THE IMMUNOMORPHOLOGY OF OVARY'S REACTION

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Ovary's passive cutaneous anaphylaxis reaction was studied by immunomorphological and electron-microscopic methods. In contrast to the first phase of the Arthüs phenomenon, in Ovary's reaction the antibodies are fixed and not free. For this reason the immunomorphology of passive cutaneous anaphylaxis reflects damage to the tissue not by immune complexes but by the reaction of antigen with antibodies fixed on the endothelium of the blood vessels. Probably for this reason, besides vascular changes, the mononuclear-histiocyte reaction in Ovary's phenomenon is well marked.

Ovary's reaction is of great interest because it simulates the morphology of the reaction of an antigen with fixed antibodies, although its immunological interpretation is still in doubt.

Ovary's reaction is the local appearance of a state of general (systemic) anaphylaxis in the skin of guinea pigs. This reaction was described in 1950 by Ovary, who called it fast anaphylaxis of the skin capillaries to intradermal or intravenous injection of immune complexes. Ovary's reaction can be obtained in two forms: as active and passive cutaneous anaphylaxis. Ovary calls active cutaneous anaphylaxis the reaction of the skin capillaries at the site of intradermal injection of antigen into a sensitized guinea pig, while he describes passive cutaneous anaphylaxis as the reaction of the skin capillaries to the antigen–antibody complex. Antihistamine drugs inhibit the development of Ovary's reaction and, in his opinion, histamine is responsible for the increase in permeability observed in this phenomenon [1, 3]. Ovary regards the mechanism of the reaction which he described as different from that of the Arthüs phenomenon in that the antibody for its development must be fixed to the tissues, whereas in the Arthüs phenomenon, in his opinion, blending of antigen with antibody and the formation of a precipitate take place in the liquid tissue media (blood, lymph, tissue fluid). To confirm this suggestion he cites desensitization experiments. Injection of a small dose of antigen intradermally into a passively sensitized guinea pig 30 min before the reaction does not exert a desensitizing effect, for the antibodies have already become fixed by the tissues during the 48 h after injection into the animal. If, however, the same dose of antigen is injected intradermally 5 min before the sensitizing injection of antibodies, the injected antibodies are bound by the antigen and passive sensitization does not develop.

The morphological picture of changes in the skin is briefly described in the few papers which have been published on passive cutaneous anaphylaxis [2, 3].

No immunohistochemical or electron-microscopic data on Ovary's reaction can be found in the literature. The present investigation was accordingly carried out to study this problem.

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TABLE 1. Ovary's Reaction

Group of animals	Number of animals	Intradermal immunization	Intravenous desensitization
Injection of rabbit antiserum against horse albumin			
Experimental	6	Rabbit antiserum against horse albumin in dilution of 1:640, 1:5120	Horse albumin
I Control	3	a. Rabbit antiserum against horse albumin in dilution of 1:640 b. Rabbit antiserum in dilution of 1:640	a. Without desensitization b. Without desensitization
II Control	6	Rabbit antiserum in dilution of 1:640	Horse albumin
III Control	3	a. Rabbit antiserum against horse albumin in dilution of 1:640, 1:5120 b. Rabbit antiserum in dilution of 1:640	a. Rat serum b. Rat serum
Injection of "pure" antibodies from rabbit antiserum against horse albumin			
Experimental	6	"Pure" antibodies to gelatin in dilution of 1:20, 1:160	Horse albumin
I Control	3	"Pure" antibodies to gelatin in dilution of 1:20	Without desensitization
II Control	3	"Pure" antibodies to gelatin in dilution of 1:20, 1:160	Rat serum
III Control	3	"Pure" antibodies to gelatin in dilution of 1:20, 1:160	Horse albumin

EXPERIMENTAL METHOD

The reaction was carried out in two forms on 33 guinea pigs: in the first, for intradermal immunization, a rabbit antiserum against horse albumin was used, while in the second form, "pure" antibodies from this serum were used (Table 1). Intravenous desensitization with horse albumin was carried out 3 h after intradermal immunization. The animals were sacrificed 5, 15, and 30 min after desensitization and the morphology of this reaction was studied. In one series, the dye Evans blue was injected together with the antigen, and in this way the reaction could be detected visually after 30 min. Many controls to the main series were set up in order to demonstrate the immunological specificity of the reaction. It was positive only in the main series of the experiment even when high dilutions of both antiserum and "pure" antibodies were used.

