Norepinephrine (NE) administration has been implicated in the production of morphologic changes in various organs and tissues. Blacket, et al.,1 in 1950, in a paper on the effects of prolonged infusion of NE on arterial pressure of rabbits, commented that these rabbits became ill, listless and did not eat, and on gross examination showed dilatation of the terminal large gut. Boughton and Sommers,2 in 1956, reported eight hypotensive patients who had been treated vigorously with NE, and who showed "unusual" microscopic degenerative changes in their kidneys. Brunson, et al.,3 in 1957, proposed that an increasing prevalence of unexplained liver necrosis found in an autopsy series, was related to the increased use of pressor amines. Greenbaum,4 in 1958, reported a case of gangrene of all four extremities following myocardial infarction and NE therapy and felt that the "use of norepinephrine must have made an important contribution to the vasoconstriction that led to gangrene." Maling and Highman,5 in 1958, presented evidence that NE in dogs produced fatty changes in the heart and liver, massive pulmonary edema in those animals which died as a result of the infusion, and occasionally, hemorrhages involving the pleura, peritoneum and gut mucosa. Szakacs and Cannon6 in 1958, reported a clinical case of NE-produced myocardopathy. In a subsequent report7 these authors described similar morphologic changes in dogs after experimental infusion of NE. These changes consisted of focal myofiber* degeneration and necrosis, subendocardial and subpericardial hemorrhages and necrotizing arteritis of the gastrointestinal tract. Hackel and Catchpole,8 in 1958, showed that the incidence of cardiac lesions was higher in dogs in hemorrhagic shock treated with NE, than in those without such treatment. Nahas et al.,9 in 1958, found that infusions of NE in heart lung preparations of dogs resulted in extensive degenerative and hemorrhagic lesions in the myocardium, cardiac valves and coronary vessels, and that these lesions were aggravated by the concomitant infusion of hydrocortisone. Brown, et al.,10 in 1959, reported a clinical case of intestinal hemorrhage and perforation associated with NE administration. Chung and Sima,11 in 1961, reported 11 cases with renal tubular necrosis following NE administration.

The present report describes experiments performed in the rabbit, cat, and dog to evaluate the pathologic effects of varying NE dose levels infused for prolonged periods of time.

Methods

1. Seventy-five rabbits weighing 2.5 to 3.5 kg were studied, without general anesthesia but with 0.5 ml of lidocaine (Xylocaine) infiltrated at the base of the left ear for local anesthesia. Norepinephrine diluted in 15 ml of 5% dextrose and water was infused into the left marginal ear vein through an indwelling catheter. Three groups of rabbits received 0.1 to 0.4, 0.8 to 1.2, and 1.5 to 3 μg/kg/min of NE base for periods of 1 to 15 hours. Control animals were infused with 5% dextrose and water. Arterial blood pressure was measured in 24 animals by means of

*Myofiber is used to mean cardiac muscle cell.
an indwelling catheter in the central artery of the left ear, and recorded with a Statham 23AA pressure transducer and a Grass polygraph recorder. Groups of animals were autopsied at intervals from 15 minutes to 2 weeks after the infusion period. Complete autopsies were performed on all animals. A minimum of 20 hematoxylin and eosin (H and E) sections of heart and 4 each of liver, pancreas, spleen, adrenals, kidneys, stomach, small and large bowel, and bladder were examined. At least one H and E section of thyroid, ovary or testis, uterus or prostate, skeletal muscle, bone marrow, and lymph node was examined. Special staining procedures for fat, by oil red O, and for glycogen by periodic acid Schiff diastase, were performed on sections of heart, liver and kidney frozen and cut in a cryostat. Special stains for iron, connective tissue, and mucopolysaccharide were used when deemed necessary.

