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The Influence of the Adrenal Cortex in Bacterial Allergy

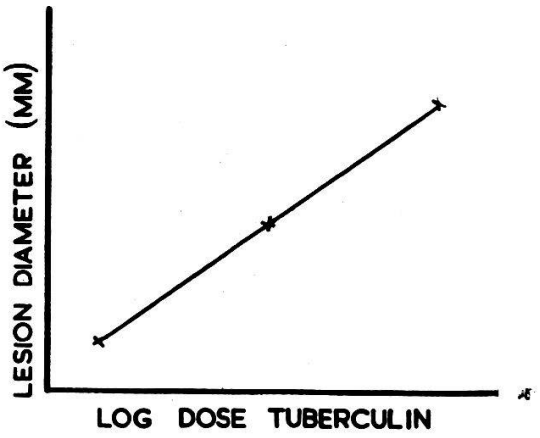
By **D. A. Long, M.D.**

Presumably as the result of a streptococcal infection, there is in rheumatic fever an association of allergy, ascorbic acid deficiency and endocrine disturbance with a widespread inflammation of connective tissue, marked œdema and collagen degeneration, an association similar to that seen in many naturally occurring and experimentally produced diseases connected with these states. Based on this broad analogy, a study was made of bacterial allergy, ascorbic acid deficiency, and the effects of ACTH, cortisone and thyroxine in B.C.G. infected guinea-pigs.

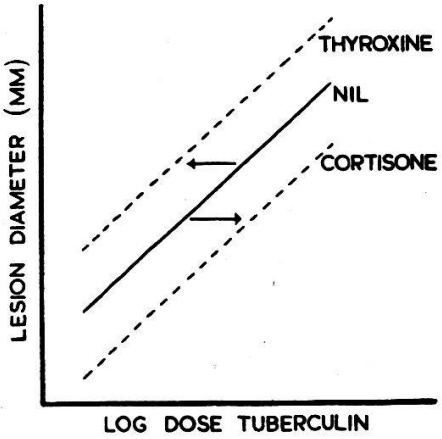
An investigation of this nature provides indirect evidence which must be confirmed in man before it can elucidate human pathology. Each fact so gained and confirmed in man strengthens the analogy, but since identity between man and animal does not exist, the resemblance must eventually end. This does not mean that the investigation ceases to be profitable; on the contrary, provided we continue to check our data in man, we shall learn how the species differ instead of how they resemble each other. The danger is, of course, to argue from animal to man without ever checking the validity of the evidence in man. This danger is obviously greatly increased when the animal does not resemble man in the essentials to be considered. In this case, it must be readily sensitized to a bacterial allergen and unable to synthesize ascorbic acid, otherwise it cannot be made ascorbic acid deficient.

But the question of ascorbic acid metabolism is doubly important because it has been implicated in much recent work on endocrine relationships. Our choice of experimental animal is therefore confined to the monkey or the guinea-pig, since they alone cannot synthesize ascorbic acid. This less obvious aspect of the problem is often and in fact usually neglected in the experimental study of adrenal physiology, thus weakening the analogy between animal and man.

For the next few minutes I shall be talking about the guinea-pig; the



Slide 1.

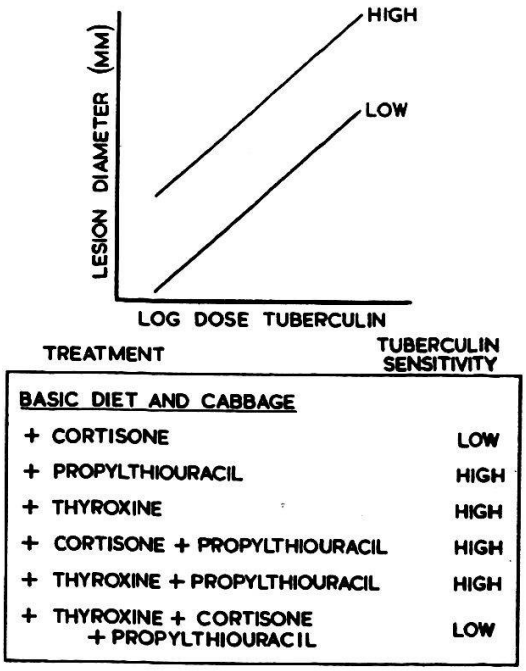


Slide 2.

evidence has not yet been checked in man so that I cannot tell you how much the two species have in common. Provided the analogy is a good one, however, it should provide the basis for a reasonable guess.

Methods. Guinea-pigs are readily sensitized to tuberculin, for the assay of which we had devised a simple quantitative measure based upon our finding that a linear relationship exists between the mean skin lesion diameter and the log dose of tuberculin (slide 1). A horizontal shift in the position of the dosage response line indicates a change in sensitivity to tuberculin. The method yields results which are susceptible to statistical analysis (*Long* and *Miles*, 1950).

