From
CARL THOMPSON

2/21/66

Dear Jim,

Concerning Dr. Hardy's paper which was sent you on February 14, we have now transcribed this and recognizing that the photostat sent you was very difficult to read, we are now enclosing a carbon of the paper as retyped.

Note that the material in brackets was material that she had crossed out in her original.

HILL AND KNOWLTON, INC.
150 East 42nd Street
New York, N. Y. 10017
OXford 7-5600

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Lead

This is a welcome opportunity to review with you certain available data and unanswered questions in the study of lead effect from the viewpoint -- which is mine -- of a physician interested in clinical preventive medicine in general and in the specific diagnostic and therapeutic problems posed by a single patient. Description of my usage of terms in this paper will be useful. The words "toxic effect" connote lead-caused change resulting in no detectable damage or harm. The key word is "detectable." The words "harm," "disability," "damage," here mean that the lead-produced effect cannot be tolerated or handled without producing abnormal function.

It is necessary to emphasize that no harmful effect of lead is unique except perhaps the motor palsy of the most-used muscle group, as in the wrist drop of a right-handed painter whose left wrist is unaffected. This non-specificity of lead intoxication means that identification of low level damage requires a combination of epidemiologic evidence, astute clinical observation to rule out other etiologies together with old and new experimental evidence critically judged for consistency and repeatability.

Another fundamental consideration that weighs heavily in this discussion is the likelihood that lead in the body at levels considered from industrial experience to be harmless can act with other factors to produce damage. If this be true, in judging what amount of lead is harmless for an individual or a population, other insults natural or manmade must be assessed. (Richard Doll in England and Theodore Hatch in this country have urged that those responsible for establishing tolerance-limits, tackle the difficult problem of measuring the multiple factors that may influence the effect of environmental hazards.)

The biological effects of lead are manifold. Those of special interest in what I have to present are as follows: First, the action of lead in destroying RBC (red blood cells) is well recognized and illustrates the two fundamentals just alluded to -- the nonspecificity of such an effect, i.e., the many causes of such destruction. Further, the hazard to the body of short supply of red blood cells if, for example, there is chronic blood loss from another cause as in GI tract bleeding from a peptic ulcer illustrates the problem of more than one factor influencing the pathologic effect. The behavior of lead in following calcium to the skeleton and its mobilization therefrom by such likely events as pregnancy and ageing (periods of starvation) is a second well established possibility pertinent to this discussion. Thirdly, of potential importance is the accumulation of lead in an organ as it does in the liver and in the case of organic lead compounds the CNS (central nervous system). A fourth biological effect perhaps of the greatest significance is the damaging influence of lead at certain levels on growth and enzyme activity. I quote from a WHO working paper of Lars Friberg as helpful in introducing this subject:

> [The question of mineral metabolism is, however, of interest (also in other connections the use of radioactive isotopes thus implies that) even minute amounts of a metal -- harmless in itself -- may be of essential biological importance.] "The possibility has also been discussed whether certain metals in such minute amounts as are normally present in the body might contribute to the development of chronic disease. The reason for this discussion is the fact that certain essential metals form complexes, for example iron and cobalt in the porphyrin chelates heme and Vitamin $B_{12}$. Against the background of

the laws of chelation it is feasible that other metals might compete for a ligand with an essential metal on a metalloenzyme. The administration of one metal would thus create a condition of deficiency of another. For example, cadmium and mercury would then displace zinc owing to their chelation with ligands which normally chelate with zinc."

Since lead is neither essential nor familiar to the body because it was not abundant in the natural world in which man evolved, it would be surprising if lead did not prove to participate in competition for position in a metalloenzyme.

Experimental evidence that lead may interfere with cellular processes at a molecular is cited by Westerman, Jenson et al in an article published 10 days ago that lead produces mitochondrial morphologic changes and ribosomal abnormalities.

