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Vascular Lesions in Human Allotransplantated Kidneys*

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Summary. Sixteen patients with allotransplanted kidneys were examined by biopsy or autopsy during the last four years. In 5 patients there was conspicuous stenosis or occlusion of the cortical arteries and arterioles; in 4, the major interlobar muscular arteries were also involved. The vascular lumen was stenosed by hyaline deposits and "edematous" intimal thickening containing abundant erythrocytes, foam cells, and various mononuclear cells. In contrast, no striking thrombosis was present and fibrinoid deposits were scarce. The ultrastructure showed signs of a severe degeneration of both muscular and endothelial cells and an accumulation of cell fragments and debris but no fibrin or preserved blood platelets. In major muscular arteries there were dystrophic changes in the deep intima and media; in the subendothelial region muscular cells (newly formed?) preponderated. In the remaining eleven patients the arteries were normal or showed moderate hyaline and fibroelastic arterio-arteriolosclerosis.

A severe obliterating arterio(lo) pathy (OA) means a grave prognosis, pointing to manifest or imminent renal insufficiency and forecasting the necessity of transplantectomy within a few months. The patients free of OA constitute a clinico-functionally nonhomogenous group, biopsies being performed for various reasons at various posttransplantation intervals; the average prognosis, however, is considerably more favourable. The pathogenesis of OA remains unclear as yet; the lesion offers, however, a rather striking morphological picture different from those of common arteriosclerotic and arteritic lesions.

Zusammenfassung. Im hiesigen Transplantationszentrum wurden in den letzten 4 Jahren 16 nierenallotransplantierte Patienten biopisch und/oder nekroptisch untersucht. In 5 Fällen fand sich eine schwere Stenose mit teilweiser Obliteration von corticalen Arterien und Arteriolen, der gleiche Befund in 4 Fällen auch an größeren interlobären Muskelarterien. Das Lumen der alterierten Gefäße zeigt jeweils eine hyalin und ödematös verquollene, von Erythrocyten, Schaumzellen und mononukleären Zellen durchsetzte Intimaschicht. Eine Thrombose oder Fibrinoidablagerungen werden selten oder gar nicht nachweisbar. Mikroskopisch finden sich schwere Endothel- und Muskelzelldegenerationen sowie eine Anhäufung von Zellfragmenten und Trümmerzonen. Dagegen werden Fibrin und intakte Blutplättchen vermißt. Größere Muskelarterien weisen eine schwere Dystrophie ihrer tiefen Intima- und Mediaschichten auf, im subendothelialen Raum überwiegen neugebildete Muskelzellen. — Die Nierenarterien und -arteriolen der übrigen 11 Patienten waren im wesentlichen gut erhalten. Sie zeigten lediglich eine diskrete bis mittelschwere hyaline bzw. fibroelastische Arterio-Arteriolosklerose.

Der Befund einer schweren „obliterierenden Arterio-Arteriolopathie" (oA) in einem Nierenallotransplantat bedeutet eine ernste Prognose. Er stellt die bevorstehende Manifestation einer Niereninsuffizienz und damit die Notwendigkeit der Entfernung des Transplantates in Wochen bis Monaten dar. Patienten ohne deutliche oA stellen in unserem Krankengut eine klinisch-funktionell inhomogene Gruppe dar, da bei ihnen eine Biopsie aus unterschiedlichen Gründen und in differenten Zeitabständen nach der Transplantation erfolgte. Die Prognose ist aber bei dieser Krankengruppe bedeutend günstiger. Die Pathogenese der oA ist bis jetzt unklar. Es liegt jedoch bei dieser Nierenschädigung ein sehr auffallendes und charakteristisches morphologisches Bild vor, welches deutlich von den üblichen arterio-arteriolosklerotischen und arteritischen Veränderungen abweicht.

* Dedicated to the 70th birthday of Prof. Dr. Antonín Fingerland, DrSc., Hradec Králové, Czechoslovakia.

In both human and experimental allotransplanted kidneys, very essential morphological changes of tubules and interstitium (Simonsen *et al.*, 1953) and more recently of glomerules and vessels (Porter *et al.*, 1963, 1964; Dempster *et al.*, 1964; Dunea *et al.*, 1964) have been observed. Arterial lesions were suspected at first to resemble advanced arteriosclerosis (Hume *et al.*, 1955) and later on, the influence of hypertension, irradiation, toxic drugs (Porter, 1964) and the possible significance of antibodies to histocompatibility antigens have been studied (Horowitz *et al.*, 1963, 1965; Williams *et al.*, 1968). Papers devoted to morphology of vascular lesions are rather scarce and mostly have an experimental character (Porter *et al.*, 1964). In the material from our clinical biopsies, it became evident however that the histology and ultrastructure of vessels, particularly of arteries and arterioles, represent an important diagnostic and prognostic feature. The present study reports the histology and fine structure of vascular changes occuring from the beginning of the transplantation till a late rejection; an attempt is made at summarizing main clinico-pathologic correlations and prognostic significance of the said changes.

Material and Methods

During the period 1966—1969, at our Transplantation Centre 30 renal allotransplantations were performed in 29 patients. For morphological studies, 6 operation biopsies, 8 punction biopsies, 3 resected transplants and 4 postmortem transplants are available. For histology, the paraffin sections of formol-fixed tissue were stained with haematoxylin-eosin, resorcin-fuchsin — van Gieson method, blue trichrome, P.A.S., toluidine blue, methyl violet and methyl green — pyronine; some of them impregnated for reticulin fibers (Gomori silver). Frozen sections from excisions, resected and autopsied kidneys were stained with Oil red 0 and Sudan black. 11 biopsies were examined electronmicroscopically too: tissue blocks were fixed with 2% isotonic buffered OsO_4 and embedded in Vestopal W or Epon 812; sections in the silver interference area were cut with a glass knife LOB on a microtome Tesla BS 478, contrasted with uranyl acetate, partly also with Pb acetate, and examined at 60 KV in a Tesla BS 242 D microscope.

Own Observations

The most conspicuous vascular lesions in our transplants (apart from the glomerular capillary changes described earlier, (Rossmann *et al.*, 1969) were those of the muscular arteries and arterioles: in 5 patients, they were severe, stenosing to obliterating, whereas in the remaining 11 ones only moderate to minimal. The findings in these two morphologically distinctly defined groups are described separately later on.