EXPERIMENTAL RESULTS

The dynamics of the morphological changes in Ovary's reaction (following injection both of antiserum and of "pure" antibodies) was as follows. The earliest changes developed in the blood vessels, capillaries, and venules of the deep layers of the dermis. Injected globulin bound with antigen was detected in the walls of these vessels. Circulatory and degenerative changes in the vessel walls which developed were due to the reaction between antigen and antibodies fixed to the endothelium. It was clear from the electron micrographs that the earliest changes in the capillaries resembled spasm: the endothelium becomes round in shape and the lumen becomes slit-like (Fig. 1a). The "spasm" is followed by paresis. Besides the changes

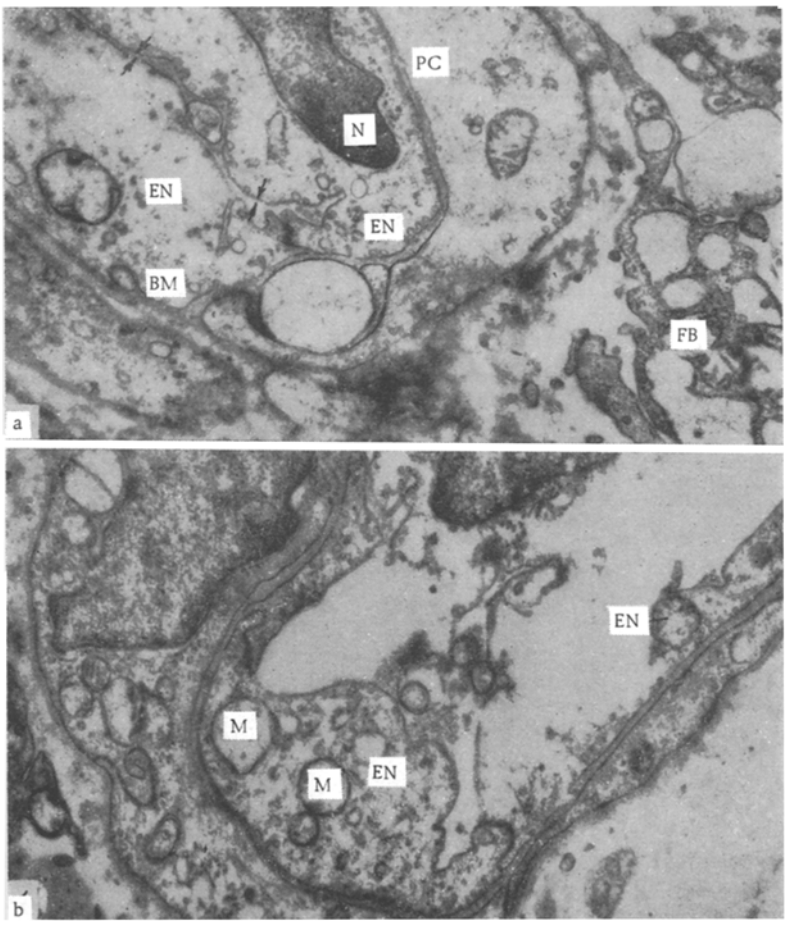

Fig. 1. Early vascular changes: a) "spasm" of capillary: endothelial cells (EN) round in shape, rich in pincytotic vesicles, lumen (arrows) slit-like, basement membrane (BM) loosened; N – nucleus; PC – pericyte; FB – fibroblast (electron micrograph; 24,000×); b) capillary with destruction of individual endothelial cells (EN); mitochondria (M) of intact endothelium considerably swollen and vacuolated (electron micrograph; 24,000×).

