Myocardial Lesions Produced by Digitalis in the Presence of Hyperthyroidism: An Experimental Study

By William H. Dearing, M.D., Arlie R. Barnes, M.D., and Hiram E. Essex, Ph.D.

Calculated therapeutic doses of digitalis and its derivatives did not produce demonstrable microscopic changes in the myocardium of experimental animals. Toxic doses of digitalis (twice a therapeutic dose) induced myocardial lesions in animals. In those animals with experimentally induced mild to moderate hyperthyroidism, calculated therapeutic doses of digitalis did produce myocardial lesions. Toxic doses of digitalis administered to animals with mild to moderate hyperthyroidism caused extensive degenerative changes in the myocardium or promptly killed the animals without associated microscopic lesions.

This investigation was undertaken in order to determine whether myocardial lesions are produced more readily in animals with induced hyperthyroidism than in normal animals when various doses of digitalis are administered. A previous study had shown that calculated therapeutic doses of digitalis fail to produce any demonstrable organic lesions in the myocardiums of normal animals.

Review of Literature

Histologic changes in the myocardiums of animals with experimental hyperthyroidism were reported in at least eight articles from 1913 to 1935. These histologic changes ranged from minor fatty degeneration in the muscle fibers to frank necrosis of the muscle fibers with exudative cellular infiltration. Fibroblasts and fibrosis have been described as replacing destroyed myocardial bundles. Lewis and McEachern in 1931, Rake and McEachern in 1931 and David in 1938, however, were unable to demonstrate specific myocardial lesions in animals with experimental hyperthyroidism. Fahr in 1916, Goodpasture, Hashimoto, and Fahr and Kuhle in 1921 and Goodall and Rogers in 1927 found evidence of histopathologic changes in the hearts of patients with hyperthyroidism. Baust and Lahey in 1930 considered that pathologic changes do not occur in the myocardiums of patients who have hyperthyroidism. Various other authors, however, have stated that heart failure does occur in hyperthyroidism without any evidence of coexisting cardiac disease (coronary sclerosis, syphilis, or rheumatic carditis), but that it is not encountered often. The voluminous literature dealing with cardiac dilatation, cardiac hypertrophy, metabolism, and chemical and physiologic changes in clinical and experimental hyperthyroidism will not be mentioned because it is beyond the scope of this article.

Histologic changes produced in the myocardiums of animals by various preparations of digitalis have been described frequently since 1904 and many investigations have dealt with the role of digitalis in hyperthyroidism. Foster, Sturgis, Grant, and others in 1925 and 1926 reported that digitalis was of value in hyperthyroidism when auricular fibrillation without heart failure was present. In 1932, Barker and his associates stated that digitalis was less effective in auricular fibrillation associated with hyperthyroidism than with auricular fibrillation associated with any other condition. Plummer in 1925 noted that administration of digitalis increased the mortality rate in cases of hyperthyroidism. This observation, in part, furnished the stimulus for this investigation. Many investigators have reported electrocardiographic changes in hyperthyroidism which are, however, not characteristic of the disorder. The changes include tachycardia, various cardiac arrhythmias (premature contractions, parasystolic auricular and ventricular tachycardia, auricular flutter, auricular fibrillation, and heart block). There were high P waves, tall T waves, decrease in amplitude of T waves, negative T waves, elevated RS-T segments, and depressed RS-T segments. The majority of investigators have concluded that there is no specific change in the electrocardiogram which is characteristic of hyperthyroidism.

The electrocardiographic changes in man and animals following the administration of digitalis also have been recorded by many investigators from 1909 to 1947. It will be seen from their papers that digitalis may not induce any significant change in the electrocardiogram or it may produce sinus bradycardia, sinus tachycardia, prolonged P-R interval, pulsat bigeminus, increase in the height of the T waves, decrease in the height of the T waves, negative T waves, elevation of the RS-T segment, depression of RS-T segment, and so forth, depending on the circumstances and the dosage of digitalis.
METHODS

Cats which appeared to be in good health were used for our studies. Each animal was trained to lie quietly on its right side while electrocardiograms were taken. A control tracing was made each day until the contour of the tracing was fairly constant, and the animal was trained satisfactorily.

