THE RELATIONSHIP BETWEEN INTERMITTENT HYPOTENSION AND THE PREVENTION BY HYDRAZINE OF ACUTE VASCULAR DISEASE IN RATS WITH STEROID HYPERTENSION

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The rapid development of hypertension in albino rats given salt and cortexone (deoxycortone acetate) is usually accompanied by the appearance of widespread acute vascular disease (Selye, Hall, and Rowley, 1943; Masson, Hazard, Corcoran and Page, 1950). The disease is focal in distribution and involves both small and medium-size arteries, as an arteritis, and arterioles in which the presence of subendothelial material with the tinctorial characteristics of fibrinoid accompanies a slight adventitial inflammatory reaction. In both types of vessel the form and evolution of these changes closely resemble those found in rats with renal (Wilson and Byrom, 1939; Loomis, 1946), pituitary (Masson et al., 1950) or adrenal-regeneration (Skelton, 1955, b) hypertension.

Many investigators assume that these forms of vascular disease in the rat, arterial and arteriolar, are part of a species-specific response to hypertension (Masson et al., 1950, Koletsky, 1955) although sufficient direct evidence of the validity of this interpretation, obtained from comprehensive comparative morphological studies, is not yet available. The animal lesions are therefore regarded as the experimental counterpart of the fibrinoid arteriolar change pathognomonic of the malignant phase of hypertension in the human (Fahr, 1919; Heptinstall, 1953). Both the human and the rat vascular disease are thought to be the results of a critical rise in blood pressure (Pickering, 1955). This view receives strong but indirect support from the demonstration that in experimental hypertension of renal origin in the rat vascular damage does not develop in the kidney to the artery of which a constricting clip has been applied (Wilson and Byrom, 1939; Floyer, 1951). By contrast, Bali and Goldblatt (1954) submit that while the necrotizing arteriolar lesions in renal hypertensive rats are dependent upon at least two factors including both hypertension and functional renal failure, the necrotizing arteritis is non-specific and independent of blood pressure.

No direct evidence is available relating intra-arterial and intra-arteriolar pressure changes to the evolution in the same vessel of mural damage in rats with experimental hypertension. The only satisfactory approach to this type of observation is provided by the work of Byrom and Dodson (1948), of Schaffenburg and Goldblatt (1957), and of Wolfgarten and Magarey (1959). Byrom and Dodson (1948) demonstrated that acute vascular disease was produced in normotensive rats by the introduction under pressure of fluid into large arteries remote from those subsequently found to be damaged. Their experiments were repeated by Schaffenburg and Goldblatt (1957) without confirmation. However, comparable work was described by Wolfgarten and Magarey (1959) who claimed to have caused
acute arterial damage by this means. Their descriptions and photographs, nevertheless, do not provide acceptable evidence that the arterial lesions which they produced were identical with those found in the commonly studied forms of hypertension in the rat. They were apparently not successful in reproducing arteriolar lesions.

In view of the complete lack of knowledge of the effects produced by such high central intravascular pressures on vascular tone, pressure and blood flow in small arteries and in arterioles of similar size to those damaged in experimental hypertension, considerable caution must be exercised in deducing from any part of the evidence presented in these three papers that the acute vascular injuries of experimental hypertension in the rat are the result of direct pressure changes. Equally, in the absence of direct human demonstration care must be exerted in reaching similar conclusions in regard to the vascular disease of the malignant phase of human hypertension. The need for direct evidence in this respect is not admitted by many authorities, perhaps with some justification in view of the strong indirect evidence available (Pickering, 1955).