Findings made in *obliterating arterio-(lo)-pathy (OA):* (4 percutaneous biopsies, 3 resected transplants and 2 autopsies). In *optical microscopy,* the *interlobular* and *afferent* vessels exhibit a strongly dilated intima (Fig. 1, at left), impregnated by faintly stainable "mucoid" substance showing some metachromasia, especially in interlobular arteries; the P.A.S. reaction gives only week staining here. The inner elastic membrane is single-layered or split, with some focal interruptions, but there is no distinct elastic hyperplasia. This "subendothelial oedema" is focally interspersed by nests of foam cells and/or erythrocytes and fragments of the latter (Fig. 1, at right). Further there are present lymphocytes, solitary polynuclears and oval spindle and reticular elements (possibly proliferated endothelia and/or host mononuclear cells). The proper endothelia have polymorphic, partly

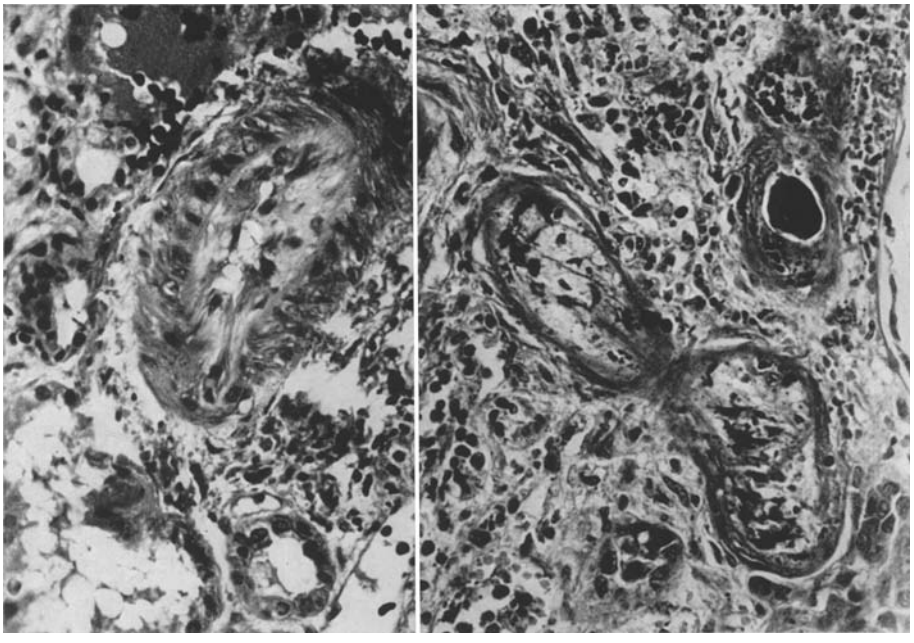

Fig. 1. At left: stenosed interlobular artery. "Oedematous" intimal thickening, polymorphic medial muscle cells. H. E. 270×. At right: obliterated afferent vessel filled with numerous foam cells, erythrocytes, and rests of latter. Trichrome. ×270

pyknotic nuclei and moderately pyroninophilic cytoplasm. Plasmocytes, "rejection" mononuclears, thrombosis (both recent and recanalized) and in the florid stage the intimal fibrosis too, are lacking. Fibrinoid deposits are rare: their relative homogeneity and red-orange tint in trichrome stain differ from the intensive red colour of intramurally located erythrocytes and their sharply demarcated rests. The medial muscle cells show irregular swelling, polymorphic, partly pyknotic nuclei and anuclear (necrotic ?) segments of media. Some vessels are strongly dilated by a mass of erythrocytes, their acidophilic fragments and cell debris, obscuring all original structures and inner surface. Rare vessels are calcified. The inconstant cellular invasion of adventitia corresponds to the general degree, often discrete, of the interstitial infiltration, but no "inflammatory cuffing", such as known in periarteritis, is evident. Numerous lipid droplets, granules and masses fill up the rests of lumen, the thickened intima and eventually the whole wall, even in such areas where foam cells are inapparent in paraffin sections. The lesions described are not diffuse: there are obliterated, stenosed as well as moderately damaged segments in one bioptic sample.

Subarcuate, arcuate and interlobar arteries were encountered in resected transplants and autopsies. *Macroscopically*, their walls were thickened, yellowish, the lumina were strongly narrowed to hardly discernible, without traces of thrombosis, embolism or compression; the ilico-renal (both arterial and venous) junctions were free in all cases revised. *Microscopically*, there is a conspicuous intimal thickening, some lumina being reduced to a mere slit (Fig. 2). The endothelia are

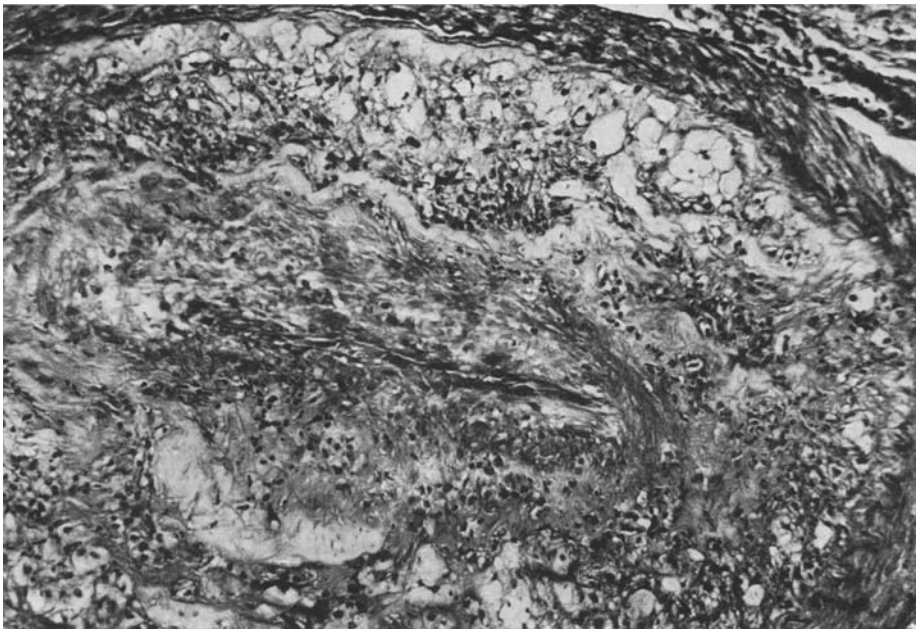

Fig. 2. Obliterated muscular artery in renal hilus. In centre cleft-shaped remnant of lumen; towards the periphery, in succession, fibrotic layer with muscle and mononuclear cells; zone of foam-cells and fibrohyalinosis; *at top* atrophic media. H.E. ×120