The animals were weighed and then fed thyroid extract, double strength U.S.P., mixed with fresh meat each day. This dose of double strength U.S.P. thyroid extract varied from 1.0 to 2.0 Gm. per kilogram of body weight. When the animal failed to eat the food containing the thyroid extract, 1.0 to 2.0 mg. of thyroxin (prepared by Dr. E. C. Kendall) per kilogram of body weight was administered parenterally each day. An endeavor was made to render the animals moderately hyperthyroid, so that each animal would lose from 18 to 28 per cent of its weight during the course of the hyperthyroidism. Attempts were made in a few animals to measure the increase in the metabolic rate after administration of thyroid extract or thyroxin, but the process was considered too time-consuming and was discarded in favor of methods which permitted us to study a larger series of animals in which the degree of hyperthyroidism was estimated on basis of loss of weight, tremor, and heart rate.

After evidence of hyperthyroidism was exhibited, various preparations of digitalis were administered parenterally in a single dose. Digitalis (2.0 cc. = 1.0 cat unit = 0.8 U.S.P. XII digitalis units), digitoxin (0.2 mg. per c. c.; 0.42 mg. per kilogram of cat = minimal lethal dose), and lanatoside A (0.35 mg. per kilogram of cat = minimal lethal dose) were the preparations used. In order to maintain hyperthyroidism after digitalis was given, 1.0 mg. of thyroxin per kilogram body weight was injected daily into each animal.

Electrocardiograms were made at least once a week during the interval of hyperthyroidism and almost every day after the digitalis was administered.

When the course of studies was completed on each animal, the animal was killed quickly with ether or chloroform. Postmortem examination was performed promptly; blocks of tissue were removed from the heart and fixed in formalin. Sections of the heart were prepared, mounted on glass slides, and stained with hematoxylin and eosin for study.

Control animals were treated exactly like the other animals except that the controls did not receive digitalis or preparations of thyroid. A series of animals was studied which received preparations of thyroid without any digitalis.

RESULTS

Histologic Studies

The animals used in these studies will be grouped, for the purpose of presentation, as follows: (1) Healthy control animals not treated with drugs, (2) animals with induced hyperthyroidism, (3) animals given calculated therapeutic or toxic doses of digitalis, and (4) animals with induced hyperthyroidism which received digitalis in various doses.

Normal Animals. Thirty-two healthy cats that had not received any drugs served as control animals. Examination of the myocar-

![Degenerative changes in myocardial fibers of animals with severe hyperthyroidism (hematoxylin and eosin X275).](http://circ.ahajournals.org/)

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killed while all those with severe hyperthyroidism died.

No myocardial lesions were found in the 8 animals with moderate hyperthyroidism. These animals are the controls for our studies on the effect of digitalis in hyperthyroidism.

The effect of severe hyperthyroidism on the myocardium was studied since changes in myocardial tissue have been described in the presence of hyperthyroidism in man and animals. Animals with severe hyperthyroidism could not

be used as controls for our studies since the animals became too ill, the duration of the study could not be satisfactorily controlled, and the animals died readily of concurrent respiratory infections or of the induced metabolic disorder. In 2 of the 8 animals with severe hyperthyroidism, lesions developed. These consisted of scattered zones of destructive changes in the myocardial fibers (fig. 1).

Animals which Were Given Calculated Therapeutic or Toxic Doses of Digitalis. It has been shown by the authors1 that calculated therapeutic doses of digitalis did not produce evidence of histologic changes in the myocardium and lanatoside C). In these experiments, 60 to 80 per cent of the minimal lethal dose of digitalis was necessary to produce myocardial lesions.

The important point to note here is that doses of digitalis which were calculated on the basis of body weight to correspond to those given therapeutically to man failed to produce any histologic changes in the myocardiums of the animals.

