Thesis Approved

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Major Adviser

Dean
FURTHER STUDIES OF THE EFFECTS OF CERTAIN DIETARY
REGIMENS ON THE BLOOD PRESSURE AND HEART RATE
OF TRAINED NORMAL DOGS WITH SPECIAL
REFERENCE TO THE BLOOD PRESSURE
LOWERING EFFECTS OF PROTEIN

BY
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A THESIS

Submitted to the Faculty of the Graduate School of the
Creighton University in Partial Fulfillment of
the Requirements for the Degree of Master of
Science in the Department of Physiology

OMAHA, 1953
DEDICATED

TO

MY PARENTS

Without Whose Sacrifice I Would Not
Now Be Writing These Words
PREFACE

The purpose of a preface is to orient the reader with the material that is to follow, and it is with this in mind that I would like to point out to the reader the scope of this thesis.

My work during the past year consisted mainly in showing that the elevated blood pressures and heart rates of dogs on high-caloric, high-carbohydrate diets could be lowered with iso-caloric high-protein diets. This data is to be found in Chapter VI.

Since this work was a continuation of work that had begun three years earlier, it was deemed necessary to include much of the earlier work in order to give proper perspective to the thesis. The first five chapters consist, for the most part, of material which has been the work of my co-workers, C. M. Wilhelmj, E. B. Waldmann, and T. F. McGuire, during the previous three years.

The Introduction is a sketch of the History of Blood Pressure, and the Blood Pressure Picture of Various Peoples throughout the world.

In Chapter VII, I have attempted to draw some conclusions as to the possible mechanisms involved in the cardiovascular responses to the different dietary regimens.
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INTRODUCTION

History

The first measurement of blood pressure was made by an English clergyman, the Reverend Stephen Hales, in 1708. He tied down a mare, laid open the left crural artery, and inserted into it a brass pipe. To this he attached a glass tube 9 feet long and found that the blood ascended 8 feet 3 inches above the level of the left ventricle. (1) Since Hales' time, there have been many attempts to measure the blood pressure in the human, but since Hales' method would have been, for practical purposes, impossible, other methods had to be sought.

One hundred and seventy-two years after Hales' discovery, Samuel von Baach introduced the first instrument for the recording of human blood pressure. His apparatus consisted of a rubber ball filled with water, to which was attached a mercury manometer. The ball was pressed down over the radial artery in the forearm, and that point on the manometer which corresponded to obliteration of the radial pulse was called the blood pressure. (1)

The von Baach manometer was improved by Potain who replaced the mercury manometer with an aneroid to which was attached an air-filled rubber bulb. The method
of taking the blood pressure with the Potain aneroid was exactly the same as with the von Basch manometer, but the former offered the advantage of being much less cumbersome. (1)

In 1896 Scipione Riva-Rocci introduced a blood pressure apparatus which was to be the forerunner of the present day mercury sphygomomanometer. The Riva-Rocci apparatus consisted of a rubber arm cuff which was placed inside a cloth bag. The arm cuff was connected to a mercury manometer and the manometer in turn was connected to a hand bulb. The arm cuff was applied and inflated by means of the hand bulb. This also caused the mercury to rise in the manometer. The cuff was inflated to a pressure well above the pressure needed to obliterate the radial pulse, then the pressure was slowly released. The point at which the radial pulse returned was the blood pressure. (1)

The method of measuring diastolic blood pressure was introduced by Korotkoff in 1905. He employed a Riva-Rocci apparatus but advocated the use of auscultation with a stethoscope directly over the artery distal to the arm cuff. The sounds described are known today as the famed Korotkoff sounds. His method involves inflating the arm cuff to a pressure well above that which is needed to occlude the artery, and then slowly releasing
the pressure while at the same time listening intently at a point directly over the artery and distal to the cuff. The point at which beats appear is the systolic pressure. Sounds continue as the pressure is released until a point is reached at which the sound becomes suddenly muffled. At a point 5-10 mm lower, these muffled sounds disappear completely. Korotkoff originally stressed the sudden muffling and not the disappearance as the point of diastolic pressure. (1)

Today's methods of taking blood pressure are nearly the same as was Korotkoff's modification using the Riva-Rocci apparatus. It is true that present-day equipment is better, and that recording devices and other gadgets have been introduced, but by far the greatest number of blood pressure determinations taken today make use of an air inflated arm cuff to which is attached either a mercury manometer or a spring aneroid. The apparatus is inflated to well above the pressure needed to occlude the artery, then the observer places the bell of his stethoscope over the artery, and listens for sounds to appear exactly as Korotkoff did in 1905.

