CORTISONE, ALLERGY, AND RHEUMATIC FEVER*

BY

D. A. LONG

National Institute for Medical Research, Mill Hill, London.

Among the infective diseases of man in which allergy is thought to play an important part, rheumatic fever is outstanding. It is associated with a haemolytic streptococcal infection of 3 to 4 weeks' duration, high antitoxin levels, and marked sensitivity to streptococcal allergens. The tissues do *not* show the "pyogenic response" commonly associated with haemolytic streptococci, but a widespread inflammation of connective tissue, which is characterized by marked oedema and collagen degeneration, and is similar to that seen in many naturally-occurring and experimentally-produced diseases associated with sensitization to various antigens, with ascorbic acid deficiency, and often with endocrine disturbance. It is irrelevant to the problem of infective allergy to discuss differences between such conditions. We are concerned with the broad analogy; diseases which resemble each other in some ways, may do so in others, so that what we learn of one may have an application in another. On this basis, we have taken certain features of rheumatic fever and studied what we think may be comparable features in the guinea-pig. We have, for convenience, selected tuberculous allergy (*not* streptococcal allergy); ascorbic acid deficiency—since it occurs both in the active stage of rheumatic fever and during convalescence; cortisone and ACTH, for obvious reasons; thyroxine, because we have a hunch that the thyroid has something to do with rheumatic fever, know that it has something to do with the adrenal cortex, believe that it has something to do with allergy, and suspect that it has something to do with ascorbic acid metabolism.

Methods

The guinea-pig is the most suitable experimental animal since, like man, it is unable to synthesize ascorbic acid. Thus, by withholding greenstuff from our animals, and feeding them only upon Bruce and Parkes (1947) pelleted diet, we could easily make them mildly deficient in ascorbic acid.

Guinea-pigs readily acquire tuberculin sensitivity, 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. 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).

* Read to the Heberden Society on July 27, 1951. This lecture has been the subject of an annotation *Brit. med. J.* (1951), 2, 37.

The hormones selected for test imposed technical limitations upon us. It is possible with a single dose of ACTH or cortisone to produce effects that can be observed in a short time, and approximate to a pure excess of the injected hormone. We avoided prolonged treatment with cortisone and the use of repeated injections, since it is impossible in such experiments to distinguish between effects due to cortisone, effects due to anti-cortisone compensatory mechanisms, and effects due 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. It is impossible, however, to do the same with thyroxine because in the several days required to produce observable effects the body is probably undergoing compensatory adjustment. We gave the hormone in excess, in the hope, not of avoiding such adjustments, but of overwhelming them. Sodium thyroxine was given in sufficient quantities to prevent a 300-g. guinea-pig from gaining weight, for approximately one week before the tuberculin test. Great caution is therefore needed in interpreting thyroxine-induced effects.

Results

Initial experiments showed that ACTH and cortisone diminished sensitivity, and that thyroxine increased it, thus suggesting a simple opposition between these hormones (Long and Miles, 1950). However, we later found that propylthiouracil prevented cortisone and ACTH desensitization, which was restored by minimal doses of thyroxine, and also that cortisone and ACTH diminished the hypersensitivity of thyroxic animals to the same final level as that produced in non-thyroxic animals (Long and others, 1951b). 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 lie in the metabolism of ascorbic acid. In the experiments 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. We concluded that there must be a factor in cabbage which influenced tuberculin sensitivity in guinea-pigs. 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 cortisone, or ACTH, antagonized the cabbage effect. Cabbage may have a direct effect on ascorbic acid metabolism, but cortisone and ACTH almost certainly have not, since both are ineffective in ascorbic acid saturated animals, and their effect is not increased in cabbage-fed animals given additional ascorbic acid (Long and others, 1951a). We are attempting to isolate the cabbage factor. To speculate for a moment, the cabbage factor may be an -SH compound, possibly similar to that isolated from brassicas and other vegetables by Astwood and others (1949). Sulphydryl compounds are known to be capable

of inhibiting the enzymic oxidation of ascorbic acid *in vitro*. In support of this, we found that the -SH compound, glutathione, inhibits the desensitizing action of ascorbic acid in pellet-fed animals. It is consistent with our findings to postulate that oxidation of ascorbic acid is associated with desensitization, that cabbage contains an -SH compound which prevents oxidation in the tissues, and that cortisone antagonizes this cabbage effect and allows ascorbic acid oxidation to take place. This process may be expressed diagrammatically as follows:

We shall test this hypothesis by identifying the cabbage factor, by testing both the anti-allergic effect of oxidation products of ascorbic acid in cabbage-fed animals, and the action of cortisone on the accumulation of such products in their tissues, and by exploring the action of drugs which have an analogous effect. The reversible change ascorbic $\rightleftharpoons$ dehydroascorbic acid occurs in the body, and further oxidation results in loss of ascorbic acid, since the change is no longer reversible. In order to determine what stage in the metabolism of ascorbic acid is associated with desensitization, we tested dehydroascorbic acid and found that it desensitized in cabbage-fed animals. It appears, therefore, that as far as allergy is concerned, cortisone affects those metabolic processes that centre in the equilibrium ascorbic $\rightleftharpoons$ dehydroascorbic acid.

By investigations of this kind we hope to relate a number of definite and striking effects which we have observed, but of which the connections are at present partly speculative.

