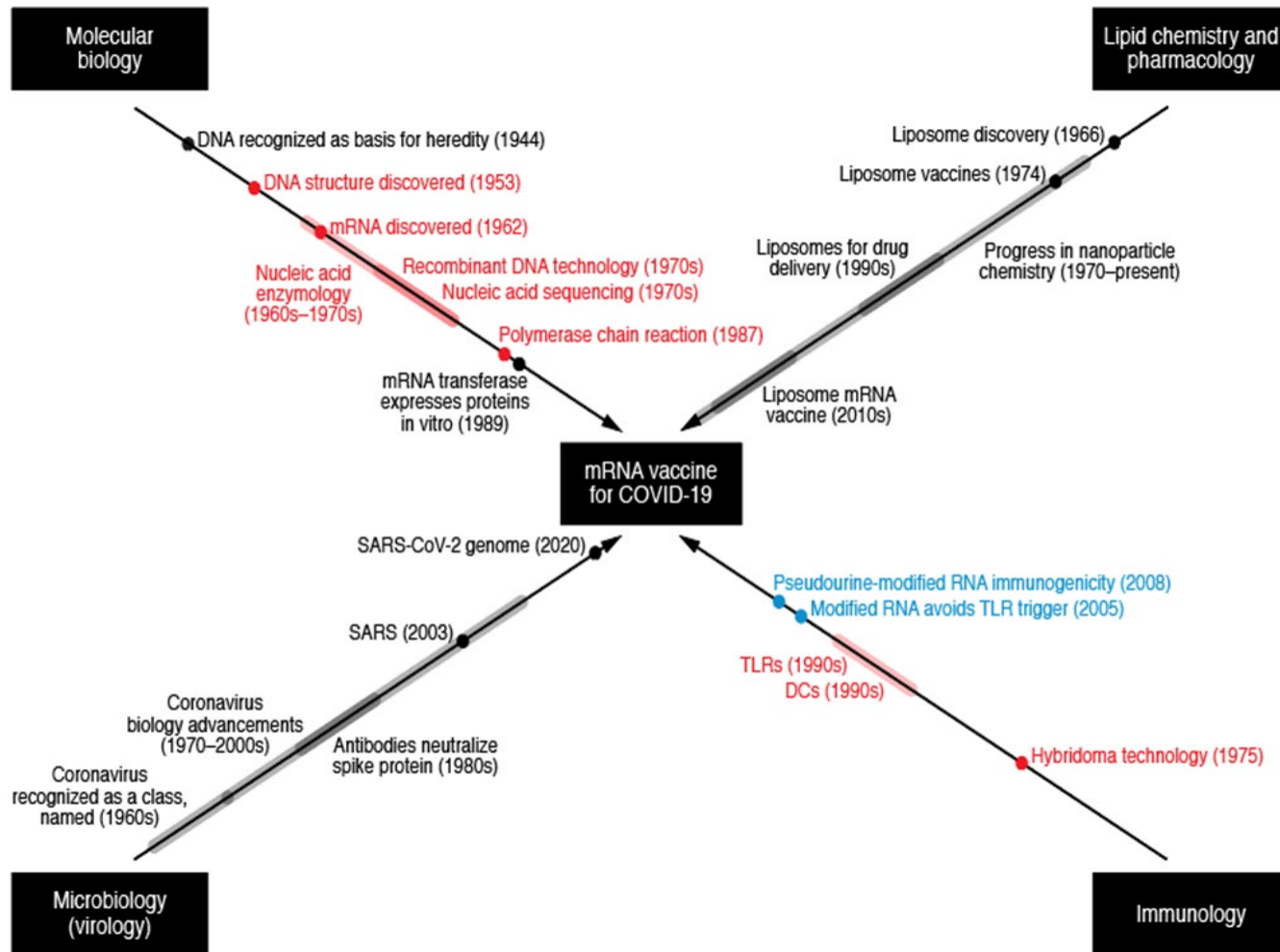
BRINGING TOGETHER DIFFERENT SCIENTIFIC DISCIPLINES TO SOLVE A PROBLEM



THE mRNA VACCINE BROUGHT TOGETHER SEVERAL STRANDS OF SCIENCE

Arturo Casadevall: The mRNA vaccine revolution is the dividend from decades of basic science research. *Journal of Clinical Investigation* 2021; 131(19):e153721





