VASCULAR LESIONS RESEMBLING POLYARTERITIS NODOSA IN RATS UNDERGOING PROLONGED STIMULATION WITH OESTROGEN

J. H. CUTTS

From the Cancer Research Laboratory and Department of Medical Research, University of Western Ontario, London, Canada

Received for publication January 27, 1966

VASCULAR lesions in animals, similar to those of polyarteritis nodosa, have been reported in a variety of species. Their occurrence has been noted in deer (Lupke, 1906 ; Jaeger, 1909), cattle (Nieberle, 1928 ; Trawinski, 1929 ; Knosel, 1931), dogs (Balo, 1924), mice (Lowenthal, 1931) and rats (Wilens and Sproul, 1938). Experimentally, similar vascular lesions have been described in the systemic and pulmonary vessels of rats given 4′-fluoro-10-methyl-1,2-benzanthracene (Hartman, Miller and Miller, 1959 ; Tange and Newman, 1963), and in rats made hypertensive by clipping the renal artery (Wilson and Byrom, 1939), by cellophane wrapping of the kidneys (Freidman, Jarman and Klemperer, 1941 ; Smith, Zeek and McGuire, 1944), or by administration of salt and deoxycorticosterone (Selye, Hall and Rowley, 1943). Polyarteritis has been reported also in rabbits and guinea-pigs injected with foreign serum (Harris and Friedricks, 1922 ; Vaubel, 1932 ; Rich and Gregory, 1943), and in rats fed thiouracil (Marine and Baumann, 1945). We wish to record the occurrence of vascular lesions, indistinguishable from those of polyarteritis nodosa in man, in rats undergoing prolonged exposure to oestrogen stimulation.

MATERIALS AND METHODS

Polyarteritis nodosa was an incidental finding among a group of 364 hooded (H/C strain) female rats that had been pelleted with a tablet of oestrone for studies of hormonally induced mammary tumours. Single pellets of pure oestrone, weighing 8–10 mg., had been implanted s.c. between the shoulder blades. About half (46 per cent) of the animals were intact, the remainder had been hysterectomized at the age of 23 days, but the ovaries remained intact. All animals were maintained on a commercial cube diet and tap water *ad libitum*, and were weighed and examined weekly.

RESULTS

Of the 364 rats pelleted, vascular lesions were found in 43, an incidence of 11·8 per cent. The average age at pelleting had been $49{\cdot}6 \pm 1{\cdot}27$ days : the mean age at the time a diagnosis of polyarteritis was made was $452{\cdot}1 \pm 11{\cdot}7$ days. Fig. 1 shows the relationship between age and occurrence of polyarteritis nodosa in rats treated with oestrone.

The appearance of vascular lesions seemed to be a relatively late occurrence in these animals. No vascular disease was seen in rats earlier than 350 days of age, and 75 per cent of the cases occurred after 390 days of age. In this same group of animals, the incidence of mammary tumours was 87 per cent, with most of the tumours arising between 221 and 358 days. The mean age for tumour

appearance was 303 days. The incidence of polyarteritis was only slightly higher in the hysterectomized animals (53 per cent) than in the intact rat (47 per cent). In a group of 67 non-treated rats kept under close observation for 18 months, no vascular lesions have been found.

At the time of autopsy, oestrone pellets were recovered from 88 per cent of the animals. The rats had borne pellets for 397·6 $\pm$ 2·8 days, and had absorbed a total of 2·8 mg. of oestrone per rat during this period.