characteristic of active pinocytosis (accumulation of intracellular granules, formation of polysomes, swelling of mitochondria, vacuolation of the ergastoplasmic reticulum), degeneration and desquamation are well marked in the endothelium (Fig. 1b). Foci of coagulation of plasma proteins are visible next to areas of degeneration of the endothelium (these structures are possibly immune complexes), and this is evidently the first stage of development of thrombi. Thrombi were found in the small vessels in the early period of the reaction. Together with these changes, the characteristic patterns of palisading of leukocytes and their migration out of the blood stream are observed. These are most probably due to the leukotaxic effect of the immune complexes.

The circulatory disorders and degenerative changes in the vessel wall are followed by infiltrative and proliferative reactions. Diffuse infiltration of the perivascular tissue by polymorphs is observed 15 min after desensitization with antigen, and these polymorphs "digest" the protein of the immune complexes. Injected globulin is found in the cytoplasm of the leukocytes (Fig. 2a). It is rich in lysosomes, and as electron-microscopic investigation showed, among the destroyed lysosomes can be seen granular and amorphous masses of protein (Fig. 2b); the possibility that these are immune complexes cannot be ruled out.

The proliferative reaction concerns the endothelium and perithelium. It reflects all the processes of elimination and repair but resembles "vasculitis" in appearance. The zone of infiltration 30 min after

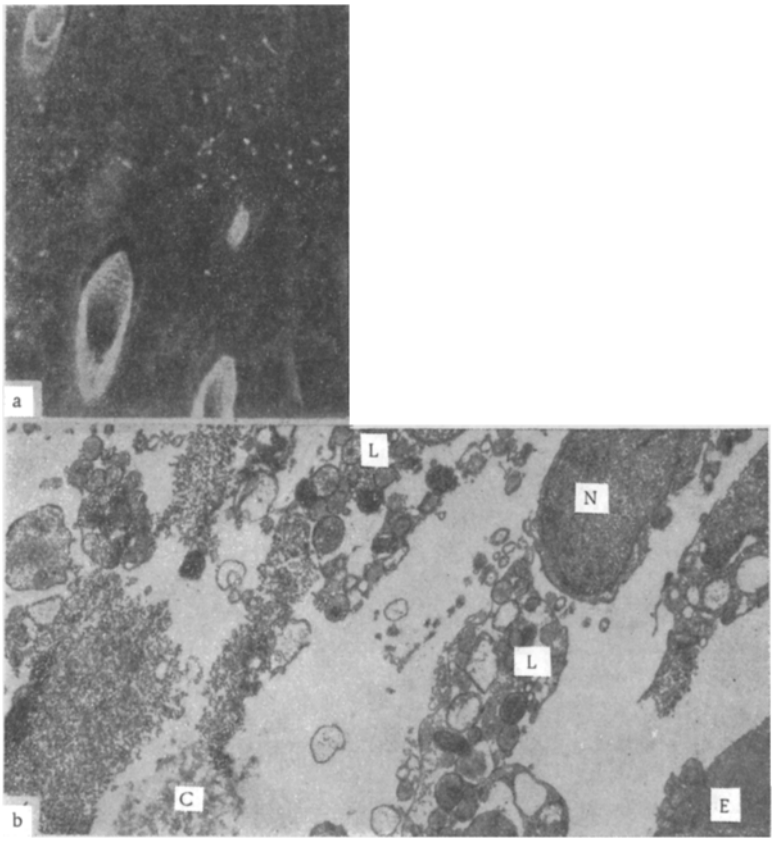

Fig. 2. Infiltrative reaction in Ovary's passive cutaneous anaphylaxis: a) leukocytes infiltrating connective tissue contain injected globulin (Coons' method, 250×); b) destructive polymorph; granular and amorphous masses (protein of immune complexes) adjacent to lysosomes (L). N – nucleus; E – erythrocyte; C – collagen (electron micrograph; 18,000×).

