THE INTRARENAL VASCULAR PATTERN OF THE CANINE RENAL ALLOGRAFT

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Extensive damage to the vessels has been ascribed a pathogenic significance in the graft rejection by producing ischaemia (Janigan, Williams, Tyler and Dempster, 1964; Porter, 1965). However, the mechanism by which vascular lesions produce ischaemia in the acute allograft reaction has not been completely investigated. This was the reason why we began to study the course, type and extent of vascular damage in various phases of rejection. No immuno-suppressive treatment was given.

Material

One series consisting of 21 allografts and 9 autografts was examined with a combined stereomicroangiographic and histologic technique (Ljungqvist, 1963; Almgard, Granberg, Lagergren and Ljungqvist, 1966). A second series of 5 allografts was followed with renal function tests and with the technique mentioned above.

Technique

General anaesthesia was induced by intravenous injection of thiopental. As a rule the left kidney was transplanted to the right iliac region. Before the vessels were anastomosed the organ was perfused with a mixture of heparin and isotonic saline. As a rule arteries and veins were anastomosed end-to-end to the iliac artery and vein and the ureter was anastomosed to the bladder. The allografts were removed 1-10 days after the operation. Most of the autografts were followed for 2-29 days.

In the second series the donor kidney was examined in the following way. A catheter was passed into the renal vein via the ipsilateral femoral vein. The renal blood flow was measured with a direct electromagnetic flowmeter on the renal artery. The flow was also estimated by the Xenon133 wash-out technique. After saturation with 2.5 mg vitamin B12 a single dose of 12-16 mg of PAH and 2 microCurie CO57 vitamin B12 was given. Samples were drawn from the renal vein and a peripheral artery 4 and 10 min afterwards. The extraction of PAH and CO57 vitamin B12 was measured.

The same surgical techniques as in series one was used in these cases. After the transplantation the functional study was repeated and the catheter in the renal vein was inserted via a vein in the pelvis. The graft was exposed 4-6 days later and the renal functional study was performed in the same manner. Afterwards the graft was angiographed and microangiographed as in the first series.

Results and discussion

The allografts removed after 2-3 days exhibited histological alterations such as infiltration by graft-reaction cells, vascular changes, tubular atrophy, oedema, necrosis and fibrosis. All these alterations have been well documented previously (Dempster, 1953; Kountz, Williams,

The allografts in the first series displayed a pathologic vascular pattern with striking venous filling; the venous tree in the greater part of the cortex was filled. Several large stellate and interlobular veins were as clearly visualized as the cortical arteries. In some of the grafts, however, the peripheral part of the cortex displayed no arterial filling, only the veins being visualized. Extensive venous filling was common to all the grafts with necrosis of the peripheral cortex, and was observed in 2 grafts with peripheral cortical oedema and no necrosis.

To study more closely the paths by which the contrast medium passed from the arterial to the venous side microangiographed blocks with abundant venous filling were serially sectioned and stained for histologic examinations. In 5 series pathologic arteriovenous communications were verified. The communications were found where arterioles coursed tangentially to larger veins, and the walls of both arterioles and veins were necrotic. Histologically, the anastomoses consisted of perforations in these damaged arteriole and vein walls. Anastomoses were found both in the peripheral and middle cortex and also in the juxtamedullary zone.

The autografts were for the most part histologically normal. Microangiographic examination disclosed a normal microangiographic architecture, previously described by von Kügelgen, Kuhlo, Kuhlo and Otto (1959).

In 4 transplants there was also irregular filling of the cortical veins. This was sparse and irregular and associated with extensive filling of the arterial tree and capillaries. While it would seem to be generally accepted that arteriovenous anastomoses occur to some extent in the normal pelvis wall and the renal capsule, it is a matter of dispute whether such vessels are normally present in the actual renal parenchyma (Hammersen and Staubesand, 1961; Rosenbauer, 1965). No intraparenchymatous anastomoses have been found in human kidneys examined by microangiography (Ljungqvist, 1963), nor were any seen in the autografts of the present series.

Since anastomoses were found in vital cortical parenchyma proximal to the subcapsular necrosis and in 2 grafts devoid of necrosis, our findings suggest that vascular impairment and formation of arteriovenous anastomoses is part of the graft reaction and not secondary to the tissue necrosis.

