One hundred years ago in the Scandinavian Archives of Physiology, Robert Tigerstedt and Per Bergman published their experiments on the kidney and the circulation (12). They found that extracts of the kidney, specifically from the renal cortex, produced a consistent pressor effect when injected intravenously in recipient rabbits. They named the substance “renin.” This discovery is the basis for a huge number of publications on the renin-angiotensin system (RAS), which is a major enzymatic cascade involved in fluid balance, hypertension, and cardiovascular disease. Although their original paper, “Niere und Kreislauf,” is sometimes cited, it is seldom read. This is partly because the pace of modern research allows little time to track down old references and perhaps because the dominant language of European physiology has changed from German in 1898 to English in 1999. To celebrate the influence of this paper over the last 100 years, we have translated the entire paper.

There are many interesting aspects to this paper, not the least of which is to see how science was done and reported 100 years ago. The paper is a record of thought and experimentation, but the presentation is made cumbersome because of the lack of statistical analysis. There are 51 tables of raw data and 5 figures in the publication (see, e.g., Figs. 1 and 2). The use of statistics in medical research did not become widespread until the 1920s. August Krogh, the Nobel Prize winner for physiology in 1915, argued with his colleagues that they should use statistics. He received this reply from Professor Francis G. Benedict at Harvard: “[O]f all the scientists, physiologists and medical writers have been the last to seriously consider the statistical treatment. The consensus of opinion has seemed to be that the statistical treatment would not receive the appreciation and would not be as well understood by physicians and medical men in general, as our present method of handling [data]” (8).

Thus, in Tigerstedt’s and Bergman’s paper (12), as in others of the day (see, e.g., Ref. 10), tables of individual experiments are given. Where there was large variation of numbers, the tables were divided into three to give the highest, lowest, and middle numbers recorded. Today this makes the papers fascinating because we can see not only their actual data but also the dates on which experiments were carried out, allowing us to almost share the thought process of the investigators as they tested their hypothesis that there was a substance in the kidneys that could influence blood pressure.

They began these experiments on the 8th of November, 1896, with a cold-water extract from the kidney of a rabbit, which was injected into the jugular vein. They recorded blood pressure every 10 s and noted that within ~80 s, blood pressure rose from a range of 62-67 mmHg to 100 mmHg, an increase of ~50%. Two days later a second extract was injected, and this time blood pressure rose from 103 to 127 mmHg, ~25%. On the 14th of November, they tried again and this time within 60 s saw an increase from 97 mmHg to 113 mmHg, an ~18% increase. Obviously, these baselines varied, but for each single animal the result that impressed the authors was the consistent increase in blood pressure following the injection of the kidney extract. Today’s reviewers would probably criticize the variable baselines...
absolute alcohol and, after filtration and air drying, solubilize the extract in water or saline. The amount of solid substance for a maximal effect was 7-17 mg. They showed that blood from the renal arteries was also effective in raising blood pressure when given to nephrectomized rabbits. They tested the effect on the heart with the Langendorff technique but found no increase in heart activity. They named this substance simply “renin.” Considering that they could have named this substance with a long, explanatory German name such as “Blutdrucksteigende Substanz aus der Niere,” we can be grateful for their eminently practical choice of a brief name.

As good scientists, they went on to discover which part of the kidney produced renin. They separately tested extracts from the cortex and the medulla and found that the cortex was the source of the renin. They also tested whether the blood pressure increase was neurally mediated or resulted from direct effects on the vascular wall. They tested the effects of high cervical section and crushing the spinal cord, neither of which abolished the pressor effect of renin. Therefore, they concluded that the central nervous system was not required for the pressor effect of renin. They concluded that renin exerted its effect on the “peripheral vascular centers.” Unfortunately,