Animals with Induced Hyperthyroidism which Received Digitalis. Calculated therapeutic doses of digitalis given to animals with mild or moderate hyperthyroidism can produce myocardial

<table>
<thead>
<tr>
<th>Degree of Hyperthyroidism</th>
<th>Administration of Thyroid</th>
<th>Dose of Digitalis (per cent M.L.D.* and drug)</th>
<th>Duration of Study After Digitalis (days)</th>
<th>Termination</th>
<th>Histologic Changes in Myocardium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>3.8-3.2 Kg.</td>
<td>16 Per cent lost</td>
<td>28 Days</td>
<td>30; digalen</td>
<td>14</td>
</tr>
<tr>
<td></td>
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<td></td>
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<tr>
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<td></td>
</tr>
<tr>
<td>Mild</td>
<td>2.6-2.3 Kg.</td>
<td>12 Per cent lost</td>
<td>28 Days</td>
<td>30; digalen</td>
<td>14</td>
</tr>
<tr>
<td>Moderate</td>
<td>2.2-1.8 Kg.</td>
<td>18 Per cent lost</td>
<td>28 Days</td>
<td>30; digalen</td>
<td>14</td>
</tr>
<tr>
<td>Moderate</td>
<td>3.7-3.0 Kg.</td>
<td>27 Per cent lost</td>
<td>25 Days</td>
<td>30; digalen</td>
<td>10</td>
</tr>
<tr>
<td>Moderate</td>
<td>3.6-2.8 Kg.</td>
<td>22 Per cent lost</td>
<td>21 Days</td>
<td>30; digitoxin</td>
<td>10</td>
</tr>
<tr>
<td>Moderate</td>
<td>3.4-2.7 Kg.</td>
<td>20 Per cent lost</td>
<td>21 Days</td>
<td>30; digitoxin</td>
<td>10</td>
</tr>
<tr>
<td>Moderate</td>
<td>3.0-2.2 Kg.</td>
<td>26 Per cent lost</td>
<td>21 Days</td>
<td>30; digalen</td>
<td>10</td>
</tr>
<tr>
<td>Moderate</td>
<td>1.8-1.5 Kg.</td>
<td>17 Per cent lost</td>
<td>21 Days</td>
<td>30; digalen</td>
<td>10</td>
</tr>
<tr>
<td>Moderate</td>
<td>2.1-1.8 Kg.</td>
<td>14 Per cent lost</td>
<td>25 Days</td>
<td>30; digalen</td>
<td>10</td>
</tr>
<tr>
<td>Moderate</td>
<td>3.0-2.4 Kg.</td>
<td>20 Per cent lost</td>
<td>21 Days</td>
<td>30; digalen</td>
<td>10</td>
</tr>
<tr>
<td>Moderate</td>
<td>1.5-1.1 Kg.</td>
<td>26 Per cent lost</td>
<td>21 Days</td>
<td>30; digalen</td>
<td>6</td>
</tr>
<tr>
<td>Moderate</td>
<td>3.4-2.6 Kg.</td>
<td>24 Per cent lost</td>
<td>21 Days</td>
<td>30; digalen</td>
<td>7</td>
</tr>
<tr>
<td>Moderate</td>
<td>2.4-1.9 Kg.</td>
<td>20 Per cent lost</td>
<td>21 Days</td>
<td>30; digitoxin</td>
<td>10</td>
</tr>
<tr>
<td>Moderate</td>
<td>2.7-2.2 Kg.</td>
<td>18 Per cent lost</td>
<td>21 Days</td>
<td>30; digitoxin</td>
<td>10</td>
</tr>
<tr>
<td>Moderate</td>
<td>2.3-1.8 Kg.</td>
<td>20 Per cent lost</td>
<td>21 Days</td>
<td>30; digitoxin</td>
<td>14</td>
</tr>
<tr>
<td>Mild</td>
<td>3.2-2.8 Kg.</td>
<td>13 Per cent lost</td>
<td>21 Days</td>
<td>30; digitoxin</td>
<td>14</td>
</tr>
<tr>
<td>Moderate</td>
<td>3.2-2.4 Kg.</td>
<td>22 Per cent lost</td>
<td>21 Days</td>
<td>30; digitoxin</td>
<td>10</td>
</tr>
<tr>
<td>Moderate</td>
<td>4.7-3.3 Kg.</td>
<td>31 Per cent lost</td>
<td>25 Days</td>
<td>30; digalen</td>
<td>9</td>
</tr>
</tbody>
</table>