PERSISTENCE

How Ronald Ross found out that
Anopheles mosquitos are the vectors
of malaria





Ronald Ross (1857-1932)

Ross suspected that the *Anopheles* mosquito was the vector of malaria, but, as a military doctor in India, he had very little time available for research and his superiors disliked his interest in research.

To reduce his capacity for research, he was transferred to a remote hill station where malaria was rare.

Military authorities almost confiscated his microscope.



Nevertheless, he spent his free time examining mosquitos under the microscope, **two hours per mosquito**, looking for the plasmodium (identified by Laveran in 1880). Here are some quotes from his memoir:

“I was tired, and what was the use? I must have examined the stomachs of a thousand mosquitos by this time..... The work ... was ... so blinding that I could scarcely see afterwards, and the difficulty was increased by the fact that my microscope was almost worn out, the screws being rusted with sweat from my hands and forehead, and my only remaining eye-piece being cracked...”



PATIENCE

HOW KOCH CULTURED THE TUBERCLE BACILLUS



Robert Koch had never come across a bacterium that would not appear within 2-3 days after plating on media. But nothing could be seen when he tried to culture the organism he had identified in people with tuberculosis. But mycobacteria are slow growing. It can take 3 weeks for the culture plates to show growth.

“But Koch waited; though to anyone’s knowledge, there was nothing in past experience to suggest that the passing of time held the key And in waiting, he won out. It was patience, and patience alone that saved the day for Koch ...”

From AK Krause’s introduction to his 1932 translation into English of Koch’s classic 1882 paper: *The Aetiology of Tuberculosis*.



COURAGE

THE BEGINNINGS OF CARDIOVERSION



Cardioversion was largely developed by the work of Bernard Lown and his associates of Harvard who experimented first on animals and then on postoperative patients. The key paper was published in 1962.

Lown, B, Amarasingham, R, Newman, J: New Method for Terminating Cardiac Arrhythmias. Use of Synchronized Capacitor Discharge. JAMA 1962; 182:548-555



BUT IN THE EARLY DAYS

“Research funds for the early stages of this endeavor were refused by the National Institutes of Health and publication of the first manuscript was rejected, the reviewer opining that the technology had ‘**little clinical relevance**’.”

Lown, B: Defibrillation and cardioversion. Cardiovascular Research, 2002; 55:220–224





Bernard Lown, MD (1921 – 2021)

Asked by a resident on rounds (ca. 1971) whether he was scared when he first placed electrode paddles on a patient's chest and sent 100 joules of electricity into the patient's heart, Dr. Lown responded -



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“Scared?”

We were terrified!”

CREATING SCIENCE THAT MATTERS

- Finding the **right question to ask** by carefully studying what has been done before
- Welcoming the **unexpected** finding
- Using **multiple** disciplinary approaches
- Personal qualities
 - **Persistence**
 - **Patience**
 - **Courage**



LESSONS LEARNED FROM MY FIRST SCIENTIFIC EXPERIENCE

1. Science requires **passion**, not to say obsession.
2. The **library** is your good friend.
3. Trials have **limitations**.
4. **Mentoring** has great value.
5. Complete the task. But if you don't, all is not lost.



NOW WHAT ABOUT ECHO?

- ECHO presents challenges because you have an existing dataset which constrains the questions you can ask.
- But you can use ECHO as a launching pad
 - Plow through the ECHO database to **find a good question** that can be answered with ECHO data.
 - **Add variables**. Create a sub-study that takes advantage of what is already collected and adds another measure.
 - **Create a new study** (A trial? A K-award?) that builds on and strengthens an ECHO finding.