irregular in shape and distribution, someones are moderately basophilic. In places, isolated lymphoid cells adhere to the intimal surface. A thin layer of subendothelial infiltration consists of lymphocytes, few plasmocytes and polynuclears and spindle-shaped and oval elements with isolated mitoses; no typical "rejection cells" are evident. More deeply there follows the layer of elongated reticulum-shaped cells with light, oval, terminally rounded nuclei and rather abundant cytoplasm. Among them, delicate wavy elastic fibers and fine reticuline net are evident. The deep zone of the intima (i. e. its major portion) is penetrated by ill-defined hyaline masses, pools of metachromatic substance, foam cells, cholesterol crystal clefts with some small giant cells, areas of calcification and rare foci of intra- and extracellular haemosiderin. Toluidine blue and P.A.S. methods give stronger results in this dystrophic layer than in arteriolar intima. The inner elastic membranes show focal defects and moderate hyperplasia, which however, does not participate in the stenosis. The muscle cells are partly atrophic and in the media there are dispersed sporadic infiltrations of lymphocytes, rare polynuclears, minute groups of foam cells and intercellular metachromatic deposits. There is a considerable intra- and extracellular steatosis: in the intima, lipids are concentrated to the deeper areas whereas the subendothelial layers are negative. In the media, both dilated intercellular spaces and groups of muscle cells are infiltrated. Strongly steatotic segments of the media sometimes alternate with moderate intimal steatosis and vice versa. In summary, the dystrophic changes are concentrated to the deep portions of intima and to the media, whereas

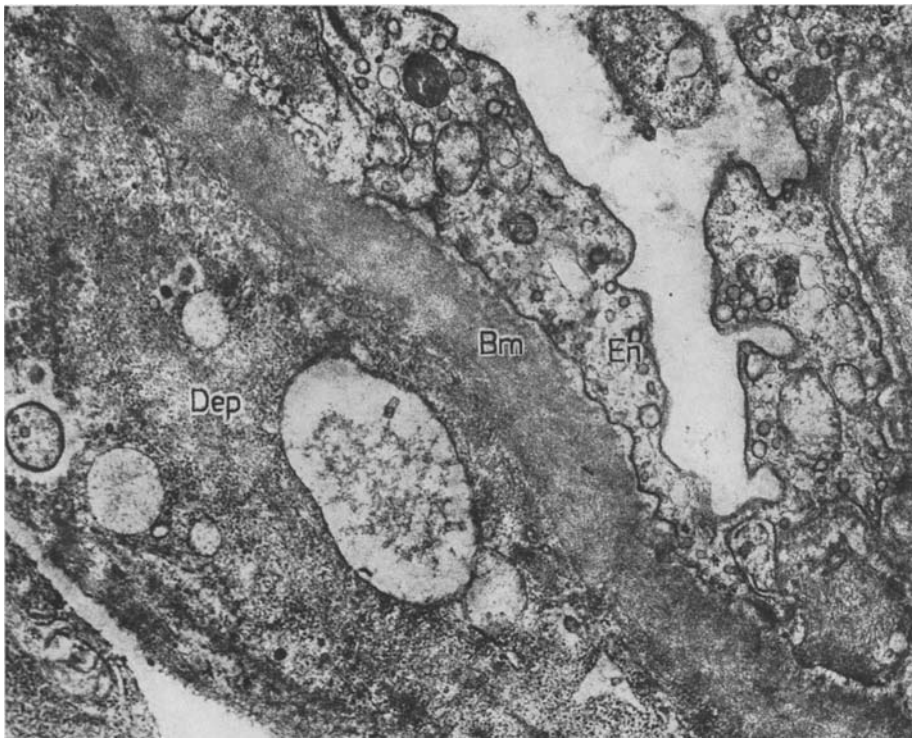

Fig. 3. Small cortical artery. Below endothelial basal membrane (*Bm*), area of deposits (*Dep*) consisting of granular substance of high and medium density, fragments of membranes and cytoplasm, and strongly osmiophilic globules. Numerous pinocytic vesicles in endothelial cell (*En*). ×23,200

in the subendothelium cellular infiltration and possibly proliferation preponderate. In three cases, both arteries and arterioles were massively affected. In one resected transplant the thickened intima resembled rather a picture of "fibrous endarteritis" but four months before, biopsy in the same patient had shown a typical above-described arteriolopathy. The latter was found also at autopsy in one transplant whose large muscular arteries displayed only moderate intimal fibrosis.

Electron microscopy is based on two *small cortical arteries* with preserved lumen and one obliterated from 2 resected transplants and one punction biopsy. The endothelia are thickened and contain multiple ribosomes and profiles of granular ergastoplasmic reticulum (GER), numerous pinocytic vesicles and smooth membrane-limited vacuoles (SMV), further some dense single membrane — coated inclusions, microbodies and multivesicular bodies. Intercellular spaces are partly dilated, the terminal bars, however, are tightly joined. We found no endothelial defects. The characteristic subendothelial deposits (Fig. 3) consist of finely granular substances of medium to focally high density, with disperse membranous, vesicular and lumpy fragments. Further coarse aggregates resembling disrupted lysosomes, fragments of erythrocytes and their peripheral membranes and myelin-like bodies are present. The lumen of *obliterated arteriole* (Fig. 4) is filled with cellular debris,