* M.L.D. = Minimum lethal dose.

of 24 animals. In the present studies, 6 normal animals were given intravenously 30 per cent of the minimal lethal dose of digitoxin but no evidence of myocardial lesions was found when these animals were killed twelve days after the drug was administered. In the previous publication we noted that toxic doses of digitalis can produce myocardial lesions in animals. Histologic changes in the heart were produced by digitalis whole leaf or crystallin products of digitalis (digitoxin, lanatoside A, lanatoside B,

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lesions as shown in table 1. It is to be recalled that comparable doses of digitalis did not induce any evidence of structural changes in the heart of animals without hyperthyroidism.

Demonstrable histopathologic changes developed in the heart muscles of 10 of the 18 animals with mild or moderate hyperthyroidism which received calculated therapeutic doses of digitalis (fig. 2). Two of these 18 animals died within one to two days after administration of the digitalis preparation. In previous studies we showed that it was necessary for animals to live for at least five days, even after highly toxic doses of digitalis, before histologic changes could be demonstrated in the heart muscle; hence it was not likely that these 2 animals which died so soon would exhibit any myocardial lesions.

Smaller doses of digitalis (5 to 20 per cent of the minimal lethal dose) were much less likely to produce histologic changes in the myocardium of animals with mild to moderate hyperthyroidism as shown in table 2. Toxic doses of digitalis, however, either killed the hyperthyroid animal before sufficient time had elapsed for the development of cellular necrosis in the heart muscle or the animal died within a few

**Table 2—Effect of Small Doses of Digitalis on Histologic Changes in the Myocardium of Animals with Hyperthyroidism**

<table>
<thead>
<tr>
<th>Degree of Hyperthyroidism</th>
<th>Administration of Thyroid</th>
<th>Dose of Digitalis (per cent M.L.D. and drug)</th>
<th>Duration of Study After Digitalis (days)</th>
<th>Termination</th>
<th>Histologic Changes in Myocardium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weight Before and After</td>
<td>Days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kg.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Per cent lost</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>4.3-3.6</td>
<td>16</td>
<td>28</td>
<td>5; digalen</td>
<td>14</td>
</tr>
<tr>
<td>Mild</td>
<td>4.4-3.9</td>
<td>11</td>
<td>28</td>
<td>5; digitoxin</td>
<td>14</td>
</tr>
<tr>
<td>Moderate</td>
<td>4.6-3.7</td>
<td>19</td>
<td>28</td>
<td>5; digitoxin</td>
<td>14</td>
</tr>
<tr>
<td>Moderate</td>
<td>1.8-1.4</td>
<td>22</td>
<td>25</td>
<td>5; digitoxin</td>
<td>10</td>
</tr>
<tr>
<td>Moderate</td>
<td>3.7-2.9</td>
<td>22</td>
<td>25</td>
<td>5; digitoxin</td>
<td>10</td>
</tr>
<tr>
<td>Moderate</td>
<td>3.8-2.9</td>
<td>23</td>
<td>25</td>
<td>5; digitoxin</td>
<td>10</td>
</tr>
<tr>
<td>Mild</td>
<td>2.6-2.2</td>
<td>15</td>
<td>25</td>
<td>5; digitoxin</td>
<td>10</td>
</tr>
<tr>
<td>Mild</td>
<td>2.9-2.5</td>
<td>14</td>
<td>25</td>
<td>5; digitoxin</td>
<td>10</td>
</tr>
<tr>
<td>Moderate</td>
<td>3.6-2.9</td>
<td>18</td>
<td>25</td>
<td>5; digitoxin</td>
<td>10</td>
</tr>
<tr>
<td>Mild</td>
<td>2.0-1.8</td>
<td>10</td>
<td>25</td>
<td>5; digitoxin</td>
<td>10</td>
</tr>
<tr>
<td>Moderate</td>
<td>3.0-2.2</td>
<td>27</td>
<td>21</td>
<td>5; digitoxin</td>
<td>10</td>
</tr>
<tr>
<td>Mild</td>
<td>3.0-2.7</td>
<td>10</td>
<td>21</td>
<td>5; digitoxin</td>
<td>10</td>
</tr>
<tr>
<td>Moderate</td>
<td>2.5-2.0</td>
<td>21</td>
<td>21</td>
<td>5; digitoxin</td>
<td>10</td>
</tr>
<tr>
<td>Mild</td>
<td>3.2-2.8</td>
<td>13</td>
<td>25</td>
<td>10; digitoxin</td>
<td>25</td>
</tr>
<tr>
<td>Moderate</td>
<td>3.7-3</td>
<td>19</td>
<td>25</td>
<td>10; digitoxin</td>
<td>25</td>
</tr>
<tr>
<td>Mild</td>
<td>4.2-3.8</td>
<td>9</td>
<td>28</td>
<td>20; digitoxin</td>
<td>14</td>
</tr>
<tr>
<td>Severe</td>
<td>3.6-2.5</td>
<td>30</td>
<td>25</td>
<td>20; digitoxin</td>
<td>10</td>
</tr>
</tbody>
</table>