2. Thirty-two cats weighing 2 to 5 kg were anesthetized with 0.8 cc/kg intraperitoneal allobarbital-urethane (Dial, Ciba). Norepinephrine base diluted in 20 ml of 5% dextrose and water was infused into a femoral vein through an indwelling catheter by means of a constant infusion pump at doses of 1, 2, or 4 μg/kg/min. Infusions were continued for 5 and 15 hours. Arterial blood pressure was measured in all animals from the carotid artery using an indwelling catheter, a Statham 23AA transducer and a Grass recorder. Complete autopsies were performed on 26 animals sacrificed immediately after the infusion. Six animals in the 2 and 4 μg/kg/min dose group, were sacrificed and autopsied one week after the infusion. The protocol of tissue examination was similar to that described for rabbits. In addition, fresh frozen sections, cut at 10 μ on a Lipshaw cryostat, of heart, liver and kidney were stained for alkaline and acid phosphatase (method of Burstone), for lactic (LDH) and succinic (SDH) dehydrogenase (method of Hess et al.), and for lipid and respiratory enzymes by a method combining oil red O and LDH or SDH.

3. Twenty-four mongrel dogs weighing 8 to 18 kg were anesthetized with intravenous sodium pentobarbital (25 mg/kg). Norepinephrine base, diluted in 40 ml of dextrose and water, was infused into a femoral vein for four hours at doses of 0.5, 1, 2 or 4 μg/kg/min. Control dogs were infused with 5% dextrose and water for an equal period of time. Measurements of left ventricular and aortic pressure, right atrial pressure, cardiac output, blood volume, arterial pH, and oxygen saturation, and serum total lactic dehydrogenase and lactic dehydrogenase isoenzymes were made at intervals throughout the infusion period. Complete autopsies were performed on 21 dogs within 15 minutes after the end of the infusion. Two dogs which had received 2 μg/kg/min NE for four hours were autopsied one week later and one dog which received this dose was autopsied two weeks later. The protocol of tissue examination was similar to that described for the cats.

Results

A. Rabbits

Table 1 summarizes the relationship of the dose and duration of NE infusion to the incidence of myocardial lesions and to the incidence of demise. Doses of NE in the range of 0.1 to 0.4 μg/kg/min produced no myocardiopathy when administered for five hours. When the infusion period was prolonged to fifteen hours, all animals had myocardial lesions. At a dose range of 0.8 to 1.2 μg/kg/min all but one of the animals had myocardial lesions. At a dose of 1.5 to 3 μg/kg/min all animals had cardiac lesions as early as one hour after the initiation of infusion. During a five-hour period of NE infusion the mortality was nearly 75%. Control animals receiving an equal volume of 5% dextrose and water for one, five and fifteen hours developed no morphologic changes in the heart and no deaths occurred.

Table 2 summarizes the nature and degree of the myocardial lesions and extramyocardial morphologic changes seen at various time intervals after a period of NE infusion. The dose of NE administered to these animals was

| TABLE 1 | Incidence of Myocardial Lesions in Rabbits Infused for 1, 5, and 15 Hours with Graded Doses of Norepinephrine |
|-----------------|-------------------------------------------------|-----------------|-----------------|-----------------|
| Infusion time   | Control no. | Dose of norepinephrine, μg/kg/min |
| no.             | 0.1 to 0.4  | 0.8 to 1.2 | 1.5 to 3.0 |
| 1               | 0/4         | —          | —            |
| 5               | 0/4         | 31/32      | 8/8          |
| 15              | 0/4         | 5/5        | —            |

*Number of rabbits with lesions/number infused at given dose.

†Numerals in parentheses indicate numbers of animals that died during or within one day of the infusion period.
TABLE 2
Nature and Degree of Cardiac and Extracardiac Morphologic Changes Seen in Rabbits Autopsied at Various Time Intervals Following Infusion of 0.8 to 1.2 μg/kg/min of Norepinephrine for Five Hours

<table>
<thead>
<tr>
<th>Number of rabbits</th>
<th>Time of autopsy</th>
<th>Cardiac lesions</th>
<th>Extracardiac changes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Ventricular dilatation, subendocardial hemorrhage</td>
<td>Myofiber degeneration, interstitial edema</td>
</tr>
<tr>
<td>9</td>
<td>15 min</td>
<td>+ + *</td>
<td>++</td>
</tr>
<tr>
<td>5</td>
<td>1 day</td>
<td>+ +</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>3 days</td>
<td>+ +</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>1 week</td>
<td>+ +</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>2 weeks</td>
<td>+ +</td>
<td>+</td>
</tr>
</tbody>
</table>

* + + : prominent.
+ + : slight.

