CHRONIC ADENOHYPOPYSISITIS IN A RHESUS MONKEY IMMUNISED WITH EXTRACTS OF HUMAN PLACENTA

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PLATE LXXXV

CHRONIC inflammatory disease of the adenohypophysis is not common in man. The lesion most frequently encountered is a giant-cell granulomatous adenohypophysitis, but the cause of this disease is not known (Doniach and Wright, 1951).

There have also been two recorded cases of non-specific chronic adenohypophysitis: in these patients, the glandular parenchyma was atrophic and the adenohypophysis was extensively infiltrated by numerous lymphocytes and occasional plasma cells (Goudie and Pinkerton, 1962; Hume and Roberts, 1967). Auto-immunity has been suggested as the cause of this lesion on the basis of the histological appearance of the adenohypophysis and the clinical association with other putative auto-immune diseases, but antibodies to human adenohypophysis have not been demonstrated (Goudie, 1968).

The lesion has not been recorded previously in the rhesus monkey or other subhuman primate species (Ruch, 1959). The present case is noteworthy because the animal had been immunised with a variety of extracts of normal human full-term placenta containing human chorionic somato-mammotropin (otherwise known as human placental lactogen, Li et al., 1968), which is antigenically related to both human and monkey growth hormones (Josimovich and Mintz, 1968).

CASE REPORT

A pregnant rhesus monkey (Macaca mulatta) gave birth to a healthy baby 2 wk after admission to the Foresterhill Animal House of the University of Aberdeen. During the following 3 yr the mother was immunised consecutively with (a) Raben (1957)-type extract of normal human full-term placenta, either emulsified with Freund's complete adjuvant and injected intramuscularly or
precipitated with alum and injected intravenously: (b) homogenate of normal human full-term placenta in 0.15M-NaCl emulsified with Freund’s complete adjuvant and injected intramuscularly: (c) human chorionic somato-mammotropin (HCSM) extract (Friesen, 1965) of normal human full-term placenta emulsified with Freund’s incomplete adjuvant and injected intramuscularly. Throughout this period, the monkey was lively and appeared healthy; it had a regular menstrual cycle.

In the course of experiments on the metabolism of HCSM, 40 mg HCSM was injected intravenously into the monkey on three occasions—5 wk and 3 wk before death, and on the last day of its life. On the first two occasions the animal was protected from an anaphylactic reaction by intramuscular injections of 25 mg promethazine hydrochloride (Phenergan) each morning for 3 days before administration of HCSM. On the third occasion, pretreatment with promethazine hydrochloride was omitted: the animal did not appear to suffer any reaction at the time of injection of HCSM, but 25 min. later it was found unconscious in the cage and it died a few minutes later despite attempts at resuscitation.

Necropsy findings

There was oedema glottidis and both lungs were congested. The pelvic and para-aortic lymph-nodes were enlarged, pale and rather soft in consistency; there were granulomatous lesions in the buttocks at the site of recent injections of adjuvant emulsion. No macroscopic lesions were seen in the other viscera.

Histological findings

Hypophysis. The normal structure of the adeno-hypophysis is distorted by a diffuse chronic inflammatory infiltrate with abundant small lymphocytes and occasional plasma cells: there are no germinal centres or endothelial cells and no interstitial fibrosis. The lesion is widespread and affects the zona tuberalis (Dawson, 1948) to the same extent as the remainder of the pars distalis. There is diffuse wasting of the parenchyma, affecting chromophil cells to a somewhat greater extent than chromophobe cells: all of the various types of chromophil cells are present. No degenerating parenchymal cells are present (figs. 1–3).

The pars intermedia and the neurohypophysis do not show any histological abnormality.

Lungs. There is widespread moderately severe capillary congestion. Occasional smaller bronchi contain plugs of mucin, but these do not contain eosinophil leucocytes and there is no evidence of bronchitis or pneumonia. Scattered throughout the lungs there are occasional small, well-demarcated, interstitial granulomatous lesions formed mainly of lymphocytes but also containing occasional plasma cells and macrophages, some of which resemble endothelial cells: these lesions are probably a reaction to Freund’s adjuvant.

Other organs. No histological abnormality was seen in sections of stomach, small and large intestines, liver, pancreas, salivary glands, heart, spleen, kidneys,
Fig. 1.—Monkey with non-specific chronic adenohypophysitis: diffuse chronic inflammatory infiltrate in adenohypophysis. Haematoxylin and eosin (HE). ×120.

Fig. 2.—Normal monkey: adenohypophysis, for comparison with fig. 1. HE. ×120.

Fig. 3.—Monkey with non-specific chronic adenohypophysitis. Adenohypophysis: diffuse infiltrate mainly of lymphocytes, but with a few plasma cells; chromophobes, acidophils and basophils cells persist. HE. ×315.
adrenal glands, thyroid gland, ovaries, uterine tubes, uterus, cervix, vagina and brain.