* M.L.D. = Minimum lethal dose.
days from extensive destructive changes in the myocardium (table 3 and fig. 3).

Table 3.—Effect of Toxic Doses of Digitalis on Histologic Changes in the Myocardium of Animals with Hyperthyroidism

<table>
<thead>
<tr>
<th>Degree of Hyperthyroidism</th>
<th>Administration of Thyroid Weight Before and After Kg.</th>
<th>Per cent lost</th>
<th>Days</th>
<th>Dose of Digitalis (per cent M.L.D. * and drug)</th>
<th>Duration of Study After Digitalis (days)</th>
<th>Termination</th>
<th>Histologic Changes in Myocardium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td></td>
<td>2.1–1.9</td>
<td>9</td>
<td>26</td>
<td>60; digalen</td>
<td>1</td>
<td>Died</td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
<td>—</td>
<td>25</td>
<td></td>
<td></td>
<td>1</td>
<td>Died</td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
<td>1.8–1.2</td>
<td>33</td>
<td>21</td>
<td>60; digitoxin</td>
<td>1</td>
<td>Died</td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td>1.7–1.3</td>
<td>24</td>
<td>22</td>
<td>60; digitoxin</td>
<td>5</td>
<td>Died</td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td>2.8–2.3</td>
<td>14</td>
<td>21</td>
<td>60; lanatoside A</td>
<td>6</td>
<td>Died</td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
<td>2.6–2.0</td>
<td>23</td>
<td>25</td>
<td>60; digalen</td>
<td>5</td>
<td>Died</td>
</tr>
</tbody>
</table>

* M.L.D. = Minimum lethal dose.

The myocardial lesions in hyperthyroid animals which received sufficient digitalis consisted of hemorrhage, cellular degeneration or necrosis, and inflammatory cellular exudates. Fibroblastic proliferation occurred if circumstances of the study permitted.

Electrocardiographic Studies

The animals in which hyperthyroidism was induced did not exhibit any characteristic electrocardiographic patterns; that is, the electrocardiographic changes were not constant and were not typical of hyperthyroidism to the exclusion of all other conditions. In the majority of the animals with hyperthyroidism, sinus tachycardia developed. At times, ventricular premature contractions, tall T waves, short T waves, negative T waves, elevated RS–T segments, and depressed RS–T segments were observed. Some of the electrocardiographic changes in the three standard limb leads when thyroid preparations had been administered to the animal for approximately three weeks are shown in figures 4 to 6.