0.8 to 1.2 μg/kg/min for five hours. The changes seen in animals in other dose groups were entirely similar qualitatively to those depicted in the table. Cross changes seen immediately after cessation of the infusion consisted of right atrial and ventricular dilatation and both local and diffuse subendocardial hemorrhages which were especially prominent in the left ventricle. Microscopic examination revealed interstitial edema, subendocardial congestion and hemorrhages, especially adjacent to Thebesian vessels, and focal myofiber degeneration. The myofiber degenerative changes consisted of loss and smudging of striations and accumulation of lipid droplets within isolated or groups of cardiac cells.

These changes were often clearly confined to single cells and demarcated by intercalated discs. An acute inflammatory cell infiltration associated with these degenerative changes was seen occasionally (fig. 1). An increase in perivascular Anitschkoff myocyte-type cells was present occasionally.

Extracardiac lesions consisted of pulmonary
edema and congestion and of moderate degrees of hepatic, splenic and renal congestion. These changes were found in approximately 50% of the animals that had cardiac lesions, but could not be correlated with the degree of myocardial involvement. One day after infusion, the gross appearance of the heart was unremarkable except for both focal and diffuse subendocardial hemorrhages. Microscopic examination revealed focal myofiber necrosis with loss of striations, and of sarcoplasmic smudging and granularity. Mononuclear cells with a characteristic "caterpillar" chromatin pattern (cardiac histiocytes or myocytes) were then abundant adjacent to degenerating myofibers. The lungs and spleen continued to show some evidence of acute congestion, while the liver and kidneys were unremarkable.

Three days after infusion, frank focal cardiac myofiber necrosis with dissolution of the sarcolemma and sarcoplasmic fragmentation was evident. Numerous histiocytes and occasional lymphocytes and plasma cells were present in the interstitium surrounding the necrotic myofibers. Thin bands of connective tissue which stained as collagen were then present (fig. 8). One week following infusion, progressive evidence of phagocytosis of necrotic fibers and healing by fibrosis was obvious, and two weeks after infusion only fibrous areas were noted (fig. 9). After three days, extracardiac morphologic changes were seen only in the lungs; these changes consisted of scattered foci of macrophages containing iron.

Rabbits which died during the course of infusion or within one day after infusion of NE, invariably showed extensive pulmonary hemorrhages, edema and visceral congestion. The cardiac lesions were, however, neither more nor less severe, than those seen in animals in the same dose group which survived. The rabbits in the highest dose group tended to have the most extensive and severe cardiac lesions.

Spontaneously occurring myocardial lesions were present in 8% of the rabbits. These consisted of an active chronic myocarditis with prominent lymphocyte and plasma cell accumulation. These lesions had no resemblance to either the acute or healed NE produced ones.

The average mean arterial pressure before infusion of NE, as measured in the ear of 24 rabbits, was 66 mm Hg. In animals of all of the dose groups, arterial pressure increased when infusion of NE was begun. The average maximum rise occurred within five minutes after the start of infusion and was 11 mm Hg with the 0.1 to 0.4 /g/kg/min dose, 26 mm Hg with the 0.8 to 1.2 /g/kg/min dose, and 41 mm Hg with the 1.5 to 3 /g/kg/min dose. Five to ten minutes after the onset of infusion, the arterial pressure began to decline from its maximal rise. With the lowest and intermediate doses of NE, the decline at the end of the infusion was usually to or slightly above the pre-infusion control level. With the highest doses, the pressure...
Incidence of Myocardial Lesions in Cats and Dogs Infused with Graded Doses of Norepinephrine

<table>
<thead>
<tr>
<th>Infusion time (hr)</th>
<th>Control</th>
<th>Dose of norepinephrine, µg/kg/min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no.</td>
<td>no.</td>
</tr>
<tr>
<td>5</td>
<td>0/4*</td>
<td>1/4</td>
</tr>
<tr>
<td>15</td>
<td>0/4</td>
<td>3/4</td>
</tr>
<tr>
<td>4 to 5</td>
<td>0/5</td>
<td>0/2</td>
</tr>
</tbody>
</table>

*Number of animals with lesions/number infused at given dose.

always fell below the pre-infusion level, the average postinfusion arterial pressure in these animals being 51 mm Hg.

