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The Effect of Cortisone on the Histology of the Tuberculin Reaction

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We have described in the Congress, which has just ended, our work on the histology of the tuberculin reaction. Our conclusion was that this reaction should not be compared with a simple inflammation, but rather with the changes which take place in lymphoid tissue of a sensitised animal after renewed contact with antigen. This work was supplemented by an investigation of the effects of cortisone on the histology of the tuberculin reaction.

Our material was taken from rabbits sensitised by the injection of dead tubercle bacilli in paraffin. Mild lesions (about 10 mm in diameter) were produced by the intradermal injection of 80 I.U. of Old Tuberculine, a dose too small to produce necrosis; these were biopsied at 4 and 22 hours. For comparison a small amount of crude brain phospholipid was injected to produce a non-progressive acute inflammatory reaction of similar size, also without gross necrosis.

Two pairs of animals were used. Four hours before the injection of tuberculin one of each pair was given 30 mg of cortisone (Merck) subcutaneously. Another injection of 10 mg was given after the 4 hour biopsy, perhaps unnecessarily.

Macroscopically treatment with cortisone produced an obvious reduction in the intensity of the tuberculin reactions as compared with those of the controls; this effect has been described by other workers. There was no obvious effect on the simple inflammatory reaction.

The histological changes are striking, although a quite obvious cellular infiltration with the characteristic focal, perivascular pattern of the tuberculin reaction occurs in the cortisone-treated animals; but it is much less intense. Detailed examination shows that the reduction is mainly due to a deficiency of mononuclear cells. There is also a reduction in the mononuclear component of the simple inflammatory reaction,

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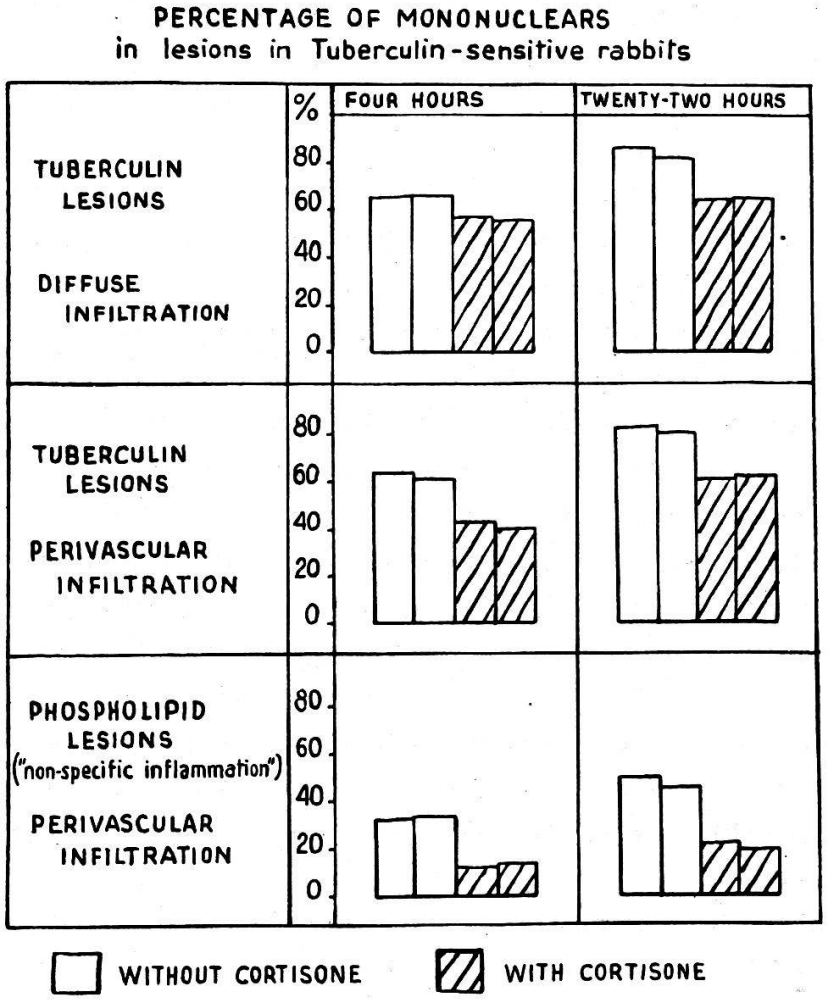

Fig. 1.

although as this is always subsidiary to the polymorphonuclear component it is not at all striking at first sight.

A quantitative estimate of the relative effect of cortisone on the two cell-types may be got from cell-counts made on comparable areas in sections from treated and untreated animals. Although the absolute figures must be treated with caution, since it is impossible to select strictly comparable areas and animals of identical sensitivity, the *proportion* of mononuclears present will show whether there has been a relative suppression of this type of cell. Counts were therefore made on two separate sites, the strip of diffuse infiltration in the superficial dermis, and the scattered foci of more intense infiltration round blood vessels. The ratios which are summarised in fig. 1 show that in every case there is a diminution in the proportion of mononuclears when treated and untreated animals are compared, which can be shown to be statistically significant.

This effect of cortisone, it must be noticed, is not equivalent just to a diminution in sensitivity. The animal pairs were of unequal sensitivity,

two being strongly and two moderately sensitive, one in each pair being treated with cortisone; but it is clear that the proportion of mononuclears is virtually identical in animals given the same treatment, although the total numbers of cells are less in the less sensitive animals.

It should also be noticed that the deficiency of mononuclears after cortisone is as striking in the non-specific inflammatory lesions as it is in the tuberculin lesions, showing that no specific anti-allergic effect of the hormone need be postulated here, the greater effect on the allergic lesion being merely because the mononuclear is the predominant cell.

One can analyse the effects of cortisone a little further, though our conclusions can only be tentative, as it is impossible to be certain where the individual reacting cells have come from. At four hours, small free mononuclear cells, very like blood monocytes, are common throughout the more vascular areas of the dermis in the normal tuberculin reaction especially immediately around small blood-vessels. In the reaction, modified by cortisone they are extremely rare, in fact the mononuclear reaction appears to consist almost entirely of a hyperplasia of the local reticulo-endothelial cells. Since these are most numerous round blood-vessels, hair follicles, etc., the characteristic multifocal pattern is preserved. The appearance of the cortisone-modified reaction suggests in fact that these are the cells which have produced what reaction there is, while it is the migration of monocytes from the blood-stream which has been largely suppressed, a not unreasonable supposition in view of the lymphopenia. There is reason to suppose that this explanation still holds at 22 hours, though it is now even more difficult to assign an origin to the developing cells.

We have suggested that the tuberculin reaction should be considered as an attempt to build up reticulo-endothelial tissue at the point of attack in the body. The effect of cortisone in interfering with such a build-up is quite consistent with its known ability to inhibit the reticulo-endothelial hypertrophy required for the production of anti-bodies.