The hormones selected for test imposed technical limitations upon us. It is possible with ACTH and cortisone to produce effects with a single dose that can be observed in a short time, and which approximates to a pure excess of the injected hormone. But it is impossible to do the same with thyroxine. We gave this in excess, in the hope, not of avoiding compensatory adjustments in the body, but of overwhelming them. Great caution is therefore needed in interpreting thyroxine-induced effects. We have avoided prolonged treatment with cortisone, and the use of repeated injections, since it is impossible in such experiments to distinguish effects due to cortisone, to anti-cortisone compensatory mechanisms, and to cortisone-induced adrenocortical deficiency resulting from ACTH inhibition. Instead, we have employed single minimal doses, which will at the same time produce maximal effects. Sodium thyroxine is the exception, sufficient being given to prevent a 300 g guinea-pig from gaining weight, for approximately one week, before the tuberculin test.



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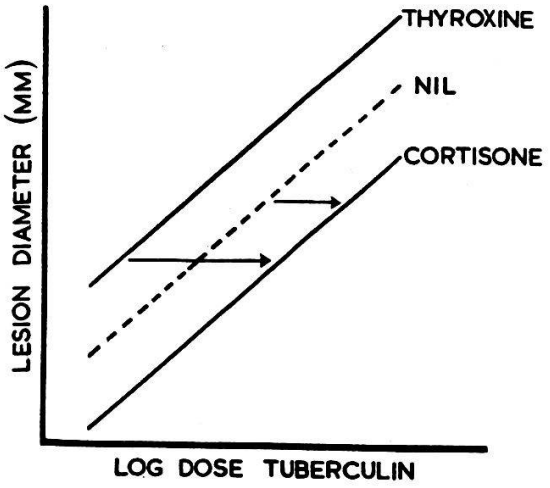
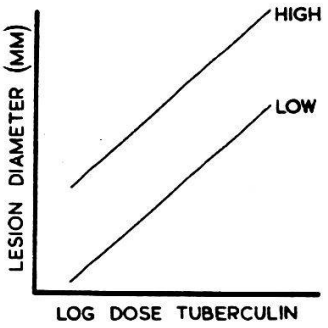


Slide 4.

Results

Initial experiments showed that ACTH diminished, and thyroxine increased sensitivity, suggesting a simple opposition between these hormones (slide 2) (*Long* and *Miles*, 1950). However, we soon found that propylthiouracil prevented cortisone and ACTH desensitization, which was restored by minimal doses of thyroxine (slide 3) and also, that cortisone and ACTH diminished the hypersensitivity of thyroxic animals to the same final level as that produced in non-thyroxic animals (slide 4) (*Long* et al., 1951 b). We concluded that thyroxine, which in itself increases bacterial allergy, is necessary in adequate amounts for desensitization of these cabbage-fed animals by cortisone and ACTH. The nature of this relationship is complex, but the linkage may be in the metabolism of ascorbic acid, and I must now consider this. In the experiments I have so far described, the guinea-pigs were fed upon a pelleted diet with a supplement of cabbage to provide ascorbic acid. In an attempt to define the diet more strictly, we substituted ascorbic acid for cabbage and found that it diminished sensitivity to a degree comparable to that obtained with cortisone in cabbage-fed animals; but, with cabbage omitted from the diet, neither cortisone nor ACTH influenced tuberculin sensitivity, and this was true both in guinea-pigs deficient in ascorbic acid and in guinea-pigs saturated with ascorbic acid. Further experiments showed that *in all cases the diminution of sensitivity that we observed was due to ascorbic acid.* There was, moreover, a factor in cabbage which reversed the desensitizing effect of ascorbic acid; the injected



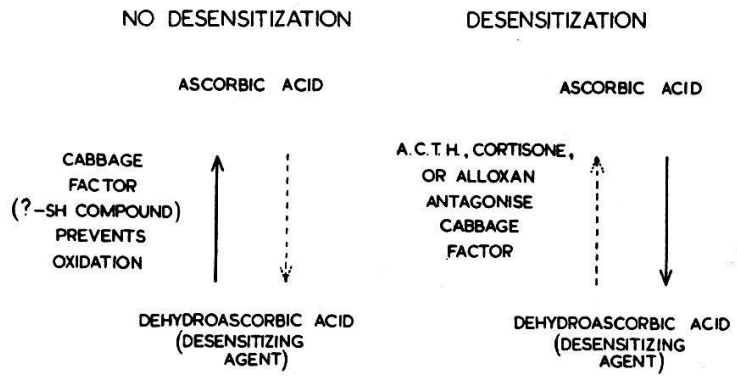
TREATMENT	TUBERCULIN SENSITIVITY
BASIC DIET ONLY	HIGH
+ CORTISONE	HIGH
+ ASCORBIC	LOW
+ ASCORBIC + CORTISONE	LOW
+ CABBAGE	HIGH
+ CABBAGE + ASCORBIC	HIGH
+ CABBAGE + CORTISONE	LOW
+ CABBAGE + ASCORBIC + CORTISONE	LOW