Now to special groups. What I have to offer is a mixture of my critical judgment of old and new data from the literature and my clinical experience. In order to present these data let us agree for the moment that study of large dose effect may be valuable...one can cite bonzal leukemia after both repeated small doses and a single large dose; the same is true of ionizing radiation. Of the elements beryllium can result in chronic long lasting disease both from an acute dose causing easily diagnosis (sic) beryllium poisoning and from lower doses so low that no diagnosable disease is produced at the time.

/This is only an example, but other mechanisms of action may be considered.

While there can be nothing definitive said at this moment, it would be surprising if lead did not prove to participate in competition for position in

a metalloenzyme. Further, since lead is neither essential nor familiar to the body because it was not originally abundant in the natural world in which man evolved, it is likely that such lead action is harmful and not easily amplified.] Westerman et al refer to current experimental evidence to show that Pb produces both ribosomal abnormalities and mitochondrial morphologic changes.]

Borrowing Dr. Alice Hamilton's expression in referring to progeny as offspring, I want to discuss them this special group as the first group vulnerable to damaging lead effect. Following is a pertinent quotation from her 1934 edition of Industrial Toxicology: I quote

> "There is incontrovertible evidence, both from animal experiments and from observations on human beings, that lead has an injurious action on the germ cells of both sexes and that in addition it passes from the maternal to the fetal blood during the months of gestation (Lewin 3.9). It is a matter of common knowledge among women who work in lead industries, such as pottery and white-lead production, that lead has an abortifacient action and this action was noted by medical observers more than a century ago. The usually accepted theory as to the mode of action is that lead kills the fetus either by its effect on the germ cell or through the maternal blood and that expulsion of the fetus follows with or without a directly stimulating effect of lead on the uterine musculature. Blair Bell, however, concludes from his studies on the action of lead on malignant cells, that lead first injuries the chorionic epitholium and thus indirectly injuries the fetus and leads to its expulsion. Evidence of the injury to the male germ-cell was first adduced by Constantin Paul (463) in 1880, and a number of French authors have since confirmed his statement as to the abnormal prevalence of abortion

and stillbirth in the marital history of male lead workers (Davidson 50, Cantarow 150, Donaufbourg 109). Perhaps the most important study in this field is that of Koinuma (336) because it is controlled by comparison with a group of workmen differing from the first group only in the lack of exposure to lead. Koinuma compared the marital life records of workmen, exposed to lead in Japanese storage-battery plants, with the histories of those working in non-lead occupations. The sterile marriages constituted 24.7 per cent for the lead group, and only 14.8 per cent for the non-lead group; the percentage of pregnancies ending prematurely or in stillbirth was 8.2 for the lead group and 0.2 for the control group. [The infant mortality rate was 24.2 per cent for the former and 19.2 per cent for the latter.]"

[While there are contradictory reports as to the damage to male germ cells both in causing sterility and in transmitting lead damage to the fetus, the literature is quite clear on this element's harm to the female reproductive system.]

A passage from Cantarow and Trumper summarizes the [impressively convincing] data on the harmful effect of lead to female reproduction: I quote

"The passage of lead through the placenta into the fetal tissues... has been demonstrated repeatedly...If born alive, the child frequently shows evidence of the deleterious effects of lead exerted during the period of intrauterine development. It is often weak and undersized, and there is a high incidence of epilepsy, muscular spasms, convulsions, and other nervous disturbances, idiocy and imbecility (Biondi; Meillere; Prendergast). [Hall reported that dentition was delayed in 80% of the offspring of Indian women living in a smelter village.] According to

Reinert, in a village where pottery glazing was done in the homes, a large proportion of children had convulsions and a peculiar form of macrocephaly, with a square-shaped head which developed slowly; this condition was not accompanied by imbecility. About 71% of a group of 79 such children in this village had either macrocephaly or convulsions or both, and the mortality was 50%. [In this instance the possibility of absorption of lead after birth must be considered, particularly since significant quantities of lead may be present in the mother's milk.] It is interesting...that Hall found that 22% of the native women in the smelter village mentioned above were unable to nurse their infants because of insufficient lactation, although no difficulty had been experienced before they were exposed to lead.