B. CATS AND DOGS

The gross and microscopic morphologic changes seen in cats and dogs immediately after infusion of NE were qualitatively similar to those described in the rabbit. The incidence of cardiac lesions related to the dose of NE infused in these animals is presented in Table 3. A dose of 1 µg/kg/min infused for five hours produced cardiac changes in 25% of the cats, while the same dose infused for fifteen hours raised this incidence to 75%. Doses less than 2 µg/kg/min in the dog produced no lesions. Doses of 2 and 4 µg/kg/min led to cardiac lesions in 100% of both the cats and dogs. No lesions were seen in any of the animals receiving an infusion of 5% dextrose and water. There was no mortality among the cats and dogs in the various dose groups.

Gross cardiac changes seen immediately after the infusion period consisted of slight to moderate dilatation of all of the cardiac chambers. This was usually more pronounced in the right atrium and ventricle than on the left side. Subepicardial and subendocardial hemorrhages were patchy and focal in cats in the 1 and 2 µg/kg/min dose groups and in dogs in the 2 µg/kg/min dose group, and diffuse and extensive in all animals receiving larger doses (fig. 4).

Microscopic examination revealed varying degrees of subendocardial and epicardial congestion and hemorrhages (fig. 2). Focal myofiber degeneration was obvious throughout the myocardium, and prominent in areas of subendocardial hemorrhage. Degenerative changes were characterized by loss of cross striations and sarcoplasmic smudging, lipid accumulation, and variations in the staining reaction for SDH and LDH. In the control animals, little to no droplet lipid was found within myofibers and the LDH and SDH activity was evenly and regularly distributed in rows of small granules throughout the sarcoplasm. In the animals infused with NE, individual myofibers showed extensive small lipid droplet accumulation (fig. 5) and large irregularly shaped or clumped dehydrogenase positive granules within the sarcoplasm which had a greater intensity of staining reaction than that in normal fibers (fig. 6). Infrequently, increased enzyme activity was noted in the sarcoplasm of adjacent myofibers at the region of the intercalated disc to produce a "zonal type" lesion. Sections stained by a method combining oil red O and either SDH or LDH, frequently showed lipid accumulation and abnormalities in enzyme activity (coarse granules and clumping) in the same fibers. Occasionally, single myofibers which contained only large lipid droplets and no enzyme activity, were found (fig. 7).

Gross and microscopic examination of the heart in cats autopsied one week after infusion revealed changes similar to those seen in rabbits autopsied after the same time interval, namely, phagocytosis of myofiber debris and connective tissue proliferation.

Morphologic changes seen in animals autopsied immediately after infusion, in organs other than the heart, consisted of a slight serous effusion in the pericardial, pleural, and peritoneal cavities, pulmonary congestion and edema, and slight visceral congestion. These changes were noted only in those animals manifesting cardiac changes. In all of the dogs showing cardiac lesions there was, in addition to the above described noncardiac changes, evidence of acute adrenalitis involving the cortex. An extensive diffuse infiltration of the adrenal cortex by polymorphonuclear cells was present and was associated with focal
lipid depletion, some cytoplasmic eosinophilia, and focal nuclear pyknosis of cortical cells (fig. 3).

The average mean arterial pressure in 32 cats before infusion of NE was 112 mm Hg. The maximum rise of pressure following the onset of infusion occurred within 10 minutes and was 40 mm Hg with the 1 μg/kg/min dose, 66 mm Hg with the 2 μg/kg/min dose and 79 mm Hg with the 4 μg/kg/min dose. As in the rabbits, the arterial pressure declined progressively following the maximum rise. This decline was most marked with the 2 and 4 μg/kg/min doses and with the largest dose amounted to an average fall of 27 mm Hg below the pre-infusion control level.

The alterations in cardiovascular dynamics and serum lactic dehydrogenase activity measured during the NE infusion in dogs are reported elsewhere.15'18

**FIGURE 4**
Dog heart, left ventricle. Autopsy within fifteen minutes after infusion of 4 μg/kg/min norepinephrine (NE) for four hours. Shows extensive subendocardial hemorrhage and slight ventricular dilatation. Results from special stains given in figures 5 to 7.