<table>
<thead>
<tr>
<th>Periods of 10 s</th>
<th>Blood pressure</th>
<th>Number of heart beats per 10 s</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maximal</td>
<td>Minimal</td>
<td>Mean</td>
</tr>
<tr>
<td>34</td>
<td>70</td>
<td>64</td>
<td>67</td>
</tr>
<tr>
<td>35</td>
<td>70</td>
<td>64</td>
<td>67</td>
</tr>
<tr>
<td>36</td>
<td>66</td>
<td>58</td>
<td>62</td>
</tr>
<tr>
<td>37</td>
<td>66</td>
<td>56</td>
<td>61</td>
</tr>
<tr>
<td>38</td>
<td>70</td>
<td>62</td>
<td>66</td>
</tr>
<tr>
<td>39</td>
<td>70</td>
<td>60</td>
<td>65</td>
</tr>
<tr>
<td>40</td>
<td>84</td>
<td>68</td>
<td>76</td>
</tr>
<tr>
<td>41</td>
<td>88</td>
<td>62</td>
<td>85</td>
</tr>
<tr>
<td>42</td>
<td>94</td>
<td>86</td>
<td>90</td>
</tr>
<tr>
<td>43</td>
<td>98</td>
<td>92</td>
<td>95</td>
</tr>
<tr>
<td>44</td>
<td>102</td>
<td>96</td>
<td>99</td>
</tr>
<tr>
<td>45</td>
<td>102</td>
<td>98</td>
<td>100</td>
</tr>
<tr>
<td>46</td>
<td>106</td>
<td>100</td>
<td>103</td>
</tr>
<tr>
<td>50</td>
<td>110</td>
<td>108</td>
<td>108</td>
</tr>
</tbody>
</table>

FIGURE 2. Experiment 1B, November 8, 1896. A kidney was pulverized with 21 ml of cold water. Injection into jugular vein. Within –80 s, there is a rise in mean blood pressure from 62-67 mmHg to 100 mmHg, i.e., an increase by ~50%. It is obvious that injected volume (5 ml) is not responsible for this rise.
these “centers” were not defined in the paper. They also concluded that the vascular musculature, i.e., the vascular smooth muscle cell, was not directly effected by renin. They obviously suspected that a peripheral autonomic system was mediating the action of renin.

Work by Oliver and Schäfer (7) in 1895 and Szymonowicz (10) in 1896 had shown that adrenal extracts increased arterial blood pressure by direct contraction of blood vessels. However, Tigerstedt and Bergman did not resolve whether renin was acting directly on blood vessels or indirectly. In their conclusion, they add a prophetic twist to their discovery. They suggest that if renin was produced in large amounts and excreted more slowly than usual, it would cause cardiac hypertrophy by increasing vascular resistance. This has turned out to be an extraordinarily accurate speculation. With appropriate humbleness of true experimental physiologists, they claim in their paper that they do not intend to propose a new hypothesis concerning the association of renal disease and cardiac hypertrophy because that would require new experiments.

Although great detail is given in the paper about the results, few details are given concerning the methods. For example, the choice of anesthetics, the preparation of the rabbits, and the methods of blood pressure measurement are not described. From contemporary papers (6, 7, 10) we know that chloroform, chloral hydrate, ether, and morphine were available, but most likely the experiments were carried out with the use of curare. Curare inhibits vasodilation. Although curare immobilizes animals, it unfortunately does not protect them from sensory input and pain. The equipment and methods were probably the same as used by Oliver and Schäfer in 1895 (7). They used the kymograph and mercury manometer invented by the great physiology teacher Karl Ludwig in 1847. Catheterization of an artery was probably by a brass tube, ligated in the vessel and attached by a saline-filled rubber tube to the manometer.