An impetus was given to the search for the cause of the acute vascular disease in hypertensive rats by the demonstration that it was possible to delay, modify or suppress such changes by prolonged treatment with hypotensive drugs (Masson, McCormack, Dustan and Corcoran, 1958). In these experiments the hypotensive drug hydralazine (1-hydrazinophthalazine) was given orally to rats in amounts shown to be sufficient to prevent a significant rise in blood pressure on a regime known to cause severe renal hypertension. These results indicated that apparently constant control of systolic blood pressure exerted in this way was associated with the virtual absence of acute renal vascular disease, that vascular disease developed if treatment with hydralazine was stopped, and that a period of uncontrolled renal hypertension led to the appearance of acute vascular lesions which responded to delayed treatment by healing. Both arterial and arteriolar changes behaved similarly. These experiments therefore confirmed that apparent control of systolic renal hypertension in the rat was accompanied by preservation of the integrity of the walls of small arteries and arterioles. From this evidence the deduction was made that the acute vascular lesions in animals with renal hypertension were the consequence of the raised blood pressure, an opinion in support of which no satisfactory direct evidence was offered.

During recent work on the toxicity of hydralazine (Gardner 1957, 1958), and for reasons not related to changes in blood pressure, it became customary to give this drug in large amounts by single daily intramuscular injection, for prolonged periods, to rats with steroid hypertension. In the course of this work it was noticed that treatment was exerting an unexpectedly severe influence on the evolution of the characteristic vascular changes caused by salt and cortexone (Gardner, 1959). Further experiments were therefore undertaken to extend these observations and to define in more detail the circumstances under which hydralazine exerted this effect. The results of the first of these experiments are presented in this paper.

MATERIALS AND METHODS

Animals.—Male and female Wistar (groups 5 and 6) and Sprague-Dawley (groups 1, 2, 3, and 4) rats were maintained on a diet containing all known essential nutritional factors. The mean weight of these rats varied from 123 to 190 g. The animals were divided at random into paired groups. Three paired groups were studied consecutively.
Cortexone (deoxycortone acetate) was used in the form of compressed tablets for subcutaneous implantation, or as a 1·25 per cent aqueous suspension with tragacanth. The reactivity of the tragacanth was excluded by the daily injection of this agent alone into a distinct group of animals for a period of 10 weeks.

Salt was given as a 1 per cent aqueous solution of analytical grade sodium chloride in tap water.

Hydralazine (Apresoline-Ciba) was used as a sterile 2 per cent solution.

Systolic blood pressures were recorded weekly by tail plethysmograph, with (groups 5 and 6) or without (groups 1, 2, 3, 4) light ether anaesthesia (Dodson and Mackaness, 1957). The use of anaesthesia did not significantly change the effects of hydralazine while the influence of ether as a hypotensive agent was excluded by its use in an independent experiment, not described here, in which an unreactive chemical was substituted for hydralazine in a further control group of animals.

Diastolic blood pressures were measured under pentobarbitone anaesthesia using a carotid cannula connected to a pressure transducer. The pulse waves were visualised on an oscilloscope and transcribed to paper with a direct writing recorder.

Histological material was fixed in corrosive formol or in neutral formol saline; paraffin sections were stained routinely with haematoxylin and eosin and by the Picro-Mallory method, while other staining techniques were used when necessary.

Procedure

The animals of each group were weighed, and the systolic blood pressures recorded. After not less than 1 week of observation, to exclude illness or infection, left nephrectomy was performed under ether or pentobarbitone anaesthesia. At the same time implants of groups 6

2 were connected to a pressure transducer. The pulse waves were transmitted to a pressure transducer. The pulse waves were visualised on an oscilloscope and transcribed to paper with a direct writing recorder.

Histological material was fixed in corrosive formol or in neutral formol saline; paraffin sections were stained routinely with haematoxylin and eosin and by the Picro-Mallory method, while other staining techniques were used when necessary.