desensitization with antigen becomes largely mononuclear in composition, a brisk histiocytic and macrophagal reaction is observed, and the injected globulin can be found in the disintegrated histiocytes (Fig. 3a). Here and there histiocytes and macrophages form focal collections (Fig. 3b). A brisk reaction of fibroblasts can also be seen (Fig. 3c).

The morphology of Ovary's passive cutaneous anaphylaxis resembles the first phase of the Arthüs phenomenon. However, in contrast to the latter, the antigens in Ovary's reaction are fixed and not free, so that the morphology of passive cutaneous anaphylaxis is the morphology of injury to the tissue not by immune complexes but by the actual reaction between antigen and antibodies fixed on endothelial cells of the blood vessels. For this reason, the morphological manifestations of Ovary's phenomenon differ from the morphology of the first phase of the Arthüs phenomenon: besides the vascular changes so characteristic of this phase, the mononuclear-histiocytic reaction is well marked in Ovary's reaction, especially toward its end.

Ovary's reaction allows certain analogies to be drawn between its morphological manifestations and the morphology observed during pathological antigen–antibody reactions in man, when either antigen or antibody is fixed to the tissues. There is reason to suppose that the so-called vasculitis, and histio-lymphocytic, macrophagal, and possibly, granulomatous reactions also are successive links in the chain of tissue elimination of immune complexes.

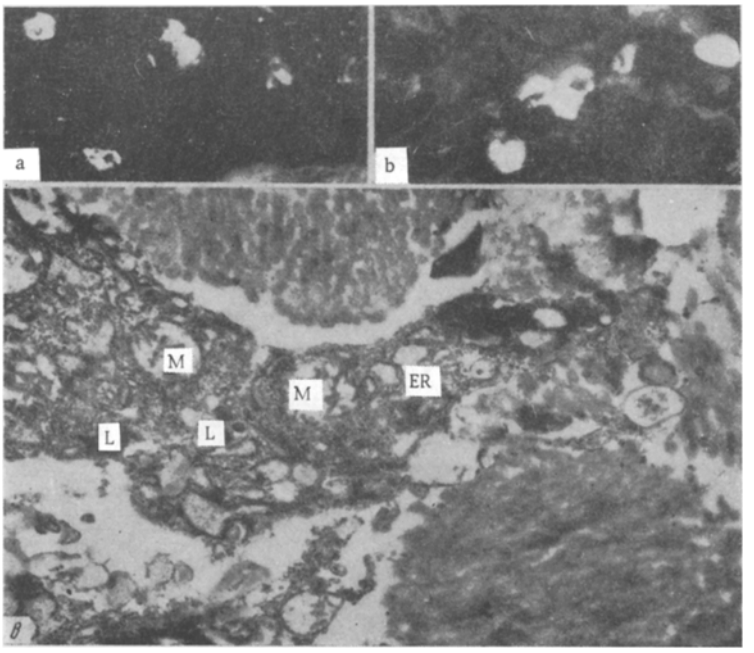

Fig. 3. Proliferative reaction during Ovary's passive cutaneous anaphylaxis: a) injected globulin can be seen in disintegrated mononuclears and macrophages (Coons' method; 600×); b) focal collections of histiocytes and macrophages (Coons' method using antiglobulin serum; 600×); c) active state of fibroblasts: cytoplasm contains strongly developed granular endoplasmic reticulum (ER), with a homogeneous substance of moderate electron density in the dilated cisterns; mitochondria (M) are swollen, cristae partly intact, numerous dense inclusions and lysosomes (L) (electron micrograph; 22,000×).

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