Blood Pressure Among the Peoples of the World

Essential hypertension is perhaps the greatest threat to life in the United States. (2) According to
vital statistics data, (3) there were 1,443,607 deaths\(^1\) in the United States\(^2\) during the year 1949. By far the greatest killer was heart disease which claimed 518,568 lives\(^3\) (neoplasm was the second cause of death with 212,186\(^4\)). Of the cardiac deaths, 89,512 were due to arteriosclerotic heart disease (exclusive of coronary disease);\(^5\) 207,023 were due to coronary heart disease;\(^5\) and 83,808 were due to hypertensive heart disease.\(^6\)

Of 164,620 deaths due to disease of the nervous system and sense organs,\(^7\) 102,443 were due to cerebral hemorrhage.\(^7\)

The role of hypertension in the pathogenesis of cerebral hemorrhage and coronary heart disease is uncertain, but it has been stated that two-thirds of the persons who die of cerebral hemorrhage,\(^4\) and three-fourths of the persons who have coronary heart disease (2) have

\(^1\) Exclusive of fetal deaths and deaths overseas.


\(^3\) Ibid., Part I, Table 9, p. 132.

\(^4\) Ibid., Part I, Table 9, p. 120.

\(^5\) Ibid., Part I, Table 9, p. 134.

\(^6\) Ibid., Part I, Table 9, p. 136.

\(^7\) Ibid., Part I, Table 9, p. 130.
hypertension. Thus hypertension, while being directly responsible for over 83,000 deaths in 1949, probably also played a major role in the 207,023 coronary deaths, and the 102,443 deaths due to cerebral hemorrhage.

The incidence of hypertension in this country has been placed as 20 per cent of the adult population by some workers, (5) while other workers place it as high as 40 per cent. (6) Is it not strange, then, that essential hypertension—so common among inhabitants of the United States—is rare among some peoples and seemingly non-existent among others?

The Chinese have been studied quite extensively in regard to blood pressure. C. H. Wang (7) studied the records of 10,310 admissions to Hsing Ya Hospital between the years of 1932-1935, and found only 58 cases of hypertension. A similar study by J. H. Foster (8) among 4,000 patients in the medical wards of Changsha Hospital revealed only one case of essential hypertension.

Not only is essential hypertension rare among the Chinese, but their blood pressures are spectacularly low as well. Kilborn (9) in a study of 150 Miao (a primitive race of Chinese living in Kweichon), ranging in age from 16 years to 70 years, found the mean of the group to be 104 systolic and 70 diastolic. Furthermore, and
of great interest, there was no increase of pressure with advancing age (Table 1).

**TABLE 1**

**BLOOD PRESSURE STUDY OF 150 MIAO IN KWEICHON**

<table>
<thead>
<tr>
<th>Age</th>
<th>Mean</th>
<th>No. Examined</th>
</tr>
</thead>
<tbody>
<tr>
<td>16-20</td>
<td>108-70</td>
<td>17</td>
</tr>
<tr>
<td>21-25</td>
<td>106-68</td>
<td>26</td>
</tr>
<tr>
<td>26-30</td>
<td>109-76</td>
<td>22</td>
</tr>
<tr>
<td>31-35</td>
<td>106-70</td>
<td>21</td>
</tr>
<tr>
<td>36-40</td>
<td>103-72</td>
<td>22</td>
</tr>
<tr>
<td>41-45</td>
<td>100-71</td>
<td>12</td>
</tr>
<tr>
<td>46-50</td>
<td>99-68</td>
<td>16</td>
</tr>
<tr>
<td>55-70</td>
<td>100-75</td>
<td>14</td>
</tr>
</tbody>
</table>

Kilborn, in another study, (10) found the mean systolic and diastolic of 700 Szechwanese students to be 111-70. The mean systolic and diastolic of 9 American and Canadian students brought up in Szechwan was 120-80. Cadbury (11) studied the blood pressures of 774 male Cantonese students attending the Canton Christian College. They lived in much better conditions than the average Chinese. They ate well, partook of athletic activities, and in general they led a type of life
equivalent to that of American school boys (Table 2).