<table>
<thead>
<tr>
<th>Group</th>
<th>Males</th>
<th>Females</th>
<th>Total</th>
<th>Mean initial weight (g.)</th>
<th>Mean initial B.P. mm./Hg.</th>
<th>Cortexone (deoxycortone)</th>
<th>Maximum dose of hydralazine (mg./kg.)</th>
<th>Duration of treatment (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12</td>
<td>0</td>
<td>24</td>
<td>188</td>
<td>117</td>
<td>35 mg. subcutaneous implant</td>
<td>—</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>0</td>
<td>24</td>
<td>188</td>
<td>106</td>
<td>70 mg. subcutaneous implant</td>
<td>—</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>0</td>
<td>14</td>
<td>190</td>
<td>110</td>
<td>70 mg. subcutaneous implant</td>
<td>—</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>0</td>
<td>14</td>
<td>190</td>
<td>111</td>
<td>70 mg. subcutaneous implant</td>
<td>—</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>4</td>
<td>16</td>
<td>116</td>
<td>107</td>
<td>2·5 mg. of suspension daily</td>
<td>—</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>4</td>
<td>16</td>
<td>130</td>
<td>100</td>
<td>2·5 mg. of suspension daily</td>
<td>—</td>
<td>12</td>
</tr>
</tbody>
</table>

At the same time the daily injection of hydralazine was begun. The initial dose of the drug was 1 mg. in each instance, but this amount was quickly and progressively increased. After 12 weeks some surviving animals of group 3 were receiving as much as 8 mg. daily. Animals of group 4 were treated in this manner for 4 weeks, those of group 4 for 8 weeks and those of group 6 for 12 weeks. The injections were given each day without exception.

At the close of the respective periods of treatment animals were killed by bleeding under anaesthesia. Representative parts of the principal organs were placed in neutral formol saline (groups 1–4) or in corrosive formol (groups 5 and 6).

At intervals during the study of each experimental group selected animals were subjected to more detailed investigation in order to determine the diurnal variation in systolic blood pressure in response to treatment. Towards the end of the experiment the diastolic blood pressure of a smaller number of these animals was measured, and the effects of the daily injection of hydralazine estimated by direct manometry.
RESULTS

The general condition and well-being of the animals

Animals injected once daily with hydralazine remained in better health than those not so treated. Many gained weight more rapidly than control animals. This effect was particularly obvious in groups treated for 8 or for 12 weeks.

Systolic blood pressure

During the preliminary experiments on the toxicity of hydralazine systolic blood pressures were recorded 4–6 hr after the daily injection of hydralazine. The data obtained by this method suggested that the mean systolic blood pressure was maintained within the limits of normality (Fig. 1). More detailed analysis quickly showed that this procedure was misleading and that following each daily injection the systolic blood pressures underwent a severe fluctuation (Fig. 2). Immediately after each injection the pressure fell abruptly, reaching a minimum within 1½–3 hr., rising again more slowly and resuming the pre-injection (hypertensive) level within 18–24 hr. Among the animals in each group there was considerable individual variation in response, because of the injection of equal doses of hydralazine into animals of varying body weight (Fig. 3).

Diastolic pressure

In view of the wide variations in systolic blood pressure, and because of the suspected inaccuracy of the plethysmographic method of measurement at levels below 80–100 mm. Hg., it was felt that an attempt should be made to confirm the extent and severity of representative blood pressure responses by direct manometry. With a sensitive recording device the rapid pulse wave of the hyper-
Fig. 2.—The change in mean systolic blood pressure in a group of 12 rats with steroid hypertension during the 24 hr. following a single large intramuscular injection of 6 mg. hydralazine.

Fig. 3.—The range of systolic blood pressure readings recorded among a group of 12 rats with steroid hypertension during the 24 hr. following a single intramuscular injection of 7 mg. hydralazine.
tensive rat could be analysed sufficiently to measure both diastolic and systolic pressures (Fig. 4). Readings made in this manner showed that both systolic and diastolic pressures began to fall within 3 min. after the usual intramuscular injection of hydralazine, and that the fall continued for periods of \(\frac{1}{2}-1\frac{1}{2}\) hr. before reaching a plateau (Fig. 5). The low pressure levels were maintained for 1–2 hr. before a rise began, and the levels present before injection were resumed in less than 24 hr. In each example measured in this way diastolic pressure fell in parallel with systolic. In other preliminary experiments in which the drug was injected intravenously the very severe and abrupt response which followed appeared to affect systolic pressure more quickly than diastolic (Fig. 6).