**FIGURE 5**
Oil red O stain shows fatty degeneration with diffuse small lipid droplet and focal large lipid droplet accumulation.

**FIGURE 6**
Lactic dehydrogenase. Focal myofibers show clumped and coarse granules with enzyme activity and an increase in staining intensity.

**FIGURE 7**
Oil red O-lactic dehydrogenase. Focal myofibers with large lipid droplets have little to no remaining enzyme activity.

**FIGURE 8**
Rabbit heart, three days after NE infusion. A myofiber is being replaced by tissue which stains as collagen (green). Chronic inflammatory cells resembling Anitschkow myocytes and fibroblasts are present. Gomori trichrome.

**FIGURE 9**
Rabbit heart, two weeks after NE infusion. Shows prominent increase in subendocardial connective tissue (blue staining). Masson trichrome.

**Discussion**
The experiments reported in this paper (a) establish that the major toxic effect of NE infusion in experimental animals is on the heart, (b) identify the evolution and fate of certain of the morphologic characteristics of the cardiac lesions, and (c) establish a dose-response relationship for the cardiac lesions.

The data obtained in our experiments offer no support for previously reported impressions that morphologic changes seen in various organs following the use of NE are causally directly related to this drug.1-5, 7'9-11 Under the experimental conditions employed, morphologic changes in the rabbit, cat, and dog were confined principally to the heart. This was true in both unanesthetized and anesthetized animals. Visceral and pulmonary congestion and accumulations of pericardial, pleural, and peritoneal fluid were probably the result of cardiac failure. Hemodynamic studies on the dogs used in this experiment, and reported elsewhere,15 indeed showed cardiac failure in those animals receiving the largest doses. An additional factor in the production of serous effusions may have been an increase in capillary pressure with subsequent transcapillary fluid leakage.17

All of the dogs which had evidence of myocardial lesions also had an acute adrenalitis with adrenal cortical cell lipid depletion and degeneration. The absence of this finding in rabbits and cats, which had cardiac lesions of equal severity to those seen in the dogs, suggests a species specific alteration in the adrenal. The occurrence of these lesions in dogs with no or slight evidence of cardiac failure further suggests a direct effect of NE on the adrenal cortex or its vasculature. Although a similar adrenal cortical degeneration has been described in rats following isoproterenol administration18 the mechanism of this and the NE produced lesions is as yet not clear.

The apparent inconsistency between our findings and the morphologic lesions in various organs other than the heart described previously,1-5, 7'9-11 might be explainable on the basis of (a) the presence of shock either
prior to and/or during the period of NE infusion, and (b) the use of excessive doses of NE by other investigators.

It is well known that shock may result in lesions in a number of organs, especially in the heart, kidneys, liver, intestine, and adrenals. In the clinical studies of Boughton et al., Brown et al., and Chung et al., NE was administered to patients for the purpose of treating shock. Under these conditions it becomes extremely difficult, if not impossible, to differentiate on morphologic grounds the etiologic factors responsible for the development of the lesions described.

The method of administration of NE in the present experiment was designed to approximate as closely as possible that used clinically. Although it is not standard practice to administer a calculated dose of NE, but rather to titrate the quantity of NE in an intravenous infusion and adjust the rate of flow with the degree of hypotension, the average dose of NE (expressed as the base) employed in a series of patients in our hospital has been in the order of 0.1 μg/kg/min for an average duration of six hours. The ranges of these values are 0.02 to 1.6 μg/kg/min and from fifteen minutes to five and one-half days respectively (unpublished work).

The selection of the smallest dose of NE for our experimental animals was based on a minimal hypertensive response of from 16 to 35% above control level. This percent change compares favorably with the 20% change in blood pressure in normotensive patients infused with 0.1 μg/kg/min of NE.

The incidence of cardiac lesions was shown to be related not only to the dose per unit time, but also to the duration of infusion. Doses which in five hours resulted in a low incidence, led to a high incidence when infused for fifteen hours. In addition, the rabbits appeared to be most, and the dogs least, susceptible for the development of cardiac lesions.