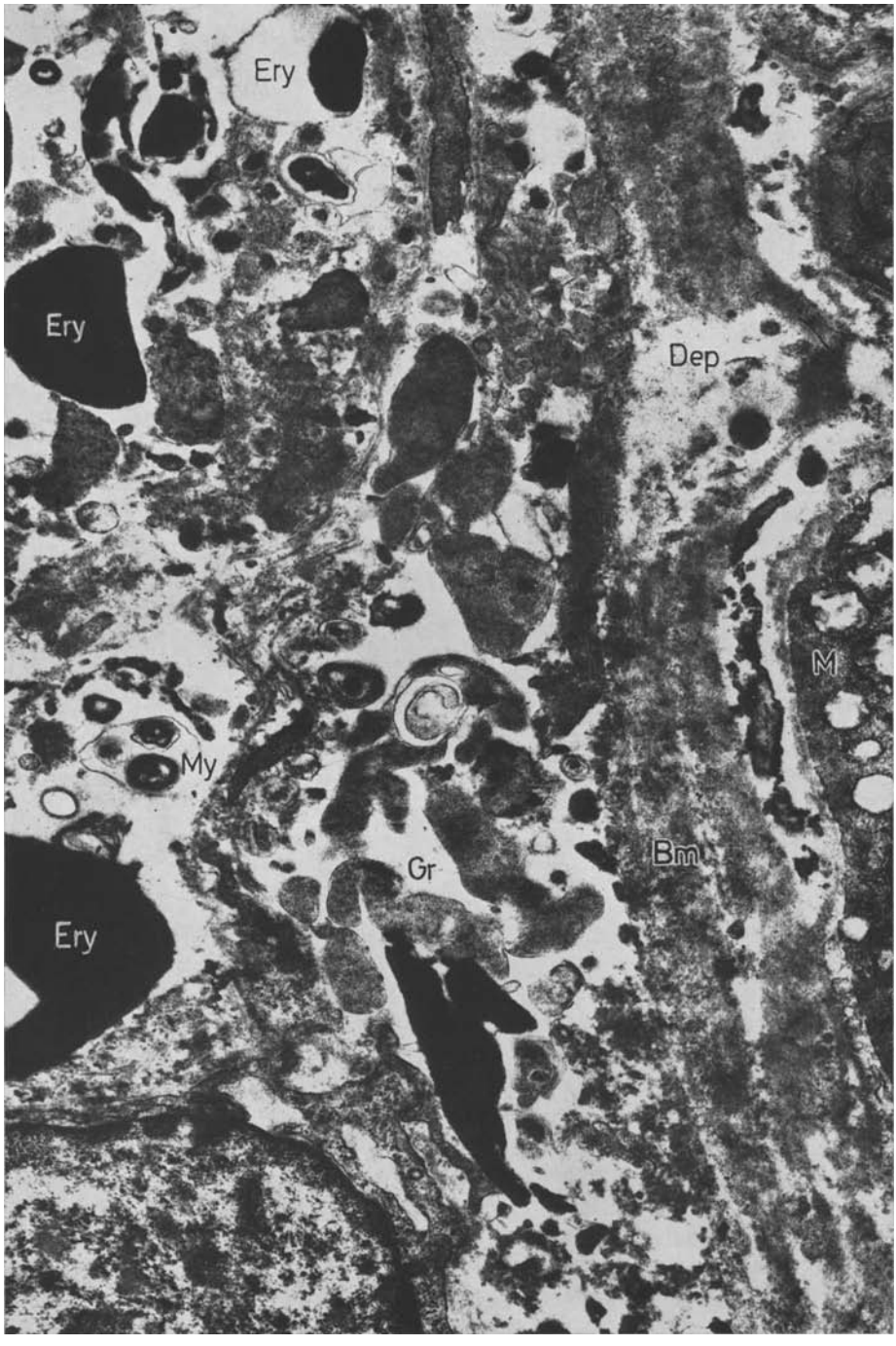

Fig. 4. Ultrastructure of obliterated cortical artery. Lumen indiscernible; intravascular spaces filled with disintegrating erythrocytes (*Ery*), granular (necrotic?) single-membrane-limited masses (*Gr*), and myelin — like bodies (*My*). Basal membrane (*Bm*) with focal interruptions by irregular deposits (*Dep*). At right, part of medial muscle cell (*M*). ×16,700

Fig. 5. Survey of ultrastructure of severely damaged but not obliterated arteriole. Extensive irregular deposits (*Dep*) in subendothelial space and intercellular spaces of media (*Ic*). Strong hyperplasia of granular ergastoplasmic reticulum (*Ger*) of muscle cells. At right, the lumen (*L*). ×12,700

membranous fragments, particles of basement membrane material and granular precipitates, partly enclosed in smooth membrane-coated bags. An outstanding structure are erythrocyte fragments with peeling peripheral membrane, crumbling of cytoplasm and apparent myelin bodies. The thickened basalis displays granular cavities and disperse osmiophilic globules. The focal calcification presents as an aggregate of delicate, spherically layered dense spicules. We found here no fibrin fibers nor preserved thrombocytes. The medial muscle cells exhibit strong degenerative changes (Fig. 5): polymorphia with peripheral clumping of chromatin and focal breaks of the plasmatic membrane. Areas of cytoplasm assume a coarse granular structure without discernible fibrils and contain indistinctly demarcated lysosome-like areas (Fig. 6). The ribosomes and GER are multiplied, the mitochondria are polymorphic, the peripheral pinocytic vesicles are irregular, some cells contain numerous SMV. Intercellular spaces are irregularly distended and filled with granular masses and cellular fragments, of a lesser extent than in the intima. The basal membranes are of variable thickness, with focal defects and translucent cavities. In summary, evident to massive signs of cellular irritation, dystrophy and disruption prevail.

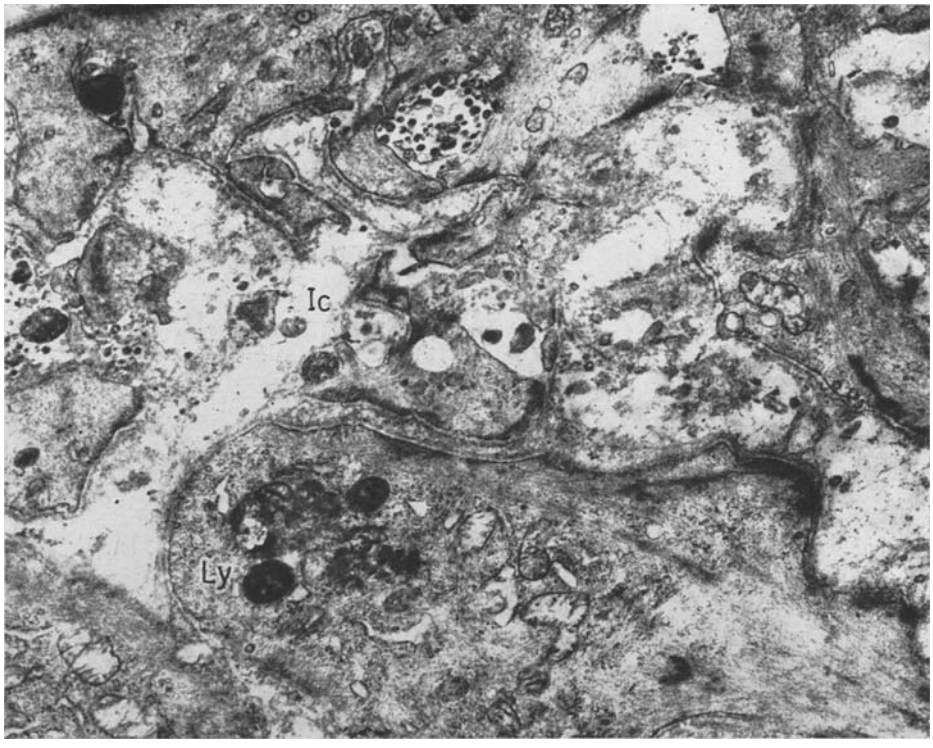

Fig. 6. Arteriolar muscle cells with large, poorly demarcated, lysosome-like bodies (*Ly*). Intercellular spaces (*Ic*) strongly irregularly dilated, with granular masses and cell debris. ×22,100

In one specimen of "subendothelial fibrosis" in a *large artery*, the elongated and spindle elements of optical microscopy are actually smooth-muscle cells (Fig. 7). Their fibrillary portion is often reduced and contains numerous fusiform densities and regular peripheral vesicles. The perinuclear zone is wide with abundant mitochondria and SMV, well developed GER and many ribosomes. Sporadic dense (lipid ?) spherical bodies are present, whereas no lysosomes are evident. The basal membrane is continuous and delicate, the intercellular spaces contain bundles of collagen and multilayered granular zones, probably elastic membranes, but no irregular deposists and debris. Consequently, there is an active, probably growing, smooth-muscular tissue without apparent dystrophy.