For reasons which are not at the moment clear, but which have been commented upon by other observers (Caster, Lentz, Poncelet and Armstrong, 1956) it proved difficult to make a direct quantitative comparison between pressure levels recorded directly and those recorded indirectly. Direct carotid manometry appeared to yield higher systolic and diastolic pressure in both normal and hypertensive rats irrespective of whether blood flow through one or both carotid arteries was disturbed. Such pressures were significantly more sensitive to hydralazine than were those recorded indirectly. Further, direct manometry not only confirmed the form of response to hydralazine already detected by indirect manometry but revealed more rapid and more extensive effects. For the present purpose the quantitative difference between the results obtained by the individual methods of manometry was therefore disregarded. Argument based on the indirect measurement appeared to gain significance when contrasted with the conclusions drawn from direct manometry.

**Weight of organs**

The mean weight of the kidney from animals treated for only 4 weeks (group 2) expressed as a percentage of terminal body weight was found to be less than that of the corresponding control group (group 1) not given hydralazine. In animals treated for longer periods of 8 or 12 weeks (groups 4 and 6) the kidneys were appreciably heavier than those of the control groups (3 and 5).

In considering the effect of treatment in different groups on the mean heart weight expressed as a percentage of terminal body weight, it is necessary to

**Table II.**—**Results: Effect of Treatment on Mean Body Weight and Mean Organ Weights**

(Weights expressed in grams)

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean body weight at death</th>
<th>Mean weight change</th>
<th>Right kidney</th>
<th>Heart</th>
<th>Adrenals (combined)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>225</td>
<td>+37</td>
<td>1.99</td>
<td>0.91</td>
<td>0.046</td>
</tr>
<tr>
<td>2</td>
<td>198</td>
<td>+10</td>
<td>1.53</td>
<td>0.85</td>
<td>0.043</td>
</tr>
<tr>
<td>3</td>
<td>273</td>
<td>+83</td>
<td>2.37</td>
<td>0.92</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>312</td>
<td>+122</td>
<td>3.01</td>
<td>1.11</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>156</td>
<td>+40</td>
<td>1.40</td>
<td>1.25</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>228</td>
<td>+98</td>
<td>3.02</td>
<td>2.24</td>
<td>—</td>
</tr>
</tbody>
</table>
emphasize that the method for weighing the hearts of animals in groups 5 and 6 differed from that used in weighing the hearts of animals in groups 1–4. With this proviso it remained clear that in most instances treatment with hydralazine did not significantly alter the mean relative heart weight, while in the groups treated for the longest period (groups 5 and 6) the injection of hydralazine led to an apparent increase in the mean relative weight of the hearts.

The terminal weight of the adrenals was determined in groups 1 and 2 and expressed in terms of total body weight. Treatment with hydralazine did not cause a significant change in the mean relative weight of the adrenals.

**Histology**

In control animals with steroid hypertension, vascular lesions were usually widespread within 4 weeks of beginning the raised sodium intake. The vascular changes were acute, and were of the fibrinoid arteriolar type characteristic of severe hypertension in the rat (Wilson and Byrom, 1939) and of the arteritic type whose origin remains in dispute (Masson et al., 1950; Bali and Goldblatt, 1954; Koletsky, 1955). Both lesions are widely known and have been described repeatedly on previous occasions (Masson et al., 1950; Skelton, 1955, a). Representative examples are shown in Figs. 7–10. The distribution of fibrinoid arteriolar change in a group observed for 4 weeks is shown in Table III. Mesentery, pancreas,

**Table III.—Group I: Distribution of Vascular Lesions in Surviving Animals**

<table>
<thead>
<tr>
<th>Rat No.</th>
<th>Kidney</th>
<th>Adrenal</th>
<th>Heart</th>
<th>Lung</th>
<th>Mesentery</th>
<th>Pancreas</th>
<th>Lymph nodes</th>
<th>Liver</th>
<th>Spleen</th>
</tr>
</thead>
<tbody>
<tr>
<td>97</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>99</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>100</td>
<td>.</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>-</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>101</td>
<td>.</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>102</td>
<td>.</td>
<td>+</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>103</td>
<td>.</td>
<td>+</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>104</td>
<td>.</td>
<td>+</td>
<td>-</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>105</td>
<td>.</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>8</td>
<td>5</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

+ = Acute vascular disease. 0 = No vascular disease. — = Not examined.