While the extent and distribution of the lesions were widespread, in general there was considerable variation from animal to animal. The mesenteric vessels

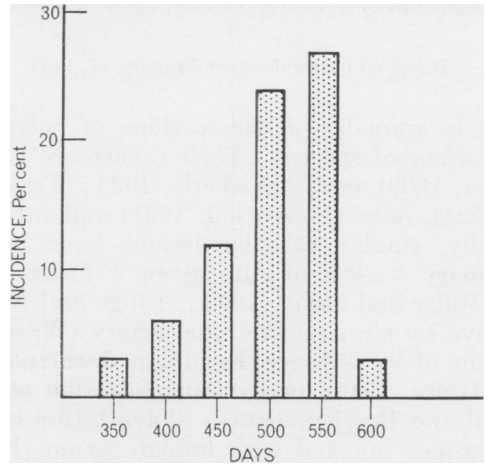


FIG. 1.—The incidence of polyarteritis nodosa, with age, in rats treated with oestrone.

were affected particularly, and from the duodenum to the caecum, the whole of the mesentery was thickened and indurated. The vessels showed striking alterations and were enlarged, tortuous and nodular ; the size of the individual branches of the mesenteric arteries was grossly increased, the diameter very often exceeding that of the aorta. The entire length of the vessels was studded with nodular protrusions (aneurysmal dilalations) many of which were occluded by thrombi. Mesenteric and peripancreatic lymph nodes were slightly enlarged.

Microscopically, the lesions were indistinguishable from those seen in man. The lesions were confined to arteries ; arterioles were involved rarely, so that vascular lesions in the mucosa or muscle of the alimentary tract were encountered infrequently. All stages of vasculitis could be found, but subacute or chronic reparative changes occurred most frequently. Acute necrotizing lesions were rare.

EXPLANATION OF PLATE

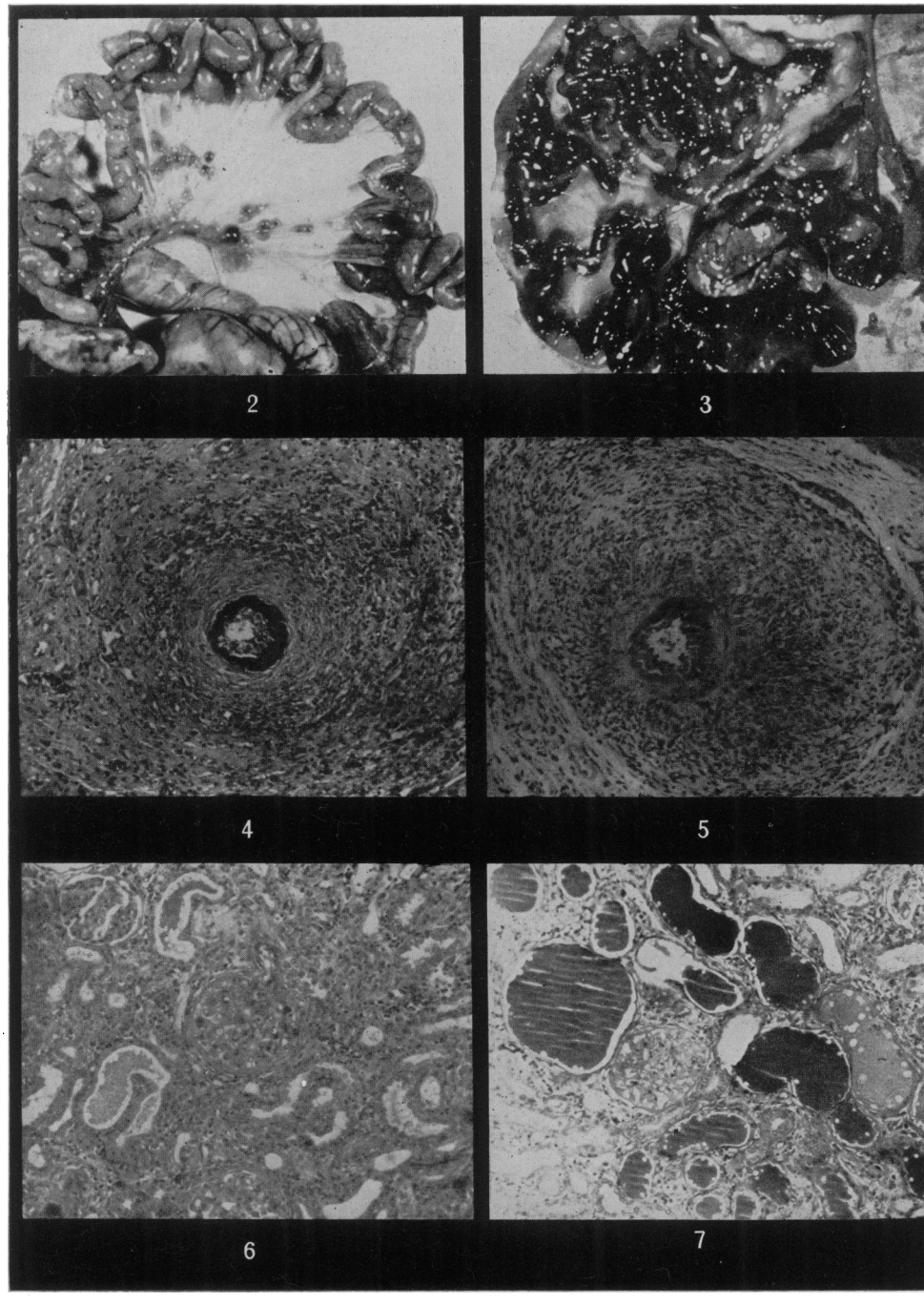
FIG. 2.—Mesentery showing minimal vascular changes. The nodular character of the lesions is apparent.