There can be little doubt that exposure of mothers to lead has a damaging effect upon fertility, the course of pregnancy and the development of the fetus."

[We heard yesterday of an essay by S. C. Gilfillan entitled "Roman Culture and Dysgonic Lead Poisoning" elaborates with fascinating evidence the author's point that Greece and Rome fell chiefly because of lead in cookery and in wine. His thesis is that when, about 150 B.C., relaxed rules allowed the wives to drink wine they failed to reproduce and the aristocracy was decimated.]

This is a good place to mention that most authors who have written on the subject are of the opinion that females [react unfavorably to] suffer harmful effect at lower doses of lead than do males. If this is true, it is important making (unclear text)... Bell, using lead as therapy for malignancy, reports the minimum toxic dose given intravenously as 40 mgm. of lead for females and 100 mgm. for males. Oliver, a great student of lead poisoning,

states that women are most liable to develop poisoning between the ages of 18 and 23 years, earlier than in men and after shorter exposure. Well studied series have established the fact that women with lead intoxication have a higher incidence of encephalopathy and a lower incidence of paralysis and colic. Such observations have been made in experimental or therapeutic situations or in industries without industrial hygiene controls. The value to us at this meeting of such observations is to point out what lead may do at levels where its effect can be identified. Let me repeat, experience with harmful agents, both chemical and physical, illustrates the critical fact that delayed effect from many small doses may be qualitatively like the more immediate acute effect of a single or fewer higher doses received over a shorter period of time.

The second special group and the one about which most data are available in discussion of lead poisoning is that of the growing child. Heralding Bell's work on the influence of lead on cell-growth one is struck by the very dilute solutions of lead acetate he found to retard growth. In the range of 1 to 100 to as little as 1 to 100,000 all very young tadpoles were killed, whereas more mature tadpoles survived but suffered retarded growth in the 1 to 100,000 solutions. Bell concludes from these and many more studies that I quote "the arrest of growth in animal organisms is strictly proportional to the capacity for, or power of, growth," and he further writes - quote "lead is not only much more toxic to the young and preadolescent than to the adult and old throughout the vertebrate kingdom but also that the effects produced by the metal are general in the young (Bell calls this somatic stunting) and local in the adult." end of quote. There are a number of studies pursuing this point. [A study that should be repeated perhaps is that of Calvery who found significant retardation of growth of male rats at relatively low levels of lead in their diet (3.53 ppm.)]

Of great importance for this discussion is the mental retardation that follows not only acute lead encephalopathy but perhaps chronic lead absorption. Here are quotations from the discussion by Byers, a pediatric neurologist at the Lead Hygiene Conference sponsored by the Lead Industries Association held in Chicago in 1958. Quote.

"Certainly when children die who have clinical pathological lead encephalopathy they die with brain stem compression. They die with slowing respiration, pulse rate and blood pressure, anuria, all the usual evidence of increased cranial pressure.

I can't believe that this isn't in some way related to interference with the brain enzyme systems through amounts of lead which may not in themselves be impressive....I originally got interested in lead because of children who had had lead poisoning and had been sent home from the hospital as cured, who then turned up in my neurological clinic because they were misbehaving in one way or another, or not learning in school. One had set the schoolroom on fire, another nice little girl danced around on the desk. None of these children had acute fulminating encephalitis. They all had evidence of lead poisoning, like stippled cells, some increase in spinal fluid total protein, GI symptoms, coproporphyrin in the urine. [At that time, we didn't know about the importance of separating them from lead. We tried, in a desultory way, to separate them. Maybe we weren't successful about that.]

The point I am trying to make about these children is that though none of them, at two or three years, had an acute encephalopathy with their acute intoxication, when they reached six or seven they showed evidence of brain injury. I think that many children get chronic encephalitis

from lead, as well as acute.