Other investigators have used both larger doses of NE and administered these over longer periods of time. Infrequently, the drug has been administered as single or multiple parenteral injections, and in some instances the quantity administered is expressed in such a manner that total doses cannot be determined. Szakacs, who in a well controlled experiment using dogs, found evidence of a necrotizing arteritis in the GI tract and splenic infarcts in addition to cardiac lesions, employed doses as high as 15 μg/kg/min for 10 hours, and doses up to 2.8 μg/kg/min for as long as 327 hours. Brown et al., in three dogs, gave 0.8 to 2.8 μg/kg/min for from four to sixteen days and also noted infarction and perforation of the ileum and a proliferative necrotizing endarteritis.

On the basis of our observations of a rapid deterioration of cardiac function with relatively small doses of NE administered over a short period of time, it is reasonable to assume that many of the morphologic changes in organs other than heart, described previously by the authors cited, may represent the effects of a combination of low cardiac output and induced increased peripheral vascular resistance with subsequent tissue hypoperfusion and tissue hypoxia.

It is at least entirely possible that excessive doses of NE may have a direct toxic effect on various organs. Since the morphologic characteristics of the extracardiac lesions which have been described are compatible with those in hyperoxic or congestive etiology, the proof of any additional direct toxic effect of NE will have to be derived from biochemical studies.

The morphology of the cardiac lesions produced by various sympathomimetic amines, and especially with NE and isoproterenol has been described previously. Our findings with NE emphasize the focal and isolated myofiber involvement which is present throughout the myocardium. These changes consist of histochemically definable myofiber degeneration and necrosis involving single cells or groups of cells. The earliest alteration discernible within myofibers is the accumulation of small lipid droplets. While this is frequently diffuse, focal myofibers, in addition, show both alterations in the staining pattern of LDH and SDH activity and large

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lipid droplet accumulation. With time, respiratory enzyme activity disappears from these fibers while the large lipid droplets remain.

The significance of these changes in terms of function is not clear as yet, although the combination of lipid accumulation and loss of respiratory enzyme probably signifies an irreversible cellular alteration. This interpretation is supported by the finding that early focal myofiber changes, as seen with respiratory enzyme stains and with the combination lipid-respiratory enzyme staining technique, have a distribution almost identical with that of subsequent necrosis as seen with conventional histologic methods.

The mechanism by which the cardiac lesions develop is unknown. The available evidence suggests that the effect of NE on myofibers is related to excessive stimulation of oxygen utilization without and adequate compensatory increase in oxygen supply via an augmented coronary flow. An additional factor of ischemia secondary to vascular alterations may be involved in the areas of subendocardial hemorrhage. Subendocardial hemorrhage has been shown to occur after carotid occlusion and section of the vagi and after stellate ganglion stimulation as well as after NE administration. The mechanism which has been proposed to explain these hemorrhages is based on an augmented and continued contraction of the ventricles even after the completion of the ejection phase. Capillary rupture and hemorrhage which occurs under these conditions could well lead to myofiber hypoxia and necrosis. The alterations in the myofibers in the subendocardial zone and in isolated foci throughout the myocardium, are morphologically indistinguishable by our techniques of microscopic analysis. Cellular hypoxia is most probably the basis of all of the myofiber alterations seen.

Healing of the lesions occurred by fibrosis. Connective tissue deposition became apparent as early as three days after NE infusion. At that time there was active phagocytosis of myofiber debris. By two weeks, fibrous scars were well developed. The very early proliferation of fibroblasts and accumulation of material which stains as collagen parallels observations on healing of myocardial infarcts in the dog.

Summary

The major toxic effect of norepinephrine (NE) infusion in dogs, cats, and rabbits in doses relatively comparable to those used clinically has been shown to be on the heart. Noncardiac lesions were those of congestion, and were seen in animals receiving the higher doses. The dogs in these dose groups showed evidence of progressive deterioration of cardiac function. All dogs which developed cardiac lesions also developed an acute adrenergic crisis.

The cardiac lesions in all animals consisted of focal degeneration and necrosis of myofibers, and subendocardial hemorrhage. These lesions healed within two weeks by fibrosis.

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Cardiovascular Effects of Sustained Norepinephrine Infusions. II. Morphology
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