Slide 5.

cortisone, or ACTH, antagonized the cabbage effect (slide 5) (*Long* et al., 1951 a). We suggested that the cabbage factor was an –SH compound, possibly similar to that isolated from Brassicas and other vegetables by *Astwood* and his colleagues (*Astwood* et al., 1949). Such compounds are known to be capable of inhibiting the enzymic oxidation of ascorbic acid *in vitro*. In support of this, we have shown that the –SH compound, glutathione, behaves like the cabbage factor and inhibits the desensitizing action of ascorbic acid in pellet-fed animals, and that dehydroascorbic acid, which occurs as the result of oxidation of ascorbic acid in the body, desensitizes both in the presence or absence of the cabbage factor (*Long* et al., 1951 c). We suggest that the cabbage factor inhibits ascorbic acid desensitization by preventing the oxidation of ascorbic acid to dehydroascorbic acid in the tissues.

Alloxan combines with –SH compounds (*Archibald*, 1945; *Leech* and *Bailey*, 1945; *Lazarow*, 1946, 1947) and should, if our hypothesis is correct, antagonize the cabbage factor and desensitize in the same manner as ACTH or cortisone. In effective doses it is neither diabetogenic nor toxic to the guinea-pig and appears to be a valid research tool. We have in fact shown that the subcutaneous injection of single doses of alloxan of the order of 20 mg/kg diminish tuberculin sensitivity and have relationships to dietary and hormonal factors indistinguishable from those described for ACTH or cortisone (*Long* et al., 1951 c).

These facts are summarized in the hypothesis shown in slide 6. We suggest that in the guinea-pig, the metabolic processes intimately con-



Slide 6.

cerned with dehydroascorbic acid, as opposed to those intimately concerned with ascorbic acid, are responsible for desensitization in all cases. It may indeed be the presence of an effective concentration of dehydroascorbic acid itself which is important, but we have no direct evidence yet to support such a contention. Ascorbic acid desensitizes only after its oxidation to this form. The cabbage factor (possibly an –SH compound) inhibits the oxidation of ascorbic acid. ACTH, cortisone and alloxan come into the picture because, we suggest, they antagonize the cabbage factor, thus facilitating the formation of dehydroascorbic acid. Since propylthiouracil does not prevent either ascorbic acid or dehydroascorbic acid desensitization, it is possible that, provided we are right in our assumption, the drug acts purely as an anti-thyroid agent, the thyroid influences the reducing system in which the cabbage factor is involved.

The discovery that dehydroascorbic acid achieves desensitization takes us nearer to the metabolic reactions that influence sensitivity to bacterial allergens and away from the complex physiology of the endocrines.

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Discussion:

L. Weissbecker (Freiburg/Brsg.): Hinweis auf die Beobachtung, daß Thiosemicarbazone die Tuberkulinempfindlichkeit herabsetzen, unabhängig von ihren tuberkulostatischen Eigenschaften. Es scheint sich hier um eine cortisonähnliche Wirkung zu handeln, da sich unter Thiosemicarbazontherapie die Nebennierenrinde charakteristisch verändert, ebenso auch die Ketosteroid- und Corticoidausscheidung. Auch haben die Thiosemicarbazone thyreostatische Wirkung, wenn auch recht schwach, auf Grund ihrer Thioharnstoffstruktur. Frage, ob die Thiosemicarbazone wie der «cabbage factor» in das Gleichgewicht der zwei Ascorbinsäurestufen eingreifen.

G. W. Pickering (London): Since no one in this discussion has spoken of experiments on man I wish to describe preliminary experiments made by Drs. *Lovell*, *Hudson*, *Goodman* and myself at St. Mary's Hospital, to determine the mode of action of ACTH and cortisone. Using patients with normal skins it is possible to establish that the relationship between size of response and log dose PPD (Tuberculin) is linear. In such patients 200 mg cortisone daily depress the response. Our experiments in other types of inflammatory reactions are insufficiently advanced to report, but we can say, that neither the response to histamine pricked into the skin, nor to morphine which *Feldberg* and *Paton* have shown to release histamine from skincells, nor the response to passively transferred pollen sensitivity in the skin are altered in the skins of these patients treated by this dose of cortisone.

D. A. Long (London): First I should like to thank Professor *Pickering* for his observations in man. I am happy to find that we are in agreement. It seems to me that this is the best way to use evidence based on animal experiment. I am grateful to him for his remarks. To turn to the questions which I have been asked, of course there are antithyroid agents in many different vegetables. The cabbage factor prevents ascorbic acid desensitization in less than 24 hours: so that, I think it unlikely that it produces its effect via the thyroid and if it had an antithyroid effect I should expect it to behave like Propylthiouracil not like the factor I have described. If on the other hand this hypothetical factor has cortisone-like activity I find it difficult to understand why it should prevent desensitization. Finally let me make it quite clear that until we have isolated the cabbage factor and shown its mode of action it must remain a matter for speculation.