USING AN EXISTING DATABASE

MgSO₄ AND CEREBRAL PALSY



BACKGROUND

- MgSO_4 has been used in labor to control hypertension and to interrupt preterm labor.
- In animal models, MgSO_4 protects against brain injury.
- Two observational studies of cerebral palsy in premature infants showed protection against CP from use of MgSO_4 in labor.
 - A case-control study in VLBW infants in California found an **OR of 0.14** ($p < .05$ - Nelson and Grether: Pediatrics. 1995;95:263-269).
 - A VLBW cohort in Atlanta found an **OR of 0.11** ($p < .05$ - Schendel al: JAMA 1996;276:1805-10).



EXAMINING THE MgSO_4 /CP HYPOTHESIS IN A LARGE COHORT OF PREMATURE INFANTS

The Neonatal Brain Hemorrhage study assembled and followed 1,105 infants < 2kg in a tri-county area of New Jersey from 1984-1991.

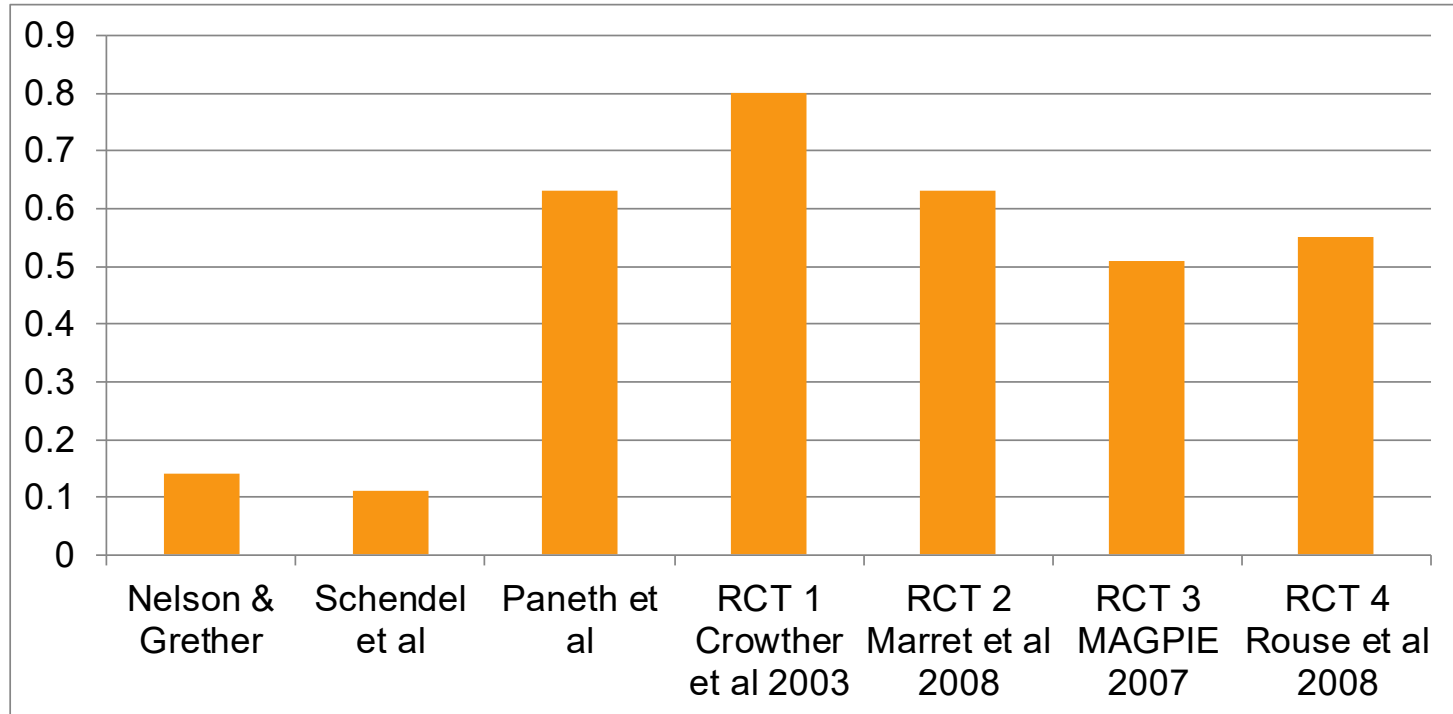
Examining the database to study the hypothesis, we found a non-significant reduction in risk of disabling CP. The OR for receipt of MgSO_4 was 0.63 (Paneth, N et al: Pediatrics 1997;99:723)