The story is, as yet, incomplete, even as far as the guinea-pig is concerned, and the facts here described apply only to guinea-pigs under the conditions of these particular experiments. To argue from animal to man by analogy amounts to little more than making a reasonable guess, and results obtained in the experimental animal may or may not hold for man. But, *if* allergy is the major aetiological factor in rheumatic fever, *if* the desensitizing action of cortisone is responsible for its clinical effectiveness in this disease, and *if* cortisone produces its effect by facilitating the formation of dehydroascorbic acid in the body, *then* dehydroascorbic acid should prove clinically effective in rheumatic fever. We can test this in man only by direct experiment. But such clinical trials could not be lightly

undertaken since dehydroascorbic acid resembles the diabetogenic drug alloxan both in its chemical structure and in many of its effects. Both are diabetogenic in the experimental animal (Patterson, 1950), and both, we have found, desensitize. We have also found that, like cortisone, alloxan is not itself anti-allergic, does not affect the anti-allergic action of ascorbic acid, antagonizes the cabbage factor, and is ineffective in propylthiouracil-fed animals. Despite the obvious dangers of using these drugs, we hope, subject to the results of full and careful toxicity trials, to give dehydroascorbic acid and alloxan a clinical trial in the treatment of rheumatic disease.

REFERENCES

- Astwood, E. B., Greer, M. A., and Ettlinger, M. G. (1949). *J. biol. Chem.*, **181**, 121.
 Bruce, H. M., and Parkes, A. S. (1947). *J. Hyg. Camb.*, **45**, 70.
 Long, D. A., and Miles, A. A. (1950). *Lancet*, **1**, 492.
 —, —, and Perry, W. L. M. (1951a). *Ibid.*, **1**, 1085.
 —, —, — (1951b). *Ibid.*, **1**, 1392.
 Patterson, J. W. (1950). *J. biol. Chem.*, **183**, 81.

Cortisone, allergie, et rhumatisme articulaire aigu

RÉSUMÉ

L'allergie est presque certainement un facteur important dans l'étiologie du rhumatisme articulaire aigu. En vue de déterminer la nature des rapports entre l'allergie et les autres facteurs—hormonaux, alimentaires, et infectieux—on expérimenta sur des cobayes sensibilisés à la tuberculine.

L'étude porta sur les effets de la carence en acide ascorbique et du traitement par la thyroxine, l'ACTH, et la cortisone.

L'allergie bactérielle était augmentée par la thyroxine et diminuée par l'ACTH et la cortisone. L'acide ascorbique exerçait une action désensibilisante, similaire à celle de l'ACTH et de la cortisone, et ces hormones n'avaient pas d'effet ultérieur chez des animaux déjà désensibilisés par l'acide ascorbique.

L'action de l'acide ascorbique était empêchée par un facteur (encore inconnu) contenu dans le chou, et l'antagonisme de ce "facteur-chou" était, à son tour, supprimé par la cortisone et par l'ACTH.

On suggère que l'acide déhydroascorbique, capable de désensibiliser directement les animaux nourris de choux, est ce facteur désensibilisant.

On note la ressemblance entre l'acide déhydroascorbique et l'alloxane, dont les rapports sont indiscernables de ceux de la cortisone avec l'acide ascorbique, le "facteur-chou", et la thyroxine.

On connaît le danger d'appliquer à l'homme les données de l'expérimentation animale et d'employer en clinique des substances diabétogènes telles qu'acide déhydroascorbique et l'alloxane. Toutefois, les tests de toxicité le permettant, l'auteur a l'intention de faire un essai clinique prudent dans le rhumatisme articulaire aigu.

La cortisona, la alergia, y el reumatismo articular agudo

SUMARIO

La alergia constituye casi ciertamente un factor importante en la etiología del reumatismo articular agudo. Con el fin de determinar la naturaleza de las relaciones entre la alergia y los demás factores—hormonales, alimenticios, e infecciosos—se ha experimentado sobre cobayos sensibilizados a la tuberculina.

Fueron estudiados los efectos de la carencia del ácido ascórbico y del tratamiento por la tiroxina, por la ACTH, y por la cortisona.

La alergia bacteriana aumentaba con la tiroxina y disminuía con la ACTH y la cortisona. El ácido ascórbico ejercía una acción desensibilizante, similar a la de la ACTH, y de la cortisona, pero en los animales ya desensibilizados por el ácido ascórbico estas hormonas quedaban sin más efecto.

La acción del ácido ascórbico era impedida por un factor (todavía desconocido) presente en la col, y el antagonismo de este "factor-col" era, a su vez, anulado por la cortisona y la ACTH.

Se sugiere que este factor desensibilizante es el ácido deshidroascórbico, el cual es capaz de desinsibilizar directamente a los animales alimentados con coles.

Se nota la semejanza entre el ácido deshidroascórbico y la alloxana, cuyas relaciones no se pueden distinguir de las de la cortisona con el ácido ascórbico, el "factor-col", y la tiroxina.

Es obvio el peligro de aplicar al hombre los datos experimentales obtenidos en los animales y de emplear en clínica las sustancias diabetógenas, tales como el ácido deshidroascórbico y la alloxana. Según los resultados de las pruebas de toxicidad el autor tiene la intención, sin embargo, de hacer una aplicación clínica cautelosa en el reumatismo articular agudo.