**TABLE 2**

**BLOOD PRESSURES OF 774 CANTONESE MALE STUDENTS ATTENDING THE CANTON CHRISTIAN COLLEGE**

<table>
<thead>
<tr>
<th>Age</th>
<th>Mean Systolic</th>
<th>Mean Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-14</td>
<td>83</td>
<td>51</td>
</tr>
<tr>
<td>15-20</td>
<td>101</td>
<td>62</td>
</tr>
<tr>
<td>21-30</td>
<td>101</td>
<td>68</td>
</tr>
</tbody>
</table>

C. L. Tung, in an interesting piece of work, took blood pressures of 30 Chinese students who had been in the United States for over two years. When these students returned to China, and had been residing there for three years, he again took their pressures. The mean systolic and diastolic for the group while in the United States was 113-72. Upon returning to China it had fallen to 102-64.

Probably the most extensive blood pressure study done on the Chinese was done by W. K. Ling. He made a statistical survey of 20,948 life-insurance applicants from all parts of China. Of this number, 15,607 were accepted as risks, of which 15,114 were males. It is interesting to compare these figures with those of Symonds' extensive study (14) on 150,419 Caucasian males.
which were gathered from life-insurance data in the United States (Table 3).

**TABLE 3**

A COMPARISON OF THE BLOOD PRESSURES OF 15,114 HEALTHY MALE CHINESE IN CHINA AND 150,419 HEALTHY MALE CAUCASIANS IN THE U.S.A.

<table>
<thead>
<tr>
<th>Age</th>
<th>Mean Systolic</th>
<th>Mean Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Symonds</td>
<td>Ling</td>
</tr>
<tr>
<td>15-19</td>
<td>123.5</td>
<td>111.4</td>
</tr>
<tr>
<td>20-24</td>
<td>124.2</td>
<td>113.6</td>
</tr>
<tr>
<td>25-29</td>
<td>124.5</td>
<td>113.9</td>
</tr>
<tr>
<td>30-34</td>
<td>125.1</td>
<td>115.0</td>
</tr>
<tr>
<td>35-39</td>
<td>125.3</td>
<td>117.2</td>
</tr>
<tr>
<td>40-44</td>
<td>126.4</td>
<td>119.6</td>
</tr>
<tr>
<td>45-49</td>
<td>128.2</td>
<td>121.9</td>
</tr>
<tr>
<td>50-54</td>
<td>130.2</td>
<td>124.6</td>
</tr>
<tr>
<td>55-59</td>
<td>133.5</td>
<td>127.2</td>
</tr>
<tr>
<td>60 &amp; over</td>
<td>135.2</td>
<td>...</td>
</tr>
<tr>
<td>All ages</td>
<td>127.6</td>
<td>115.8</td>
</tr>
</tbody>
</table>

Another group of people studied is the Eskimo. MacMillan (15) during an Arctic expedition did not find one single case of hypertension among Polar Eskimos.
although he found hardening of the arteries quite common. Levine (16) during an expedition to Alaska recorded the blood pressure of 823 Eskimos. He excluded all those with a systolic greater than 129, and/or a diastolic greater than 82, following the procedure of Robinson and Brucer.(6) He reported the means and standard-errors for males and females in the age range of 21-80 years. Male systolic was 109.9±0.68, and diastolic was 71.0±0.44. Female systolic was 109.6±0.72, and the diastolic was 70.6±0.44 (Table 4).

The Eskimo is a Mongoloid subsisting on a high meat diet. His blood pressure is below that of the White race, and falls within the range determined for other Mongoloid groups such as Chinese, Japanese, and Koreans.(16)

Thomas (17) studied the blood pressures of 142 Greenland Eskimos and found the mean systolic and diastolic of the group to be 127-76. Of the entire group, only three had a systolic pressure greater than 150.