**EXPLANATION OF PLATES.**

Fig. 4.—Pulse wave of 190 g. rat with steroid hypertension shortly after the intramuscular injection of 8 mg. hydralazine. Pulse rate 460/min.

Fig. 5.—Fall in systolic and in diastolic blood pressures of 190 g. rat with steroid hypertension following the intramuscular injection of 8 mg. hydralazine. The point of injection lay immediately to the left of that part of the tracing shown in this figure.

Fig. 6.—For comparison with Fig. 5, the fall in systolic and in diastolic blood pressures of a 260 g. rat with steroid hypertension following the intravenous injection of 0.5 mg. hydralazine.

Fig. 7.—Right kidney from control animal of Group I. Material with the staining characteristics of fibrinoid occupies much of the enlarged glomerulus and forms part of the acute arteriolar reaction. There is the usual tubular dilatation. Haematoxylin and Eosin × 133.

Fig. 8.—Arteriolitis, with the presence of much subintimal fibrinoid, in a mesenteric lymph node from the same animal. H. and E. × 133.

Fig. 9.—A focus of ventricular myocardial inflammation, with arteriolar fibrinoid and peri-vascular fibrosis, in an animal of Group I. H. and E. × 133.

Fig. 10.—Necrotizing arteritis of a medium-size mesenteric artery. The inflammatory reaction is severe. Subendothelial hyaline material is present. H. and E. × 53.
Gardner.
Gardner.
omentum and kidney were implicated most frequently, but acute arteriolar fibrinoid change was common in heart, lymph nodes, liver, adrenals and other organs. Acute arteritis of the so-called necrotizing variety was also common, and was found most often in regions related to the sites of previous surgical intervention. The lesions were not limited to these places however and were also commonly present in the mesenteric border of the gut, in the kidney and in other sites with increasing frequency as the period of observation lengthened. In rare instances, and for no apparent reason, an animal failed to develop vascular disease within the period of observation. This failure occurred only when subcutaneous hormone implants were used and was not noted in groups given daily subcutaneous injections of cortexone.

In animals given hydralazine, fibrinoid arteriolar lesions were few. Very occasionally an isolated arteriole appeared damaged. This was interpreted as individual biological variation in response, possibly associated with varying rates of growth in the face of constant doses of hydralazine. Many small and medium-size arteries in the mesentery, omentum and pancreas were surrounded by aggregates of inflammatory cells. The majority of these cells were histiocytes, apparently containing the residual detritus always found in the retroperitoneal space following the operation of unilateral nephrectomy and associated with the presence of foreign suture material at the site of renal arterial ligation. In no instance however were the walls of these vessels infiltrated by inflammatory cells, and in none was subendothelial eosinophilic hyaline or fibrinoid present.

Treatment with intermittent hydralazine therefore appeared to offer virtually complete suppression of both acute arteriolar fibrinoid and of acute necrotizing arteritis in rats with steroid hypertension for periods of up to 3 months while leading to long-continued profound repetitive fluctuations in systolic and in diastolic blood pressures.

**DISCUSSION**

Hydralazine is known to lower the systemic pressure of rats with experimental steroid hypertension (Gaunt, Antonchak, Miller and Renzi, 1955), with renal hypertension (Gross, 1955), and with adrenal-regeneration hypertension (Chart, Ulsamer, Quinn, Howie, Sullivan and Gaunt, 1957). The mechanism by which the drug exerts its effect is not fully understood but it may include central (Schmitt and Gicquel, 1955), renal (Hartman and Flagg, 1956) and peripheral vascular components (Schmid and Kellner, 1953). Tolerance to the drug is quickly acquired and large amounts can be given to rats without evident harm. When the drug is administered by single daily injections, as in the present experiment, an abrupt fall in systolic and in diastolic blood pressure is succeeded, in the hypertensive animal, by a less rapid rise.