In transplants with *moderate to minimal arterial changes* (6 operation and 3 punction biopsies, 2 autopsies), the *interlobular and afferent* vessels are normal or present a usual picture of arteriolosclerosis characterized by slight to moderate fibrohyalinosis, elastic hyperplasia and deposits of fibrinoid (5 times), the same both in earliest and later posttransplantation periods. There is no obliteration or distinct stenosis. Foam cells, thrombosis and cellular invasion are lacking and staining for lipids (6 times) is negative except fibrinoid-hyaline deposits. In *major muscular arteries*, moderate to medium severe, diffuse or focal fibroelastic arteriosclerosis is current, generally proportional to the degree of arteriolosclerosis. Any

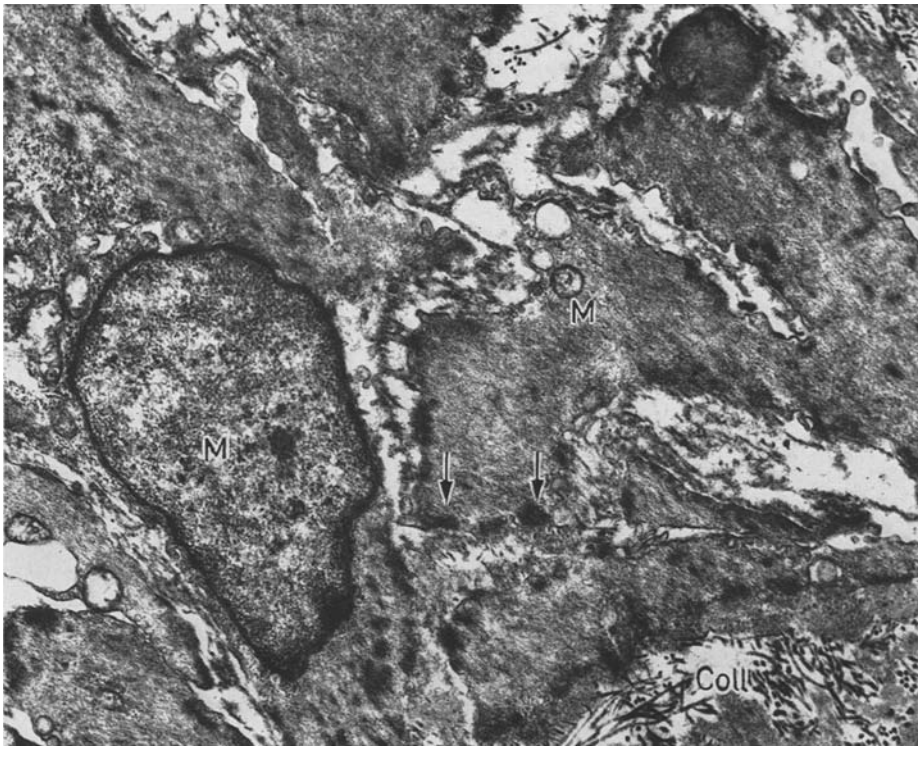

Fig. 7. Ultrastructure of spindle and reticular cells from "subendothelial fibrosis" of muscular artery. Muscle cells (*M*) with typical fusiform densities (arrow) without distinct dystrophic changes. In intercellular spaces, bundles of collagen fibers (*Coll*) and basal-membrane-like material ×18,500

evident stenosis, thrombosis, steatosis, fibrinoid or cellular infiltration are absent here. In small cortical arteries of 4 biopsies, *electron microscopy* reveals inconstant endothelial thickening with numerous pinocytic vesicles and SMV, twice also minute subendothelial cavities without actual cell defects. Many endothelia are rich in ribosomes and GER; also microbodies and multivesicular bodies occur. The thickened basalis exhibits dense and translucent lamellae. In all four biopsies, subendothelial granular deposits of medium to high density with some osmiophilic globules and lumps (lipid?), fragments of membranes and organelles, bundles of fine nonperiodic fibrils, small groups of collagen fibrils, extensions of unidentified cells and "empty" areas are conspicuous. In the muscle cells the Golgi zones, fairly numerous SMV, GER vesicles and free ribosomes are developed. Isolated cells show irregular shrunken nuclei, distended perinuclear spaces and granular cytoplasmic condensation interspersed with abundant, partly ribosome-surrounded cisterns. The plasmatic and basal membranes are continuous, discrete intercellular deposits resemble the subendothelial ones. No erythrocyte fragments, myelin bodies, cell disruption areas, thrombocytes or fibrin are evident and the general fine architecture is not distorted.

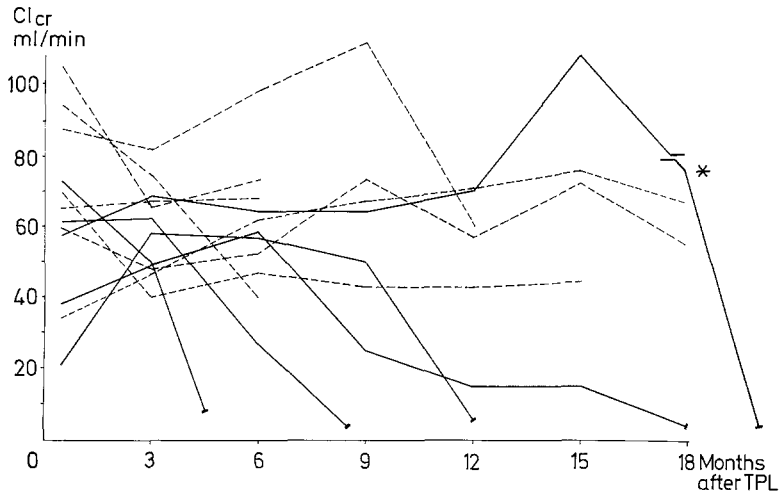

Fig. 8. Follow-up of average endogenous creatinine clerance in 5 patients with OA in renal transplant (—) as compared with a group of 7 patients (- - - -) lacking obliterative arterial lesion in biopsy. Failure of transplant function in the former group within 4—18 months; in one patient (*) transplant function satisfactory for 2 years, then downhill course to renal insufficiency