Crile and Quiring (18) studied the blood pressures of 63 Eskimos and 13 Chippewa Indians. Of the Eskimos, 30 were males and 33 were females. The males averaged 119-75 and the females averaged 112-72. Mean age for the males was 38.3 years, and for the females was 31.4 years. The Chippewas were from Northern Canada, and lived much like the Eskimos. Six were males and seven were females. The average blood pressure of the
### TABLE 4

**THE NORMAL BLOOD PRESSURE OF THE ESKIMO AT VARIOUS AGE GROUPS**

<table>
<thead>
<tr>
<th>Age</th>
<th>Systolic</th>
<th>N</th>
<th>Diastolic</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8-12</td>
<td>97.9 ± 1.18</td>
<td>80</td>
<td>65.6 ± 0.81</td>
<td>82</td>
</tr>
<tr>
<td>13-15</td>
<td>101.2 ± 1.45</td>
<td>67</td>
<td>65.9 ± 0.93</td>
<td>67</td>
</tr>
<tr>
<td>16-20</td>
<td>107.2 ± 1.22</td>
<td>51</td>
<td>67.6 ± 0.96</td>
<td>52</td>
</tr>
<tr>
<td>21-30</td>
<td>110.5 ± 1.15</td>
<td>77</td>
<td>71.0 ± 0.75</td>
<td>83</td>
</tr>
<tr>
<td>31-40</td>
<td>108.7 ± 1.30</td>
<td>55</td>
<td>71.8 ± 0.88</td>
<td>55</td>
</tr>
<tr>
<td>41-50</td>
<td>110.1 ± 1.45</td>
<td>45</td>
<td>70.5 ± 0.91</td>
<td>43</td>
</tr>
<tr>
<td>21-80</td>
<td>109.9 ± 0.68</td>
<td>191</td>
<td>71.0 ± 0.44</td>
<td>216</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8-12</td>
<td>97.1 ± 1.23</td>
<td>60</td>
<td>65.7 ± 0.67</td>
<td>61</td>
</tr>
<tr>
<td>13-15</td>
<td>105.6 ± 1.5</td>
<td>37</td>
<td>67.5 ± 1.06</td>
<td>37</td>
</tr>
<tr>
<td>16-20</td>
<td>108.4 ± 1.28</td>
<td>51</td>
<td>69.6 ± 1.0</td>
<td>52</td>
</tr>
<tr>
<td>21-30</td>
<td>108.4 ± 0.99</td>
<td>101</td>
<td>68.0 ± 0.62</td>
<td>100</td>
</tr>
<tr>
<td>31-40</td>
<td>109.9 ± 1.4</td>
<td>52</td>
<td>70.9 ± 0.85</td>
<td>53</td>
</tr>
<tr>
<td>41-50</td>
<td>105.6 ± 2.15</td>
<td>28</td>
<td>70.6 ± 1.29</td>
<td>30</td>
</tr>
<tr>
<td>21-80</td>
<td>109.6 ± 0.72</td>
<td>198</td>
<td>70.6 ± 0.46</td>
<td>208</td>
</tr>
</tbody>
</table>
males was 120-80, and of the females was 124-75. Orile and Quiring (19) also made a study of 35 male Maya-Quiche Indians, 30 of whom were soldiers, and the other 5, laborers. These Indians live in Guatemala, Central America. Average pressure for the 30 soldiers was 111-77, and for the 5 laborers was 104-73.

In a comparative study of the blood pressures of 500 male Hindus aged 20-25 years with a similar group of Europeans living in Calcutta, McCay (20) found the systolics of the Hindus ranged from 90-105, while the Europeans living in Calcutta ranged from 115-130. McCay employed the palpatory method, and while his comparison between Hindus and Europeans is legitimate, his values cannot be legitimately compared with those of other workers who use an auscultatory method.

A study of the blood pressures of 903 healthy Korean prisoners by Mikamo (21) found the systolic for each age group almost the same—the range being 113.6-114.4. The mean diastolic pressure was found to advance slowly with age from 69.3 in the 20-24-year-old group to 75.9 in the 60-64-year-old group.

In a study on 915 native Filipinos of which 697 were males and 218 were females, Concepcion and Bulatao (22) found that the mean systolic and diastolic for the males was 115.6-79.1, and for the females was 116.0-83.4.
Musgrave and Sesen (23) studied 40 Filipinos and 97 Americans living in the Philippines. They used a palpation method and found the mean systolic for the male Filipinos was 108, and for the female Filipinos was 113. The Americans showed a strong tendency to a decrease in blood pressure as the length of residence in the Philippines increased. Those residing from one month to one year had a mean systolic of 124, while those residing for more than ten years had a mean systolic of 113.