It was with the express purpose of avoiding such fluctuations in blood pressure that Masson et al (1958) abandoned the administration of hydralazine to rats by stomach tube, preferring to substitute a hydralazine solution for the drinking water. This enabled a constant influence to be exerted on the blood pressure level, maintaining systolic pressure apparently within normal limits. No mention was made of the possibility that the nocturnal feeding and drinking habits of the rat may have disturbed this constant state and nocturnal blood pressure records were not quoted. Nevertheless treatment was successful in preventing the appearance of acute vascular disease.
In the present experiment treatment of rats with large single daily intra-
muscular injections of hydralazine resulted not only in abrupt daily falls in blood
pressure but in rapid subsequent rises to preinjection levels. It appears reason-
able to compare these rises with those which various authors hold responsible for
the development in severe hypertension of acute damage to small arteries and
arterioles (Pickering, 1955). However this comparison may only be made with
care since it is not certain that the small vessels during recovery from a single
injection of hydralazine are in the same morphological or physiological state as
are those during rapidly progressive acute experimental hypertension. Direct
visual observation of exposed mesenteric vessels following the injection of hydral-
azine into rats with steroid hypertension has not yet provided unequivocal evidence
on this point, possibly because the small vessels studied were not those which
determine systemic blood pressure control (unpublished personal observations).

If the vascular lesions of other forms of experimental hypertension in the rat
are accepted as similar to those of steroid hypertension, and as far as the arterial
and arteriolar disease is concerned this appears to be the case, the present experi-
ment suggests the generalization that complete control of absolute blood pressure
levels in the systemic circulation is not essential for the prevention of acute
hypertensive vascular disease. Because of the different circumstances under
which the experiments were conducted the present results do not conflict with
those of Masson et al. (1958), but they suggest that the interpretation placed upon
their results by these authors was incomplete. It appears possible that had Masson
and his colleagues adopted their original plan for the intermittent administration
of hydralazine by stomach tube this treatment might have proved as effective in
controlling acute vascular disease as that which they selected, in spite of the
varying blood pressure levels.

It was noticeable that treatment with intermittent hydralazine influenced
equally the development of both arterial and arteriolar disease. This was thought
to provide additional indirect evidence that both forms of vascular lesion were
individual morphological components of the same response. It did not accord
with the views of Bali and Goldblatt (1954) that the necrotizing arteritis and the
arteriolitis of rats with renal hypertension were distinct.

The prevention of both lesions by treatment which led to fluctuating blood
pressure suggested that the involved segments of arteries and arterioles in exper-
imental rat hypertension were damaged by some mechanism dissociated from the
absolute levels of systolic and diastolic blood pressure. For this reason it appeared
desirable to search for the smallest amount of hydralazine which, given once
daily, would prevent the evolution of acute vascular damage in animals with
steroid hypertension. A further experiment was therefore performed. Albino
male rats were subjected to the same steroid hypertensive regime, and were in-
jected once daily with 1.0 mg., or with 0.2 mg. hydralazine (Fig. 11, Table IV).
When the animals were killed at the end of 6 or 7 weeks treatment it was clear
that the injections had not prevented acute vascular disease although the single
1.0 mg. injections had resulted in significant daily falls in systolic and in diastolic
blood pressures.

It was therefore concluded that the dissociation between acute vascular
disease and absolute blood pressure levels was not complete. Prevention of acute
vascular damage by single daily injections of hydralazine was inevitably asso-
ciated with some change in systolic and in diastolic blood pressures. Consideration
was given to the possibility that the prevention of acute vascular disease by hydralazine was a function of an overall reduction in the mean blood pressure, or that discontinuous hypertension, for a period of some hours each day, had not allowed the operation of a mechanism, the nature of which is at present unknown,

which initiated acute vascular damage. Alternatively, and in accordance with the views of Goldblatt (Bali and Goldblatt, 1954) the treatment adopted in the present experiment may have led to a constant influence upon some unknown function, possibly renal in nature, more sensitive to the action of hydralazine than was the blood pressure. In this way treatment may have controlled one of two

![Figure 11](image-url)  
**Fig. 11.**—Response of the systolic blood pressure in an animal with steroid hypertension to varying doses of hydralazine injected intramuscularly.