This group of children deteriorates gradually without ever having had any acute lead encephalitis....I think that lead does something to the growing brain which is different from what it does to the adult brain." end of quote

Dr. Rabe, a pediatric neurologist, and I have just begun a five-year study with N.I.H. support of this problem and are including study of siblings of lead-poisoned children with as careful an possible quantitative assessment of the lead to which these children are exposed. Variation in diagnosis and reporting of childhood lead poisoning from urban communities make it certain that little is known of the total number of cases of acute intoxication and nothing of lead absorption in quantities that may pose a risk to normal growth. Some knowledge is provided by Christian et al in Chicago. They report that of 9,833 cases of accidental childhood poisoning between 1959-1961, 439 or 4.7 per cent were cases of acute lead poisoning, and of the 85 deaths, 67 or 79 per cent were due to lead. Colleagues in Boston report 5 to 25 acute cases per year; Baltimore figures (through the courtesy of Dr. Baetjer) -- in this city there is an excellent detection program -- are double this number, reaching over 60 in some years, averaging 57.

During acute lead poisoning in childhood there is reliable evidence that kidney function is disturbed. While the blood sugar remains normal, there is readily detected glycosuria, and renal tubular damage has been further demonstrated by aminoaciduria and phosphaturia. In fatal cases acidophilic inclusion bodies in the kidneys are recognized as a pathologic lead effect. These findings may arise from other causes and identification of the lead exposure as causative is sometimes difficult. While Tepper was unable to confirm the findings in Massachusetts,

the Toronto (Australia) experience associating serious renal disease in the fourth decade with childhood plumbism is an important epidemic observation. Studies in other communities are required with an attempt to assess lead exposure which increases the potential for harm to the lead-exposed child, clinical illness which can be recognized being delayed.

[For our purposes today the lessons of acute obvious lead damage may be useful.] If as seems likely from the accumulated and growing evidence, growing tissue is more vulnerable to lead than adult tissue, for smaller doses than those required to produce diagnosable lead poisoning in a healthy adult male worker become important. In addition, because homeostasis is not well established in childhood so that shifts in pH, variation in intestinal acidity or alkalinity which may dissolve ingested lead mean that absorption, distribution and storage of lead are not as well governed as in later life -- added reasons that smaller amounts of lead pose greater risks in children. Growing bone is labile, and as it readily follows calcium in and out of the bone, unpredictable amounts of lead are indiscriminately deposited and released from the skeleton, this creates the danger of intoxication if lead ingested or inhaled is added at a time of sudden release of lead from bone (?).

Because of the dominance of my clinical experience, I have been interested in considering what effect lead absorption without detectable evidence of poisoning might have in the medical events of an otherwise healthy individual. The diagnosis of lead damage is not always easy to make because of the nonspecificity of symptoms, signs, laboratory findings, sequelae that might all be related to other etiologies. From this line of thinking I conclude that an apparently well lead worker constitutes a third special group for the purpose of this session. Dr. Kehoe's elegant studies are fundamental to the points I raise. With an unmeasured quantity of lead stored in skeleton and liver, with lesser amounts in other parts of his body, such an individual is in some jeopardy, a point Dr. K made yesterday, and may not be able

to withstand either more lead intake without evident harm or may be in more serious trouble than a worker without such lead burden if he suffers an unrelated medical event such as serious blood loss. To illustrate, in a series of men under his care, Dallavy reported the hemoglobin values of 15 lead workers (not ill) as between 9.8 and 13.7 grams with 4 under 12 grams although the lead in urine was not very alarming, ranging from 0.12 mgm/L to 0.39 mgm/L. Through the courtesy of Dr. Elkins and Mr. Smith of the Massachusetts Department of Occupational Health I have some pertinent data of similar findings in the storage battery industry in that state.

Of 72 workers in Pb using industries in Mass. -- chiefly in storage battery mfgt. -- the average lead excretion during a 7 to 10 yr. period of exposure is in the range of 0.17 to .58 mg/24. The urine coproporphyrin values (average) ranged from 0.2 to 0.0. The urinary lead excretion was above normal during this period on all occasions of assays in all cases except one. The coproporphyrin excretion followed a less orderly pattern -- above normal in a time to time in 15 of 72 cases.