In order to determine the functional significance of these findings renal function studies were performed in a second series. Some of our data are summarized in Table I. There was a marked decrease in renal blood flow measured by the electromagnetic flow-meter and the

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<td>64</td>
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<td>B</td>
<td>142</td>
<td>53</td>
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<td>C</td>
<td>454</td>
<td>138</td>
<td>0.69</td>
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<td>D</td>
<td>138</td>
<td>74</td>
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<td>138</td>
<td>63</td>
<td>0.66</td>
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<td>t = 10.6**</td>
<td>6.4*</td>
<td>11.2**</td>
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* p < 0.01 ** p < 0.001
Xenon wash-out technique. The reduction was expected and has been earlier documented (Dempster, 1955; Williams, Williams, Kountz and Dempster, 1964; Cohn and Kountz, 1964; Jackson and Mannick, 1964; Truniger, Stanley, Rosen, Kriek, Merril and Murray, 1965).

The extraction of PAH was reduced; this might depend upon the functional impairment of the tubular tissue but could also be the result of a shunting mechanism. Accumulation of PAH in vitro has been demonstrated in slices of renal cortex in spite of advanced rejection (Nathan, Foulkes, Wilchins and Miller, 1962). This observation together with our results would speak in favour of a shunting mechanism.

The extraction of CO\textsuperscript{57} vitamin B\textsubscript{12} was greatly reduced and is certainly due to shunting of blood past glomerular tissue. The glomeruli were usually well preserved, with no sign of thickening of the capillary walls or fibrinoid staining (Almgard et al., 1966). The reduced extraction of CO\textsuperscript{57} vitamin B\textsubscript{12} is in accordance with the findings of Herdman, Michael, Vernier and Kelly (1966), in human transplants with signs of rejection, as they found a reduction of the filtration fraction.

The angiography disclosed filling of the veins in all the grafts in this series. Only one of them has yet been microangiographed and revealed a pathologic venous filling. Thus it seems almost certain that the other grafts will also have the same microangiographic pattern.

**Summary**

The effect of the allograft reaction on the vascular pattern of the kidney has been examined by a combination of stereomicroangiography and histology in a series of 21 dogs; autografts served as controls of the effect on the vessels of the operation. In a second series of 5 dogs renal function studies and anatomical studies were performed.

Allografts with signs of rejection disclosed at microangiography a pathologic filling of the veins and in serial sections of microangiographed specimens pathologic arteriovenous communications were found. Our studies suggest that the renal allograft reaction can lead to the formation of pathologic arteriovenous anastomoses and that they contribute to the functional impairment of the graft.

**REFERENCES**


Acta med. scand., Suppl. 401.


DISCUSSION

MERRILL (Boston): Dr. Stanley Rosen and Dr. Hollenberg in our laboratory have made some observations which bear on Dr. Almgard’s presentation. Using the Krypton washout technique which measures the distribution of blood flow through the various segments of the kidney, as well as radio autographs which visually confirm these findings, they have demonstrated that during the rejection of dog kidneys blood is diverted from the cortex, in all probability, to the medulla. In serial studies one can see a progressive diminution of cortical blood flow, i.e. flow to compartment I, which actually appears prior to the rise in blood urea nitrogen as the dog is rejecting his allograft. Radio autography done on kidneys during a similar sequence shows blood being diverted from the cortex in a rather patchy fashion. The whole picture during early rejection is that of blood bypassing segments of cortex and being redistributed to the corticomedullary and medullary areas. This actually takes place before a total diminution in renal function, at least as measured by the glomerular filtration rate.

The CHAIRMAN: Thank you very much, Dr. Merrill.

Are there any other questions? You see how difficult these correlations between anatomy and function are.

If there is no other question, I should like to ask Dr. Almgard if he is sure that this arteriovenous anastomosis he has shown us is really significant.

It could be so that the first phenomenon is, let us say, a thrombosis or a spasm of the arterial tree, with a shunt of the blood to the medulla as Dr. Merrill has shown to us, and that the ruptures in the wall of the artery are secondary to the ischaemia.

ALMGARD (Stockholm): We have studied several series of these, and we found that in this sort of anastomosis, they develop about two to three days after the transplantation.

It starts with infiltration in the vein wall. We think that these deposits of graft reaction cells are the beginning of the damage to the rest of the wall. The damage starts, then, with a thrombosis.

I may also say that we have the same findings when we give immunosuppressive treatment. The difference is that these communications, in some species, develop already after a week, but sometimes they may take fourteen days up to several months.

We may also say that we have found specimens where these anastomoses have healed. We have the scarred tissue, and we have thrombosis in the artery and the vein.

So it seems even that with immunosuppressive treatment, we may prolong and prevent some of these anastomoses.