The lesions of *capillaries* and *veins* are less conspicuous and not proportional to the arterial ones. Advanced rejection is accompanied by focal capillary dilatation, hyperaemia, interstitial patches of erythrocytes and their fragments, while thrombosis is exceptional. Changes in glomerular capillaries have been described elsewhere (Rossmann *et al.*, 1969): severe OA tends among others to be accompanied here by focal capillary dilatation, hyperemia and leukostasis. Wide interstitial sinusoid spaces (postcapillary?) with polymorphic irregular (by places probably defective) endothelia and focal superficial layering of lymphoid cells are frequent in cellular rejection; they are usually surrounded by considerable infiltrates of lymphocytes, plasmocytes and pyroninophilic mononuclears. The wall and adventitia of some hilar veins are pervaded by scanty mononuclear cells; the intima, lumen and staining for lipids are irrelevant except isolated organizing thrombosis in one resected kidney. The ultrastructure of capillaries approaches that of slightly damaged arteries; some endothelia are thickened up to "sprouting capillary" pattern, but normal fenestrated areas are common too. A frequent finding is that of isolated erythrocytes and their rests in the interstitium; fibrin fibers (period cca 210 Å) were recorded only once here in an advanced rejection with OA. We have never seen platelet thrombi nor fibrin within a capillary as yet and in one case only the cytoplasmatic contact between an endothelium and a host blood cell was recorded (Rossmann *et al.*, 1969).

The *clinico-pathological correlations* will be studied in detail elsewhere (Reneltová *et al.*, 1970) and only some relevant results will be summarized here. The clinical course of the patients with OA is unfavourable, always leading to more or less rapid loss of function (Fig. 8). When compared with the group of slight vascular lesions, those with OA reveal a more frequent incidence of severe, protracted

rejection crises, an early and profound fall in the glomerular filtration rate and persisting altough not malignant hypertension. The nephrotic syndrome appears in both groups, but more frequently in that with OA. Both these groups, however, do not differ in the degree of incompatibility of the main transplantation antigens nor in the mode of immunosuppression. In the clinically inhomogenous group of slight vascular lesions (biopsy in various situations between the first moment of transplantation and 16 months afterwards), the clinical course proves more satisfactory. Three deaths and one transplant resection in this group are due to intercurrent complications. The rest of our transplanted patients, not subjected to biopsy, exhibits also favourable clinical course and is thought to be free from severe vascular lesions as yet.

Discussion

According to the presence or absence of severe OA in the transplant, we could divide our patients in 2 distinctly characterized groups. We shall now try to comment three problems, viz., the morphological specificity of the OA, its pathogenesis and diagnostic value.

In the group of slight arterial lesions, arteries are normal or suggest a banal moderate fibrinoid-hyaline and fibroelastic arterio(lo)sclerosis. Both those appear already in biopsies made very early, even at the moment of transplantation and consequently should exist still in the donor (in 7 cases a parent), i. e. the tissue transplanted is up to 36 years older than the recipient himself. None of the donors was hypertonic over 170/110 torr and nine had normal blood pressure. Moderate renal arteriolosclerosis is known to be common in normotonic subjects too, even in young ones (Biava *et al.*, 1964) and estimations of probable blood pressure levels based on the degree of arterio(lo)sclerosis in renal biopsy proved to be rather inaccurate (Rossmann, 1965). The corresponding "moderate" ultrastructural lesions are the subendothelial deposits at preserved integrity of endothelia and muscle cells, as observed also in hyaline arteriolosclerosis (Esterly and Glagov, 1963; McGee and Ashworth, 1963; Biava *et al.*, 1964; Fisher *et al.*, 1966), toxemia of pregnancy (Fisher *et al.*, 1969) and scleroderma (Pardo *et al.*, 1966). They consist of fine granular matrix and minute osmiophilic (lipid?) droplets (Bencosme and Morin, 1967), and appear larger and more frequent than optical microscopy reveals, affecting also medial intercellular spaces. In our observations, in addition coarser vesicular and membranous aggregates, probably cellular fragments, are identifiable, but no fibrin, thrombocytes, leuko- or erythrocytes. Endothelial and muscular ultrastructure seems to correspond to nonspecific irritation and cell hyperactivity, perhaps correlated with increased functional irritability of the vascular wall in earlier stages of rejection (Hollenberg *et al.*, 1968; Gardner *et al.*, 1968). Thus, our "moderate vascular changes" are hardly distinguishable from the banal, possibly preexistent arterio(lo)sclerosis. We are not sure as yet to ascribe some minor differences in the deposits to transplant-specific disorders.

On the other hand, the OA distinctly differs both from the above — discussed moderate changes and from the common benign arteriolosclerosis (Porter, 1964; Porter *et al.*, 1964; Ormos and Nemeth, 1964). The fibrinoid-hyaline deposits and elastic hyperplasia are less conspicuous or even absent; possibly they are merely signs of original arterio(lo)sclerosis superposed by a severe obliterating process.

Massive inflammatory infiltration and "fibrinoid necrosis" are absent here as well, in contrast to hypersensitivity arteritis, polyarteritis and oth. (Allen, 1962; Hume *et al.*, 1955; Dammin, 1966). Much more problematic is the differentation from lesions seen in malignant hypertension, which the transplant vascular lesions have been found to resemble (Kincaid-Smith, 1967) and interpreted as residues of organized parietal thrombi. We ourselves could not visualize thrombosis, recent or organized; possibly however, at the stage examined it was already past recognition. Segmental necrotic and fibrous glomerular lesions of malignant hypertension were never seen in our transplants and neither donors nor recipients ever exhibited clinical signs of malignant hypertension. Both the main arterial trunk and the suture were always free, both in autopsy and (at least macroscopically) in surgical revisions, so that any "retrostenotic obliterative endarteritis" is hardly to be spoken of, as well as rare patterns of intimal fibroplasia (Aboumrad *et al.*, 1963). Recently, severe arterial stenosis has been observed in treated malignant hypertension (Cormack *et al.*, 1958) and after long term haemodialysis treatment (Tolnai *et al.*, 1969). Severe fibroelastic or fibrous intimal hyperplasia is characteristic however, here, as observed also by ourselves in similar cases.