That such data reflect a harmful burden of lead is supported by the December 1965 report of Westerman et al. These authors found relatively smaller amounts of lead in bone by biopsy than in urine of lead workers (?) the time asymptomatic. This same study included the important observation that the red cell survival of 3 nonanemic lead workers without clinical complaints was reduced and the reticulocyte count elevated suggesting accelerated red cell destruction (unclear text)... [Although these men are not ill such lead absorption means toxic lead effect. My clinical prophecy has come true in several cases in my own experience.] In my clinical experience the following stand out.

Cases of peptic ulcer, not held related to work with lead, proved

were difficult to handle, requiring transfusion with minimal bleeding. After years of well tolerated job-related lead exposure, I have seen a case of severely disabling illness with jaundice and two cases of severe headache and dizziness with electroencephalographic evidence of toxic encephalopathy changes which reversed -- these cases following a temporary brief exposure to higher lead levels....I mention these data to urge that it is necessary to consider the additive effect of lead in and out of industry. Grossly, easily seen damaging lead effects are at one end of a scale; industrially acquired lead absorption sufficient to reduce hemoglobin in a healthy male may be described as in the moderate potential risk part of such a scale. I believe that low level constantly though slightly increasing amounts of lead in the body at the lowest end of this imaginary scale may present the body with problems, acting alone or with other harmful agents whose mechanisms of action and site of action are identical with that of lead....This is an appropriate point at which to tackle the ever present variation in individual response to lead exposure. I found a helpful passage in Cantarow and Trumper -- the some of the statements are controversial: Quote

> "Although a similarly wide difference in individual susceptibility exists in uniform groups of experimental animals, it is important that, as pointed out by Minot, there is a consistent quantitative relationship between the amount of lead and the intensity of its effect upon single tissues, such as blood cells, muscle, intestinal strips, etc., no such variability of response being observed as occurs when the intact organism is exposed to lead. As she suggests, the individual difference in susceptibility to lead poisoning is therefore probably due largely to variations in factors which influence the amount of lead to which the tissues are exposed rather than to variations in

the degree of resistance of the tissues. These include factors influencing absorption, storage, mobilization and excretion (diet, alcohol, constipation, malnutrition, acute and chronic infections, trauma, renal, vascular, and hepatic disease, vitamin deficiencies, drugs, such as iodides, and acid-forming substances and alkalies). Thus, acute symptoms of plumbism may follow injury (Shufflebotham), pneumonia or influenza (Shie), alcoholism (Oliver; Legg and Cosby), renal disease (Edsall; Oliver), etc. As stated by Aub and his associates, immunity is always relative and may be broken down by several factors which influence the general physical condition. Then, too, local tissue damage may render these tissues more susceptible to the toxic action of lead, e.g., renal, vascular, or hepatic disease and anemia (hematopoietic organs)." End of quote

/The use of chelating agents in the diagnosis of chronic lead poisoning has brought to the attention of those interested the fact that healthy young adults in cities not exposed to lead at their jobs excrete 0.5 mgm/L of lead after a single dose of CaNa EDTA of 3 - 5 gm. intravenously. Reported blood leads in./

Included in possible lead risk to the healthy U.S. male in a Pb using industry we have learned that cigarette smokers have a slightly higher blood lead than do non cigarette smokers. In addition, if he drinks beer he will take in .1 mgm Pb/Li of bur -- if wine from .08 to .86 mgm Pb/Li -- a problem more serious for European born workers than most U.S. workers. However these points are pressed to urge that the problem of control of damaging lead exposure be considered not as that of one isolated source but rather a series in view of the widespread presence of Pb in nature and its ubiquitous. What is wanted is to consider the total Pb dose the body is expected to handle without irreversible damage.