Chamberlain (24) recorded systolic pressures of 1,042 healthy American soldiers stationed in the Philippines aged 20-40 years, and of 36 Filipinos under 40 years of age. He used a palpation method. The American soldiers averaged 115 for the 15-30-year-old group, and 118 for the 30-40-year-old group. The Filipinos averaged 115-116. He concludes that there is no significant difference in the blood pressures of white men living in the Philippines, and blood pressures of native Filipinos, although the blood pressure of white men living in the Philippines is quite lower than the blood pressure of white men living in temperate climates.

Ferrer (25) studied the blood pressure of children of various nationalities living in the Philippines. The nationalities included Americans, Mestizos (half breeds), Chinese, Spanish, Germans, British, Syrians, and Russians,
and native Filipinos. There was no essential difference between the mean blood pressures of the various nationalities and the Filipino group.

B. H. Kean (26) made an interesting study of the blood pressures of the Cuna Indians. These Indians live on the San Blas archipelago which lies a few miles off the mainland in the Atlantic Ocean, and stretches from the northern tip of Colombia to within 100 miles of the Canal Zone. The Indians number about 15,000 and are very primitive—living mainly on fish, coconut milk, and fried or boiled green bananas and occasional minor agricultural supplements. The data were collected on 407 of the natives (Table 5). The spectacularly low pressures, plus the fact that these people show no tendency to have an increasing blood pressure with advancing age, is extremely interesting.

Donnison (27) studied the blood pressure of 1,000 African natives and concluded that, although young males had blood pressures as high as their European brothers, blood pressure in the African native does not increase with advancing years as it does in the European.

Hypertension and its serious complications was found to be quite rare among native Africans by Williams. (28) In a study of 1,000 natives, systolic pressures above 144 were seldom encountered, while
systolics below 100 were found in 110 persons.

TABLE 5
BLOOD PRESSURE OF CUNA INDIANS BY AGE GROUPS

<table>
<thead>
<tr>
<th>Age</th>
<th>Mean Systolic</th>
<th>Mean Diastolic</th>
<th>Number Examined</th>
</tr>
</thead>
<tbody>
<tr>
<td>16-25</td>
<td>107.9</td>
<td>70.9</td>
<td>90</td>
</tr>
<tr>
<td>26-35</td>
<td>104.4</td>
<td>69.0</td>
<td>115</td>
</tr>
<tr>
<td>36-45</td>
<td>103.7</td>
<td>69.4</td>
<td>90</td>
</tr>
<tr>
<td>46-55</td>
<td>104.5</td>
<td>70.0</td>
<td>64</td>
</tr>
<tr>
<td>56-65</td>
<td>105.3</td>
<td>66.0</td>
<td>35</td>
</tr>
<tr>
<td>66 &amp; over</td>
<td>109.4</td>
<td>66.7</td>
<td>13</td>
</tr>
<tr>
<td>Total</td>
<td>105.2</td>
<td>69.3</td>
<td>407</td>
</tr>
</tbody>
</table>

The findings of Donnison (28) and Williams (28) are interesting in the light of a study by Adams (29) of the blood pressures of American Negroes. He investigated 5,000 employees of an industrial center, one-third of whom were Negroes. He found higher systolic and diastolic averages in the Negroes for all age groups than were found in the white workers. After the age of 40 years, the increase of pressure with advancing years was more rapid in the Negro than in the white race.
This treatise would not be complete without some mention of the factors which may account for the difference between the low blood pressures of Asians, Africans, and others, and the higher blood pressures of their American and European brothers.

Among the factors which may play a role are:
- (a) modern civilized life,
- (b) diet,
- (c) climate.

Modern civilized life, with its complex social patterns and high degree of mechanization, may be an important factor in the development of much hypertension. It is conceivable that the incessant grinding of the machines, the speed at which we live, and the myriads of social problems with which modern civilized man has to contend produces a stress on the cardiovascular system which, if applied for a long enough time, will engender permanent adaptation of the system.