FIG. 3.—Mesentery showing gross involvement with periarteritis nodosa. The vessels are greatly enlarged, twisted and tortuous and engorged with blood.

FIG. 4.—Microscopic changes of polyarteritis nodosa in splenic vessels from the same animal as Fig. 2. H. and E. $\times$220.

FIG. 5.—Mammary vessels from same animal as Fig. 2 showing narrowed lumen and thickened walls of polyarteritis. H. and E. $\times$220.

FIG. 6 and 7.—Kidney changes in polyarteritis nodosa. The tubules are dilated and obstructed by hyaline casts. H. and E. $\times$220.



Cutts

In vessels showing subacute changes, the intima was replaced by a thick layer of fibrin, often covered by a layer of regenerating endothelium. The muscle and adventitia were destroyed and replaced by a thick band of proliferating smooth muscle cells which gradually merged with a vascular granulation tissue containing many neutrophil and eosinophil leucocytes and plasma cells. Where chronic lesions were found, the wall of the affected vessels were greatly thickened and replaced by a fibro-cellular or fibrous connective tissue. Many of the vessels showed aneurysmal dilalations, and rupture occurred as a result of the loss of muscle and the consequent stretching of the vessels.

Polyarteritis nodosa was found in almost every organ and tissue examined, except the brain. Secondary changes resulting from obstructed blood supply were seen in the kidneys, spleen and pancreas, but definite infarction was not a feature.

DISCUSSION

The incidence of polyarteritis nodosa (11·8 per cent) which we have noted in rats subjected to continuous stimulation by oestrogen, does not differ significantly from that reported by Wilens and Sproul (1938) as occurring spontaneously in old rats. However, the great discrepancy in the age at which the disease occurred, should be noted. In the series studied by Wilens and Sproul, polyarteritis nodosa occurred late in life, with the average age being 856 days. No such vascular lesions were found in rats earlier than 500 days of age. In our series, the disease was manifest much sooner—between 350–550 days of age, with the average age being 452 days. It should be added also, that the incidence of polyarteritis reported here is probably low, since no particular pains had been taken to uncover vascular lesions, and in many of the animals in this group, only the mammary glands and mammary tumours were examined.

Some relationship between the development of polyarteritis nodosa and the presence of oestrogens seems to be inferred by the decided predilection of the female animal to develop the disease. Marine and Bauman (1945) and Wilens and Sproul (1938) both report a 2 : 1 incidence in the female, relative to the male. Oestrogens have been implicated in other vascular lesions. Beall, Simpson, Pritchard and Harms (1963) reported a high incidence of aortic rupture in turkeys fed diethylstilbestrol, and anovulatory drugs (combinations of oestrogens and progestins) have been linked by some to the occurrence of thrombophlebitis in the human (Powell, Guest and Pond, 1965 ; Jordan, 1961 ; Danforth, Manalo-Estrella and Buckingham, 1964).