### Table IV

**Effect of Small Intermittent Dosage of Hydralazine**

<table>
<thead>
<tr>
<th>Group</th>
<th>Cortexone (deoxy-cortone)</th>
<th>Hydralazine daily</th>
<th>Duration of treatment</th>
<th>Mean weight change (g.)</th>
<th>Terminal mean weight (g.) of:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R. kidney</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>1 mg.</td>
<td>7 weeks</td>
<td>+34</td>
<td>2.32</td>
</tr>
<tr>
<td></td>
<td>Single 35 mg. subcutaneous implants</td>
<td>0.2 mg.</td>
<td>6 weeks</td>
<td>+60</td>
<td>2.92</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Incidence of Vascular Lesions**

<table>
<thead>
<tr>
<th>Group</th>
<th>Kidney</th>
<th>Adrenal</th>
<th>Heart</th>
<th>Lung</th>
<th>Mesentry</th>
<th>Pancreas</th>
<th>Lymph nodes</th>
<th>Liver</th>
<th>Spleen</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 (5)</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>1</td>
</tr>
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factors necessary for the development of acute experimental hypertensive vascular disease, the other factor, raised blood pressure, being ineffective in isolation.

This experiment suggests that it should no longer be assumed that acute vascular disease in the rat with steroid hypertension, and perhaps with other forms of experimental hypertension, is the direct result of a critical rise in blood pressure alone. The relationship of this conclusion to the pathogenesis of hypertensive vascular disease in other animals and in man, and to the mode of action of other hypotensive drugs remains entirely speculative. Nevertheless, it is tempting to consider these results in reviewing the work of Leishman (1959) who observed that patients given a hypotensive drug (hexamethonium) by injection twice daily responded well to such treatment in spite of the difficulty of maintaining constantly lowered blood pressure levels. In the light of the present evidence it appears that this result may have been the consequence of an unexpectedly sustained and beneficial influence of such intermittent treatment on the evolution of hypertensive vascular disease and its complications.

**SUMMARY**

During the development of systemic hypertension in albino rats treated with salt and cortexone the small arteries of many organs became the site of a focal segmental necrotizing arteritis. These lesions were usually accompanied by a widespread focal arteriolitis often involving the afferent glomerular arterioles and characterised by the presence of subintimal material with the staining properties of fibrinoid. Both arterial and arteriolar lesions resembled morphologically those found in several other forms of experimental hypertension in the albino rat.

When rats were subjected to this regime of salt and cortexone and were simultaneously injected with increasingly large amounts of hydralazine once daily, neither form of vascular lesion developed during periods of observation which extended for up to 3 months.

The single daily injections of hydralazine caused severe repetitive daily fluctuations in both systolic and in diastolic blood pressures, leading to intermittent reduction in the mean systemic blood pressure. Each injection was followed by a rapid and profound fall in systolic and in diastolic pressure and was succeeded within 24 hr. by a slower rise to the pre-injection level.

These results show that the prevention of acute vascular disease in rats with steroid hypertension may take place in spite of repetitive abrupt rises in systolic and diastolic blood pressure. This evidence lends weight to the theory that a critical rise in blood pressure alone is not an adequate explanation for the appearance of acute arterial and acute arteriolar lesions in rats with experimental hypertension.

It is suggested, on the basis of these observations, that the necrotizing arteritis and the fibrinoid arteriolar disease of experimental rat hypertension are related phenomena, and that intermittent hydralazine prevents their development either by a discontinuous influence upon the mean blood pressure or by affecting a factor, at present unrecognised, which is more sensitive to the action of the drug than is the blood pressure.

In the absence of further evidence, caution must be exercised in translating the significance of these results to other animal species or to man.
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