The role played by diet in the production of hypertension is still conjectural. It is interesting to note that the primitive Eskimo--subsisting almost entirely on a meat diet--is blessed with a rarity of hypertension. Contrast this with a note from Martinet's Clinical Therapeutics for 1925 (30) on the treatment of uncomplicated high blood pressure:
There is advantage in carefully regulating the amount of food protein of whatever source. The normal daily allowance of proteins in the adult may be put down as approximately 90 grams. There is advantage in restriction below this figure in the presence of high blood pressure . . .

Probably of more importance than the type of foodstuff is the amount of food that is eaten. There is a definite correlation between overweight and high blood pressure. (31,32,33) The level of caloric intake in this country is notoriously high—probably because food is so easy to procure. Primitive man, on the other hand, is not so fortunate (or unfortunate, as the case may be). The procurement of food is for him a constant struggle, and he must be content with small amounts. The low level of caloric intake may well be a factor in the rarity of hypertension among Chinese, Africans, Eskimos, and others.

The vaso-relaxant action of heat may be a factor in the low blood pressures of people living in the Tropics. However, the Eskimo has low blood pressure even though he is exposed to the vaso-spastic action of cold. Thus, climate probably plays a role which is minor.

**Summary**

1. Hypertension is extremely common in the United States and in Europe.

2. Many peoples of the world, viz., Chinese, Africans, Filipinos, Hindus, Eskimos, and others, not only show
a paucity of hypertension, but have blood pressures which are spectacularly low when compared with Americans and Europeans.

3. Factors which may play a role in the difference of blood pressures between Americans and Europeans, on the one hand, and Chinese, Africans, etc., on the other hand, are: the pace of modern civilized life, diet, and possibly climate.
CHAPTER I

THE AUSCULTATORY METHOD OF ALLEN

In 1923, Fredrick M. Allen (33) described a method of taking blood pressure in the dog by means of auscultation. He claimed that the auscultatory method gave readings which agreed closely with readings obtained by arterial puncture and direct mercury manometry, and that the auscultatory method offered many advantages over the direct puncture method.

Previous to this time, all blood pressure studies in the dog were carried out by direct manometry. In this method, a needle, or a cannula is inserted into one of the large arteries (usually the carotid or the femoral). This is then connected to a suitable mercury manometer, so that the column of blood is allowed to act directly on the mercury. The height of the mercury column is a reliable index of the pressure of the blood within the artery. This method, while being highly accurate, has several serious disadvantages. Chief among these are:

(a) Mean pressure is recorded instead of systolic and diastolic pressure. Due to the high degree of inertia of mercury, the oscillations of the mercury column do not reflect the animal's pulse pressure. Thus, instead of systolic and diastolic recordings,
one must settle for mean blood pressure recordings.

(b) Pain. The method involves inserting a needle into an artery and this is liable to be quite painful to the dog. This pain may in itself raise the blood pressure by stimulating the sympathethic-adrenal medullary system. If the procedure is repeated often enough, the animal may anticipate the pain, and this may engender apprehension and fear. These latter emotions also involve stimulation of the sympathethic-adrenal medullary mechanism, and so they too are associated with an elevation of the blood pressure. These emotional rises are highly undesirable, and may have an adverse effect on the course of the experiment.

(c) Inability to carry out long term experiments. Since the method involves puncturing the skin and the artery, the procedure cannot be carried out too often, because excessive trauma is apt to occur with a resulting hematoma, inflammation, or thrombosis. These complications make it difficult or impossible to obtain further recordings.

The advantage of Allen's method over direct mercury manometry is that Allen's method does not have the disadvantages inherent in the latter method. Both systolic and diastolic readings can be taken by the auscultatory method. Also, since there is no puncture,
readings can be taken as often as desired, and there will be no pain.

In describing the method, Allen (33) suggests first, shaving the dog's leg; second, placing the receiver of the stethoscope directly over the anterior tibial artery just above the ankle, and securing it in place with rubber bands (the stethoscope receiver is specially built; the bell has about the same diameter as a penny, and it is 5-6 mm thick); third, wrapping a pediatric size blood pressure cuff snugly but not tightly around the leg so that its lower part encloses the receiver of the stethoscope; fourth, auscultating in the same manner as is done on the human.(33)

Allen (33) said the method gave readings (systolic) which were in good agreement with those obtained by direct mercury manometry, although the direct method gave readings which were usually a few millimeters lower. He also stated that if adrenaline is given intravenously, the two methods reflect the rise in blood pressure in a parallel fashion.