Robert A. A. Tigerstedt (1853–1923) was, at the time of the discovery, Professor of Physiology at the Karolinska University in Stockholm, Sweden. He was famous for his work on neurophysiology and circulation. He was the author of a textbook on the physiology of circulation published five years earlier (11). He had summarized in that book the work of Claude Bernard, Brown-Sequard, and others showing that nerve stimulation reflexively dilated or constricted smaller arterioles. Tigerstedt was to preside over a congress of medicine in Moscow in 1897, and it has been suggested that the research was started because he needed a paper to present at the congress. He recruited a medical student, Per Gustav Bergman, to work with him on the study. At the time, the French physiologist Brown-Sequard had started a trend for discovering “inner secretions” in organs by injecting extracts from donor organs into animals. Brown-Sequard and d’Arsonval (4) had used kidney extracts in nephrectomized animals and noted how it improved their condition. English physiologists from London University, Oliver and Schäfer (7) first demonstrated the powerful vasoconstrictive effects of adrenal medulla extracts in 1895. “Press-juicing” was applied to other tissues. Brown-Sequard and d’Arsonval even injected himself with a liquid extract of animal testes (3). Tigerstedt was obviously impressed by Brown-Sequard’s approach, which he describes in the opening line of the paper as “the ingenious thought of Brown-Sequard.” Tigerstedt suspected that something in the kidneys might also influence blood pressure; hence, the simple but profound title for Tigerstedt and Bergman’s report, “Kidney and circulation.”

Although Tigerstedt enjoyed a reputation for elegant and precise experimental studies and was an influential figure in physiology, the paper did not lead to a flurry of confirmatory studies. There was still plenty left to do. Was the effect species specific? Did any other organ secrete renin? How did the dose compare to adrenal medulla extract? However, the experiments stopped in October, 1897, and nothing more followed from the laboratory. Perhaps they were just for the conference in Moscow in 1897. Tigerstedt moved on, both scientifically and geographically, and never studied renin again. In 1900 he moved back to his native Finland to become Chair of Physiology at the University of Helsinki and pursued research on metabolism. Bergman apparently did not follow up the discovery either and eventually left academia to become a physician in Malmo, Sweden.

Thus, for lack of an advocate, this extraordinary discovery and the careful and insightful paper were almost forgotten for nearly 40 years. No mention of the discovery appears in Starling’s most influential English physiology textbook (9), even in 1933! The kidney was there to excrete urine, the textbook said, and no connection to blood pressure control was made. Yet the work did not go entirely unnoticed. In 1909, A. Bingel and E. Strauss (1) from Frankfurt not only published confirmatory results but also showed that renin was equally effective if extracted from pig and other animals. Unfortunately, their work was also forgotten. It was not until Goldblatt et al. (5) showed persistent ele-
vation of blood pressure by renal ischemia that
the interest turned once again to a substance
secreted by the kidney. Simultaneously, the
search for the action of renin became the focus
of Page, Helmer, and Kohlstaedt in Indianapolis
and Braun-Menendez, Fasciola, and Leloir in
Argentina. By 1939, the two groups had worked
out that renin was, not by itself a pressor sub-
stance, but the specific enzyme for a substrate,
the end product of which was the powerful little
peptide vasoconstrictor that became known as
angiotensin II (2).

References
1. Bingel, A. and E. Strauss. Uber die blutdrucksteigernde
1909.
3. Brown-Sequard, C. E. Demonstrant la puissance
dynamogenique chez l’homme d’un liquide extrait de
testicules d’animaux. Arch. Phys. Norm. Pathol. 21:
651–658, 1889.
sub-cutanees ou intraveineuses d’extraits liquides de
nombre d’organes, comme methode therapeutique. C. R.
Acad. Sci. 64: 1399–1404, 1892.
5. Goldblatt, H., J. Lynch, R. F. Hanzal, and W. W. Sum-
merville. Studies of elevation of systolic blood pressure
by means of renal ischaemia. J. Exp. Med. 59: 347–379,
1934.
6. Hunt, R. The fall of blood pressure resulting from the
stimulation of afferent nerves. J. Physiol. 18: 384–409,
1895.
7. Oliver, M. D., and E. A. Schäfer. The physiological effects
of extracts of the suprarenal capsules. J. Physiol. 18:
230–408, 1895.
8. Schmidt-Nielsen, B. August and Marie Krogh, Lives in Sci-
9. Starling’s Principles of Human Physiology (6th ed.)
Physiol. 8: 223–271, 1898.