While the numbers of individuals known to be suffering with such disease may not be great, assessment of the effect of small doses of lead on patients with certain diseases underlines the necessity of evaluating the interaction of lead of another disease entity with a quite (?) separate etiology. For example, I have chosen 2 diseases. First -- because lead destroys red blood cells it has occurred to me that patients with sickle cell trait (thought to be genetic-inheritance due to numberless years of exposure to the malaria plasmodium) might not be more vulnerable to lead. I have seen one such case but was not able to make certain of the quantity of job related lead and hence ...(unclear text) certain of lead as the reason for the markedly decreased red blood cell count. In June 1964 2 well studied cases were reported -- two Sudanese workers with sickle cell trait suffered severe hemolytic anemia as a direct result of lead exposure. Such a lead deserves further study.

Cirrhosis of the liver both from excess alcohol intake and disturbance in iron excretion is the second disease. Studies of the metal content of such livers show an excess of lead over that found in livers not so affected. Butt et al have studied this problem and report that one third of alcoholics with cirrhosis store iron and present a metal pattern similar to that in hemochromatosis. They speculate as follows, quote "Does lead, in response to iron storage, have an insidious and latent effect on hepatic cells, affecting their ability to excrete iron?" End of quote. Since alcoholic cirrhosis is not a rare disease, the influence of small doses of lead acting in combination with iron or another metal deserves further study.

Finally, is there any evidence that lead accumulation influences life expectation or is responsible for an excess mortality of diseases encountered in adult life? Canterow and Trumper have collected human data and experimental

animal evidence up to 1944 and while the [interpretation] conclusions of available studies varies, it does appear that lead accumulates with age. More recently Tipton, Schroeder and Balassa have shown that lead in human tissues increases with advancing years. Schroeder has shown that in a carefully controlled lead-free environment, mice and rats fed lead accumulate the metal. In addition, life span was shortened when the lead in the small animal tissues was in the concentration range currently found in humans. Such observations might be repeated and extended.

Turning to knowledge of human disease, the occurrence of nephrosclerosis related to lead is important. The Australian work of Henderson (1955-1957) is impressive. He delineated a distinctive clinicopathologic renal entity in which increase in lead in bone and/or history of childhood lead poisoning was documented. Older literature is pro and con the point that lead causes renal disease, but the majority of investigators believe that either an acute episode of lead poisoning followed by freedom from work exposure to lead or repeated lower level exposures may be responsible for nephrosclerosis. Most convincing is the work of Lane and his colleagues known to many of you, reported at the Symposium on Lead held in Cincinnati in 1963 and at the International Congress in Madrid that same year. Briefly, the Manchester group presents data to show that lead workers have an excess mortality from renal disease and cerebrovascular disease and at an earlier age than do other males in the United Kingdom.

Lane makes in his well-chosen words the points I raised earlier, regarding the hazard to the health and longevity of the worker who absorbs lead but is not ill:

> The man who is a "bit below par," who has become slowly and insidiously poisoned with lead but shows none of these acute manifestations, rarely goes to his doctor. Does this matter? This slightly poisoned man is

able year after year to carry on with his work. There is apparently little wrong with him. He complains of nothing and he continues to do his job. I maintain that it does matter, that a substantial proportion of these men are being damaged, and that from this group come those who, later on, show evidence of this damage and in some cases die before they should. I believe that from this group come those cases of chronic nephritis due to lead, as well as a number of cases of cerebral hemorrhage.

Let me pull together this review. Nonspecificity of sign and symptom, delayed diagnosable damage because of the body's incredible margin of safety, action of more than one insult acting like lead or with lead require sophisticated attention to the potential effect of low doses of lead -- in much the same manner as low levels of ionizing radiation have been studied since the use of atomic energy for military purposes in 1945.

Comment:

I have reviewed several groups designated as special for the purposes of this meeting. Let me end with what I with others at this meeting see as needed change in concepts.