There is much evidence supporting the belief that polyarteritis nodosa is an expression of hypersensitivity (Gruber, 1925 ; Rich and Gregory, 1943 ; McLetchie, MacDonald and Cutts, 1957). Most of the rats showing polyarteritis also showed lesions in the adrenals, and it may be that injury to this gland rendered the animals more susceptible to sensitization.

SUMMARY

In a series of 364 female hooded rats which had been subjected to prolonged stimulation by oestrogen, polyarteritis occurred in 43. The lesions appeared after 300 days of treatment, and while most prominent in the mesenteric vessels, were widespread throughout the animals. Histologically the lesions were indistinguishable from those occurring in man.

This work was supported by the National Cancer Institute of Canada. The author would like to thank Mr. Barry Forbes for photographic work, and Mrs. E. Fraser for technical assistance.

REFERENCES

BALO, J.—(1924) *Virchows. Arch. f. path. Anat.*, **248**, 337.
BEALL, C. W., SIMPSON, C. F., PRITCHARD, W. R. AND HARMS, H.—(1963) *Proc. Soc. exp. Biol. Med.*, **113**, 442.
DANFORTH, D. N., MANALO-ESTRELLA, P. AND BUCKINGHAM, J. C.—(1964) *Am. J. Obstet. Gynec.*, **88**, 952.
FRIEDMAN, B., JARMAN, J. AND KLEMPERER, P.—(1941) *Am. J. Med. Sci.*, **202**, 20.
GRÜBER, G. B.—(1925) *Virchows Arch. f. path. Anat.*, **258**, 441.
HARRIS, W. H. AND FRIEDRICHS, A. V.—(1922) *J. exp. Med.*, **36**, 219.
HARTMAN, H. A., MILLER, E. C. AND MILLER, J. A.—(1959) *Proc. Soc. exp. Biol. Med.*, **101**, 626.
JAEGER, A.—(1909) *Virchows. Arch. f. path. Anat.*, **197**, 71.
JORDAN, W. M.—(1961) *Lancet*, ii, 1146.
KNÖSEL, W.—(1931) *Ztschr. f. Fleisch. u. Milchhyg.*, **41**, 413.
LOWENTHAL, K.—(1931) ' Kreislauforgane. Anatomie und Pathologie der Spontanerkrankungen der kleinen Laboratoriumsterie '. Berlin (Julius Springer), **1**, 11.
LÜPKE, F.—(1906) *Verhandl. d. deutsch. path.* Gesellsch., **10**, 149.
MCLETCHIE, N. G. B., MACDONALD, R. M. AND CUTTS, J. H.—(1957) *Can. Med. Ass. J.*, **76**, 213.
MARINE, D. AND BAUMANN, E. J.—(1945) *Arch. Path.*, **39**, 325.
NIEBERLE, K.—(1928) *Virchows. Arch. f. path. Anat.*, **269**, 587.
POWELL, L., GUEST, M. AND POND, T. P.—(1965) *Am. J. Obst. Gynec.*, **93**, 167.
RICH, A. R. AND GREGORY, J. E.—(1943) *Bull. J. Hopkins Hosp.*, **72**, 65.
SELYE, H., HALL, C. E. AND RAWLEY, E. M.—(1943) *Can. Med. Ass. J.*, **49**, 88.
SMITH, C. C., ZEEK, P. M. AND MCGUIRE, J.—(1944) *Am. J. Path.*, **20**, 721.
TANGE, J. D. AND NEWMAN, R. G.—(1963) *Am. J. Path.*, **43**, 897.
TRAWINSKI, A.—(1929) *Arch. f. wissench. v. prakt. Tierh.*, **59**, 207.
VAUBEL, E.—(1932) *Ziegel. Beitr.*, **89**, 375.
WILENS, S. L. AND SPROUL, E. E.—(1938) *Am. J. Path.*, **14**, 201.
WILSON, C. AND BYROM, F. B.—(1939) *Lancet*, i, 136.