**Immunological investigations**

The methods will be described elsewhere (Beck, Melvin and Masson, unpublished). There were no appreciable differences in the findings in serum samples removed at intervals during the last year of life.

*Gel diffusion tests.* The serum samples gave precipitin lines against HCSM, but not against human growth hormone (HGH). There were also antibodies to several other serum and tissue antigens, but none of these was organ-specific.

*Antiserum titration with radioisotope-labelled antigens.* The serum samples bound $^{125}$I-HCSM to high titre ($2^{19}$), but they did not show any evidence of specific binding of $^{125}$I-HGH.

*Immunofluorescent staining experiments.* In experiments on sections of formaldehyde-fixed, paraffin-embedded tissue, with the indirect technique, serum from this monkey gave specific immunofluorescent staining restricted to the cytoplasm of syncytiotrophoblast in normal human full-term placenta: it did not give any specific staining of normal human pituitary gland, normal monkey pituitary gland or normal monkey full-term placenta.

In experiments with the indirect technique on unfixed frozen sections of pituitary glands from another two monkeys, serum from this monkey did not give any specific staining.

**DISCUSSION**

Chronic adenohypophysitis was found as an incidental lesion of moderate severity in a monkey that died of anaphylaxis. There was, however, no evidence of impairment of pituitary function, since the thyroid and adrenal glands were not atrophied and the animal had had a regular menstrual cycle. There was, moreover, no evidence of a similar lesion in the pituitary gland of two other adult female monkeys immunised at the same times with the same antigen preparations, nor in the pituitary glands of three adolescent monkeys that had been immunised with Friesen-type extracts of HCSM only.

Although it was possible that the chronic adenohypophysitis had been caused by some undiscovered agency, such as intercurrent infection, it is tempting to speculate whether it was related to the experimental immunisation. If so, it is improbable that the lesion is a reaction to the adjuvant or to a latent virus present in the human tissue from which the antigen was prepared, since two other monkeys immunised with the same antigen-adjuvant emulsion did not develop this lesion. If, therefore, the lesion had been caused by the immunisation procedure, then it must have resulted from the stimulation of auto-reactive immunity by the injection of heterologous human placental antigens that are related to antigens in the monkey adenohypophysitis. This mechanism is analogous to that postulated by Pepys *et al.* (1966) to explain the “hetero-stimulated auto-reactive antibodies” to pituitary gland found in the serum of diabetes insipidus patients, who had been treated with “pituitary
snuff” of animal origin. Furthermore, Beall et al. (1969) have shown that chronic thyroiditis can be induced in baboons in an analogous manner by immunisation with a microsomal fraction of human thyroid glands.

There is no record of any attempt to produce auto-immune adenohypophysitis in the rhesus monkey, but the disease has been successfully induced in rats (Levine, 1967). The rhesus monkey is, however, known to be susceptible to auto-immune disease, since chronic thyroiditis (Rose et al., 1966), chronic gastritis (Andrada, Rose and Andrada, 1969) and chronic orchitis (Andrada, Andrada and Witebsky, 1969) have developed after immunisation with the appropriate monkey antigen. Circulating organ-specific antibodies to thyroid gland or stomach were demonstrated in the serum of animals with active chronic thyroiditis or atrophic gastritis: anti-testis antibodies could be detected only after removal of the target-organ by castration.

It is probable that the principal mechanism in the pathogenesis of the organ-specific auto-immune diseases is cellular immunity. Humoral auto-antibodies are usually also present in both clinical and experimental auto-immune disease; these antibodies are presumed to have the same specificity as the cellular immunity. In an attempt to establish that the chronic adenohypophysitis had been caused by auto-immunity, we have attempted to demonstrate organ-specific antibodies to monkey pituitary gland. Antibodies to HCSM and to human serum proteins were detected in serum from the affected monkey. We have shown that the anti-HCSM antibodies do not cross-react with HGH (Beck et al., unpublished), and it is improbable that this antibody will react with monkey growth hormone since the serum does not give immunofluorescent staining of monkey pituitary gland: there is, therefore, no evidence that immunity to HCSM has provoked the adenohypophysitis. It is improbable that immunity to human serum protein could be responsible since the lesion is anatomically organ-specific. It is, however, not possible to conclude that the serum does not contain auto-antibodies to monkey adenohypophysis from our failure to demonstrate immunofluorescent staining, since this technique is relatively insensitive. It is unfortunate that we did not have sufficient monkey pituitary gland tissue available for further study, since it is possible that we would have been able to demonstrate organ-specific auto-antibodies with more sensitive techniques if the adenohypophysitis had been auto-immune in origin.

**Summary**

Chronic adenohypophysitis was found in the pituitary gland of an adult female rhesus monkey that had been immunised with various preparations of human placenta. An auto-immune pathogenesis was suspected since there are antigenic similarities between human placenta and monkey adenohypophysis, but this mechanism was not proved and the cause of the lesion remains unknown.

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