A substantial ultrastructural feature of OA is severe cellular wasting to disruption (necrobiosis?) of muscular (in obliterated areas also endothelial) cells, disintegrating erythrocytes and various cell rests, but no fibrin or intact platelets; since the latter disrupt rapidly outside the lumen (Hovig *et al.*, 1968), their occurence cannot be fully excluded. Fibrin and blood platelets were described in both experimental and clinical allotransplants (Porter *et al.*, 1964; Dempster *et al.*, 1964; Kincaid-Smith, 1964, 1967) and xenotransplants (Rowlands *et al.*, 1967), but earlier stages of rejection were probably involved here. We have not seen the thrombo-haemorrhagic acute rejection as yet (Hamburger *et al.*, 1962, 1965; Hamburger, 1965; Dormont and Leski, 1967; Loewenhaupt and Nathan, 1968; Starzl *et al.*, 1968). — The OA consequently seems to exhibit a rather distinctive "destructive" morphology, different from arteriolosclerosis and from various other obliterative lesions as well. The changes in OA are focal but dense (Darmady *et al.*, 1964; Dunea *et al.*, 1964) and minor vessels are probably affected earlier (Porter, 1964). Capillary lesions are much less conspicuous and do not essentially differ from those seen in autotransplants, nonspecific inflammation and oth. (Schoeff, 1963; Wiener *et al.*, 1969).

Various pathogenetic problems in transplant vascular lesions have been summed up by Porter (Porter *et al.*, 1963; Porter, 1964). No distinct differences in irradiation, corticotherapy, pretransplantation — ischaemia, selection of donors and immunotypization exist between the two groups of our sample. The benign hypertension alone, though present before biopsy in all patients of the OA-group and though perhaps not irrelevant, could hardly explain all massive arterial changes described above. We have been lacking yet immunofluorescence studies (Lange *et al.*, 1966; Horowitz *et al.*, 1963, 1965; Williams *et al.*, 1967; Porter *et al.*, 1968; Williams *et al.*, 1968) and cannot bear own contribution to these delicate aspects.

In two resected transplants we noticed a narrow subendothelial infiltration of poorly differentiated mononuclear cells and a muscle-cell layer in the relatively

"quiet" inner zone as compared with severe dystrophy of deep intima and media: sometimes, an impression of "vessel in vessel" is created. This poses the question, as expressed also by Trentin (Trentin, 1966) whether these subendothelial cells do not actually originate from the host, whose blood monocytes would be capable of differentation to endothelia, fibroblasts, spongiocytes and possibly muscle cells (Florey *et al.*, 1962). They would gradually cover the original — biologically inacceptable vascular surface to block its direct contact with the host's blood. Bohle (Bohle, 1968) reports caryological studies in an allotransplant from a male donor, the subendothelial cells of which are likely to originate from the female recipient. Should this concept of heterogenous vessel layers be verified, then the described OA would be entirely unique, pathogenetically different from all lesions discussed above: the biological equilibrium attained on the inner surface would be paid for however by a stenosis to occlusion of the lumen and severe (immunological and/or anoxic ?) degeneration of deeper layers, as demonstrated above in the ultrastructure. Studies in different organs (Flax and Barnes, 1966; Kosek *et al.*, 1968) will show whether the OA is characteristic for kidney only or (rather ?) is a general manifestation of biological incompatibility.

For practical purposes, the OA is rather easy to identify; its frequency in our sample is comparable with that of vascular rejections of Porter (Porter *et al.*, 1963) whereas Hamburger (Hamburger *et al.*, 1964; Hamburger, 1967) as well as Hume (Hume, 1966) report only rare cases of severe vascular lesions. At the time we diagnosed the OA, severe functional disturbances were always present and out of 5 patients thus afflicted three died within 5—12 months and the fourth is surviving under chronic haemodialysis (transplantectomy 3 months after biopsy). Once we observed some "fibrous healing" of OA in repeated biopsy, without effective functional improvement; in early stages however, reversibility of vascular lesions is conceded (Dempster *et al.*, 1964; Dunea *et al.*, 1964). Whenever the OA is absent in the biopsy, a more favourable outlooks can be expected though not guaranteed; even in such cases severe vascular changes may develop later. Once we found OA even after a 2 years-period of satisfactory course. The sure diagnosis of OA does not seem easy without biopsy as yet: clinically suspect are, however, persistent hypertension, nephrotic syndrome and frequent and protracted rejection crises followed by a torpid decrease of the transplant function.

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References

Aboumrad, M. H., Fine, G., Horn, R. C.: Intimal hyperplasia of small mesenteric arteries. Arch. Path. **75**, 196—200 (1963).

Allen, A. C.: The kidney. New York: Grune & Stratton 1962.

Bencosme, S. A., Morin, P. A. F.: Ultrastructural pathology of the glomerulus. Lesion of arteries and glomeruli in hypertension. In: Dalton-Haguenau, Ultrastructure of the kidney. NewYork: Acad. Press 1967.

Biava, C. G., Dyrda, J., Genest, J., Bencosme, S. A.: Renal hyaline arteriolosclerosis, an electron-microscopic study. Amer. J. Path. **44**, 349—363 (1964).

Bohle, A.: Über die pathologische Anatomie der Nierentransplantation. Langenbecks Arch. klin. Chir. **322**, 87—93 (1968).

Cormack, Mc L. J., Beland, J. E., Smeckloth, R. E., Corcoran, A. C.: Effects of antihypertensive treatment on the evolution of the renal lesions in malignant nephrosclerosis. Amer. J. Path. **34**, 1011—1021 (1958).

Dammin, G. J.: Renal transplants: correlation of histologic pattern with function. In: Mostofi-Smith, The kidney. Baltimore: Williams & Wilkins 1966.

Darmady, E. M., Offer, J. M., Stranack, F.: Study of renal vessels by microdissection in human transplants. Brit. med. J. **1964**, No. 5415, 976—978.

Dempster, W. J., Harrison, C. V., Shackman, R.: Rejection process in human homotransplanted kidneys. Brit. med. J. **1964**, No. 5415, 969—976.

Dormont, J., Leski, M.: La pathologie du rein transplanté. Presse méd. **75**, 57—58 (1967).

Dunea, G., Hazard, J. B., Kolff, W. J.: Vascular changes in renal homografts. J. Amer. med. Ass. **190**, 199—202 (1964).

Esterly, J. A., Glagov, S.: Altered permeability of the renal artery of the hypertensive rat, an electron microscopic study. Amer. J. Path. **43**, 619—638 (1963).

Fisher, E. R., Pardo, V., Paul, R., Hayashi, T. T.: Ultrastructural studies in hypertension (toxemia of pregnancy). Amer. J. Path. **55**, 109—131 (1969).

— Stable, E. P., Pardo, V.: Ultrastructural studies in hypertension. Lab. Invest. **15**, 1409—1433 (1966).

Flax, M. H., Barnes, B. A.: The role of vascular injury in pulmonary allograft rejection. Transplantation **4**, 66—78 (1966).