There must be a departure in thinking from the present U.S. attitude that prevention of occupational disease is the only requirement of those responsible forthe use of such toxic agents as lead. Prevention of diagnosable Pb pois in healthy male workers is important but not enough in our society. There is a wealth of knowledge of the biologic effects of Pb and its compounds at hand. With the exception of Flury's reports that small amounts of Pb promote growth in plants and lower forms of animal life, all data point to Pb effect as harmful..... The body's ability to repair damage, its incredibly large reserve, the non-specificit of its responses help explain the fact that the questions raised by Professor Patterson in his recent controversial article were not raised

What action can reasonably be proposed? Well designed prospective studies of such special populations as I have briefly described here should help establish how long and at what low levels can those in such identified groups tolerate the extra burden of Pb in air, water, soil, food -- very different from quantities of Pb that an average healthy 70 kilo man can handle. Cell culture studies with isotopes of lead or stable lead compounds as they occur in 20th century urban air should give those in authority a feeling for how much toxic Pb effect specific organs can tolerate without measurable damage leading to loss of function. Bolder attempts to study the effect of multiple factors acting with Pb on an organ or system must be made. For example, the effect on iron defficient young animals and adult animals with a source of chronic blood loss given varying amounts of lead might cast light on some of the clinical points I have made. Extension of studies such as those of Byers, Smith and our study at M.I.T. among others, relating mental retardation and psychic distrubances in children with measurable excess lead stores both with and without overt Pb pois will be helpful. Certainly the sad populations of hospitals for retarded children provide an opportunity to assess the quantity of stored lead with accurate data on lead intake. As ability to study genetic defects increase such mentally retarded children can be studied with a view to seeing what, if any role, can be assigned to the insult of man-made lead stores.

[Others will discuss measures to reduce the amount of Pb in air, soil, and water.] Finally, I want to quote from Bradford Hill's Presidential Address at the recent founding of the Section of Occupational Medicine of the Royal Society. The Title of His address was The Environment and Disease: Association or Causation. I quote

"Our observations reveal an association between two variables, perfectly clear-cut and beyond what we would care to attribute to the play of chance. What aspects of that association should we especially consider before deciding that the most likely interpretation of it is causation?"

Prof. Hill then discusses the following aspects - strength of association, consistency, specificity, the temporal relationship of the association, dose-response curve, plausibility from the biological standpoint, coherence with generally known facts, experimental evidence, and judgement by analogy (using rubella experience to suggest one could agree that another viral disease in pregnancy might be harmful).

/Hill then discusses tests of significance and I quote briefly from these paragraphs:

"Between the two world wars there was a strong case for emphasizing to the clinician and other research workers the importance of not overlooking the effects of the play of chance upon their data. Perhaps too often generalities were based upon two men and a laboratory dog while the treatment of choice was deduced from a difference between two bedfuls of patients and might easily have no true meaning. It was therefore a useful corrective for statisticians to stress, and to teach the need for, tests of significance.

I wonder whether the pendulum has not swung too far -- not only with the attentive pupils but even with the statisticians themselves. To decline to draw conclusions without standard errors can surely be just as silly? Fortunately I believe we have not yet gone so far as our friends in the U.S.A. where, I am told, some editors of journals will return an article because tests of significance have not been applied."/

Professor Hill ends his address with a section entitled The Case for Action:

> "Finally, in passing from association to causation I believe in 'real life' we shall have to consider what flows from that decision. On scientific grounds we should do no such thing. The evidence is there to be judged on its merits and the judgment (in that sense) should be utterly independent of what hangs upon it - or who hangs because of it. But in another and more practical sense we may surely ask what is involved in our decision.
>
> On fair evidence we might take action on what appears to be an occupational hazard, e.g., we might change from a probably carcinogenic oil to a non-carcinogenic oil in a limited environment and without too much injustice if we are wrong. But we should need very strong evidence before we made people burn a fuel in their homes that they do not like or stop smoking the cigarettes and eating the fats and sugar that they do like. In asking for very strong evidence I would, however, repeat emphatically that this does not imply crossing every 't'. and swords with every critic, before we act.
>
> All scientific work is incomplete - whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That doesmnot confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time."

I cannot improve on these quotations as satisfying support of my own view of our obligation in the prevention of man-made lead damage, and I look forward to our afternoon session on Control of Lead Pollution.