So we wrote the following in the abstract:

“The hypothesis that magnesium sulfate use reduces the risk of neonatal brain lesions or CP in low birth weight infants was not statistically supported in this study, although a modest reduction in risk of disabling CP cannot be excluded.”



ODDS RATIOS RELATING MAGNESIUM AND CP: SEVEN STUDIES



TRANSLATION INTO POLICY

“The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine continue to support the short-term (usually less than 48 hours) use of magnesium sulfate ... for fetal neuroprotection before anticipated early preterm (less than 32 weeks of gestation) delivery.”

ACOG Committee on Obstetric Practice and Soc Mat Fet Med: Obstet Gynec 2013; 122:727-8



FINAL THOUGHTS

- ECHO is much like a laboratory. It is a location to which you can bring hypotheses to test.
- In a laboratory the space, the equipment, and the supplies set limits on what questions can be asked.
- In ECHO the size and content of the database sets limits on the questions that you can ask
- Just as in the laboratory, the critical task is to find the right question to ask of ECHO.
- Posing that question is your scientific creativity at work



FEATURES OF THE RIGHT QUESTION IN ECHO

1. The right question addresses **a real public health problem**. It requires you to consider the burden (mortality, morbidity, cost) that might be alleviated if the question were to be answered.
2. The right question also considers the practicality of implementing a solution. If a risk factor for a key outcome is uncovered, **how feasible is it to eliminate or at least control this factor?**
3. The right question emerges from knowing what has already been asked and answered, so that you know **what question now most needs to be asked**.



ABOVE ALL ENJOY YOURSELVES!

NOW – LET'S DISCUSS

This presentation is posted on my departmental website

<https://epibio.msu.edu/research/paneth>





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EXTRA SLIDES

CONVENTIONAL WISDOM ON TEMPERATURE

“Environmental temperature is regulated between 82° and 88°. No other attempt is made to sustain body temperature and this frequently stabilises at 93°-98°.” Cooke RD: Care of the Premature Infant PCNA 1954;1:649.

“The incubator temperature should be regulated to keep the infant's temperature between 95° and 98° or 99°. The tiny infant gets along well with a mildly subnormal temperature.” Crawford, W. L.: Newer Concepts of Premature Care, PCNA 1: 639, 1954.

“In our experience it is advisable to keep prematures of up to 2,000 grams at a low temperature if admitted cool.” Kintzel, Von H W: Arch f. Kinderh 1957;154:238.

“A permissive attitude towards the temperature of small infants, has, however, become widespread in recent years.” Day RL, Caliguiri L, Kamenski C et al” Pediatrics 1964: Aug;34: :171.



NOTICE THAT LESS THAN TWO YEARS ELAPSED FROM THE FIRST PAPER ON THE TOPIC TO POLICY

- Review of the literature showing that vaginal adenocarcinoma is a disease of older women
 - Description of young women with this cancer
 - Case-control study implicating DES in these cancers
 - FDA ruling that DES is not to be used in pregnancy
- January 1970
 - April 1970
 - April 1971
 - November 1971



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