When doses of digitalis, which were calculated not to exceed corresponding therapeutic doses for man, were given to animals with experimental hyperthyroidism, the following changes were noted with varying frequency among more than 500 electrocardiograms (each with three standard limb leads): (1) no significant alteration when compared to the control tracing; (2) sinus tachycardia; (3) sinus brady-

Fig. 3.—Extensive degenerative changes in myocardium of moderately hyperthyroid animal which received toxic dose of digitalis (hematoxylin and eosin ×275).
Fig. 4.—Series of electrocardiograms made on one animal comparing the control tracing with those made after three weeks of hyperthyroidism and then one day and ten days after a calculated therapeutic dose of digitalis was given. No histologic changes were found in the myocardium on the tenth day after digitalis was administered.

Fig. 5.—Series of electrocardiograms made on one animal comparing the control tracing with those made after three weeks of hyperthyroidism and then one day and ten days after a calculated therapeutic dose of digitalis was given. Definite myocardial lesions were found on the tenth day after digitalis was administered.
pressed RS-T segments in one or more leads, usually in Leads I and II or Leads II and III; (8) elevated RS-T segment in Leads I and II or Leads II and III; (9) decrease in height of T waves, and (10) negative T wave in Leads I and II, Leads II and III, or occasionally in all three leads.

We were unable to correlate any definite electrocardiographic pattern with myocardial lesions, although elevation of the RS-T segments as in figure 6 was usually associated with demonstrable cellular necrosis in the heart muscle. Negative T waves and depression of the RS-T segments are not necessarily indications of observable histologic myocardial lesions.

**COMMENT**

It is apparent that digitalis in calculated therapeutic doses may produce myocardial lesions in animals with hyperthyroidism while the same dose of digitalis will not induce any demonstrable pathologic changes in the heart of normal animals.

It should be pointed out that certain sources of error exist in these studies: (1) We have estimated the degree of hyperthyroidism rather than performed an actual determination of the increase in the metabolic rate with special apparatus. (2) We have calculated the dose of digitalis for the cat on the basis of body weight of the animal and have compared it with the dose used for human beings on the basis of units of body weight. We have no way of knowing whether the cat and man are equally sensitive to digitalis. We think this statement applies to whole-leaf digitalis that has been standardized by the cat unit method or for crystallin products (digitoxin and the lanatosides) which have been prepared gravimetrically for administration. (3) The morphologic study of the myocardium does not indicate the multitude of chemical and metabolic changes that may occur in the myocardium of animals treated with thyroid preparations or with digitalis preparations. Our studies show that animals treated with these preparations may die without any demonstrable lesion having developed in the myocardium.

It was noted that the older the animal, the more likely it is to have changes in the myo-
cardium after digitalis has been administered. None of the animals had any signs or symptoms suggestive of cardiac decompensation.

**SUMMARY**

No demonstrable microscopic lesions were found in the myocardium of 32 normal animals to which drugs were not administered. Thyroid extract (double strength U.S.P.) and thyroxin produced myocardial lesions in 2 animals of 8 animals with severe hyperthyroidism but did not induce any demonstrable pathologic change in the myocardiums of 8 animals with moderate hyperthyroidism. Calculated therapeutic doses of digitalis did not produce definite myocardial lesions in 30 animals without hyperthyroidism but did induce myocardial lesions in 10 out of 18 animals with mild to moderate hyperthyroidism.

Toxic doses of digitalis, when given to animals with mild or moderate hyperthyroidism, caused extensive degenerative changes in the myocardium if the animals survived more than five days or resulted in death within one to two days among animals in which microscopic changes could not be found in the myocardium. The myocardial lesions produced by digitalis in animals with hyperthyroidism consisted of hemorrhage, degeneration or necrosis of myocardial fibers, and inflammatory cellular exudates. Fibroblastic proliferation occurred if circumstances permitted healing of the damaged myocardium.

Numerous electrocardiographic changes were noted in the presence of experimental hyperthyroidism both when digitalis had been administered and when it had not. None of the electrocardiographic changes could be ascribed to any pattern which was characteristically associated with the myocardial lesions.

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Circulation. 1950;1:394-403
doi: 10.1161/01.CIR.1.3.394
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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