Florey, H. W., Green, S. J., Kiser, J., Poole, J. C. F.: The development of the pseudointima lining fabric grafts of the aorta. Brit. J. exp. Path. **43**, 655—660 (1962).

Gardner, L. B., Guttmann, R. D., Merrill, J. P.: Renal transplantation in the inbred rat. Transplantation **6**, 411—418 (1968).

Gee, Mc W. G., Ashworth, C. T.: Fine structure of human hypertensive arteriolopathy (abstr.). Fed. Proc. **22**, 485 (1963).

Hamburger, J.: Résultats de 45 homotransplantations rénales humaines. Actualités néphrol. Hôp. Necker **6**, 83—123 (1965).

— A reappraisal of the concept of organ rejection based on the study of homotransplanted kidneys. Transplantation **5**, 870—884 (1967).

— Crosnier, J., Dormont, J., Réveillaud, R. J., Hors, J. H., Alsina, J.: Homotransplantation rénale humaine. Presse méd. **73**, 2793—2798 (1965).

— Vaysse, J., Crosnier, J., Auvert, J., Dormont, J.: Homotransplantation rénale chez l'homme. Presse méd. **70**, 671—674, 1962.

Hollenberg, N. K., Retik, A. B., Rosen, S. M., Murray, J., Merrill, J. P.: The role of vasoconstriction in the ischemia of renal allograft rejection. Transplantation **6**, 59—69 (1968).

Horowitz, R. E., Burrows, L., Paronetto, F., Dreiling, D., Kark, A. E.: Immunologic observations on homografts. Transplantation **3**, 318—325 (1965).

— — — Wildstein, W.: Immunocytochemical observations on canine kidney homografts. Fed. Proc. **22**, 274 (1963).

Hovig, T., Jörgensen, L., Packham, M. A., Mustard, J. F.: Platelet adherence to fibrin and collagen. J. Lab. clin. Med. **71**, 29—40 (1968).

Hume, D. M.: Renal homotransplantation in man, studies in 63 cases. In: Mostofi-Smith, The kidney. Baltimore: Williams & Wilkins 1966.

— Merrill, J. P., Miller, B. F., Thorn, G. W.: Experiences with renal homotransplantation in the human. J. clin. Invest. **34**, 327—382 (1955).

Kincaid-Smith, P.: Vascular changes in homotransplants. Brit. Med. J. **1964**, No 5376, 178—179.

— Histological diagnosis of rejection of renal homografts in man. Lancet **1967II**, 849.

Kosek, J. C., Hurley, E. J., Lower, R. L.: Histopathology of orthotopic canine cardiac homografts. Lab. Invest. **19**, 97—112 (1968).

Lange, K., Treser, G., Sagel, J., Ty, A., Wassermann, E.: Routine immunohistology in renal diseases. Ann. intern. Med. **64**, 25—40 (1966).

Loewenhaupt, R., Nathan, P.: Platelet accumulation observed by electron microscopy in the early phase of renal allotransplant rejection. Nature (Lond.) **220**, 822—825 (1968).

Ormos, J., Nemeth, A.: Morphologische Beobachtungen bei der menschlichen Nierentransplantation. Virchows Arch. path. Anat. **337**, 395—406 (1964).

Pardo, V., Fischer, E. R., Stable, E. P., Rodnan, G. P.: Ultrastructural studies in hypertension. Lab. Invest. **15**, 1434—1441 (1966).

Porter, K. A.: Pathological changes in transplanted kidneys. In: Starzl, Experience in renal transplantation. Philadelphia: Saunders 1964.

— Andres, G. A., Calder, M. W., Dossetor, J. B., Hsu, K. C., Rendall, J. M., Seegal, B. C., Starzl, T. E.: Human renal transplants, immunofluorescence and immunoferritin studies. Lab. Invest. **18**, 159—171, (1968).

— Calne, R.Y., Zukoski, C. F.: Vascular and other changes in 200 canine renal homotransplants treated with immunosuppressive drugs. Lab. Invest. **13**, 809—824 (1964).

— Thomson, W. B., Owen, K., Kenyon, J. R., Mowbray, J. F., Peart, W. S.: Obliterative vascular changes in four human kidney homotransplants. Brit. med. J. **1963**, No. 5358, 639—645.

Reneltová, I., Jirka, J., Rossmann, P., Málek, P.: Clinico-morphological correlations in the biopsy of renal allotransplants. In preparation (1970).

Rossmann, P.: Histopathology of percutaneous renal biopsies [in Czech]. Diss. thesis, Charles Univ., Hradec Králové, 1965.

— Jirka, J., Brod, J., Málek, P.: Histologie und Feinstruktur der Biopsien allotransplantierter Nieren. Beitr. path. Anat. **138**, 377—404 (1969).

Rowlands, D. T., Kirkpatrick, Ch. H., Vatter, A. E., Wilson, W. E. C.: Immunologic studies in human organ transplantation. Amer. J. Path. **50**, 605—622 (1967).

Schoeff, G. I.: Studies on inflammation — growing capillaries, their structure and permeability. Virchows Arch. path. Anat. **337**, 97—141 (1963).

Simonsen, M., Buemann, J., Gammeltopf, A., Jensen, F., Jörgensen, L.: Biological incompatibility in kidney transplantation in dogs. Acta path. microbiol. scand. **32**, 1—35 (1953).

Starzl, T. E., Lerner, R. E., Dixon, F. J., Groth, C. G., Brettschneider, L., Terasaki, P. I.: Schwartzman reaction after human renal transplantation. New Engl. J. Med. **278**, 642—648 (1968).

Tolnai, G., Sarkar, K., Jaworski, Z. F., Irvine, A. H.: Obliterative intimal fibrosis in kidneys of dialyzed patients. Presented at the 4th Internat. Congr. Nephrol., Stockholm, 1969.

Trentin, J. J.: The arterial obliterative lesions of human renal homografts. Ann. N.Y. Acad. Sci. **129**, 654—656 (1966).

Wiener, J., Lattes, R. G., Pearl, J. S.: Vascular permeability and leukocyte emigration in allograft rejection. Amer. J. Path. **55**, 295—327 (1969).

Williams, G. M., Hume, D. M., Hudson, R. P., Morris, P. J., Kano, K., Milgrom, F.: „Hyperacute" renal homograft rejection in man. New Engl. J. Med. **279**, 611—618 (1968).

— Lee, H. M., Weymouth, R. F., Harlan, W. R., Stanley, C. M., Millington, G. A., Hume, D. M.: Studies in hyperacute and chronic renal homograft rejection in man. Surgery **62**, 204—212 (1967).

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