When work was begun on blood pressure in this laboratory four years ago, a method of taking the dog's blood pressure over long periods of time was desired. Consequently, Allen's method was adopted. The method has been modified by Wilhelmj, Waldmann, and McGuire,(34)
but it is essentially the same as Allen originally de-
scribed it.

Wilhelmj and co-workers (34) made a comparison
between the auscultatory technique and direct mercury
manometry. Pitressin (1U/kg/I.V.) was used to raise the
blood pressure; and mecholyl (4 drops of a 25 per cent
solution intranasally) was used to lower the blood pres-
sure (Fig. 1).

Wilhelmj (34) lists the following modifications
of Allen's method:

1) An observer who has had considerable experience
   in taking blood pressure with the auscultatory
   method on dogs.
2) Selection of dogs with long slender hind legs
   in which the tone quality is good.
3) Careful training. This is of prime importance
   and may require from a few weeks to several
   months in different dogs. In untrained animals
   the pressure may be very high (200-250/100-150)
   and irregular, but as training proceeds these
   values decline and finally reach the level and
   constancy characteristic for each particular
   animal. In untrained animals, the sounds may
   be very variable in quality and show ausculta-
   tory gaps or even complete disappearance of all
   sounds (vasospasm) but these irregularities
   tend to disappear with proper training.
4) When by trial, the proper spot is found to obtain
   good tones, it should be marked by tattooing and
   the stethoscope always placed over this spot.
5) The stethoscope should be held firmly over the
   spot by proper-sized rubber bands which do not
   constrict, and the cuff wound firmly and smoothly
   over it.
6) The animal should lie on the back or side on a
   comfortable rack.
7) The leg should be held in extension by a leg
   strap.
Fig. 1.—A Comparison of the Direct Puncture and the Auscultatory Methods of Measuring Blood Pressure.
CHAPTER II

TRAINING OF DOGS FOR BLOOD PRESSURE STUDIES

When blood pressure studies were begun in this laboratory four years ago, it was decided to use dogs selected as randomly as possible. There were, however, some qualifications which had to be satisfied before a dog was judged suitable. One of these was size. Optimum weight was between 25 and 35 pounds, because the rack upon which the dog is placed is adapted to about this size of dog. Dogs of this size are also easier to handle than very small or very large dogs.

Another qualification was a leg that good blood pressure readings could be taken from. Long slender legs were found to be best in most cases; however, the only way to tell definitely whether a dog was going to be adequate was to wrap a cuff around the leg and take the pressure.

Tones on the dog are much softer than on the human. Care must be exercised when taking the dog's pressure to center the stethoscope receiver over the artery—and this is important. If it is haphazardly placed on the general area (as is often done on the human), tones will not be heard.

When it is established that a dog can be used
for blood pressure studies, the next step is the training. The importance of training cannot be over-emphasized.

The mechanisms which regulate the blood pressure are extremely labile. In fact, any afferent impulse coming into the central nervous system can affect the blood pressure. Apprehension, fear, in fact any of the emotions can cause pronounced alterations in blood pressure. These changes are highly undesirable in our studies, because they constitute factors which may have a marked influence on the experiment. To minimize fear and apprehension, the procedure of taking the blood pressure must be built into the dog's living pattern.

The key to proper training is ritualism. Every time a set of readings is taken, the identical procedure must be followed if the animal is to be properly conditioned. The procedure begins as soon as a dog is taken from his cage. He is immediately led to a large pen in which he is supposed to evacuate his bowels, and void his urine. The dogs learn to do this remarkably early. Usually, they "unload" the very first time they are put in the pen. The inviting stimulus is probably the presence of other dogs' excreta.

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1 Personal communication from Dr. Wilhelm.
Next, the dog is led by leash into the blood pressure room. Some dogs can be trained to jump up onto the rack, but others must be lifted; and once the pattern is established, it must be followed. After the dog is on the rack, he is put down on his right side. If pressure on the shoulders is used to initiate movement, then pressure on the shoulders should henceforth be used. These are little things, but nevertheless, they are important. Unless the dog is taught (through constant repetition of the same pattern) what to expect from moment to moment, apprehension is liable to develop, and apprehension affects the blood pressure.

Next, the left leg is put in extension by means of a leg strap. After that, the receiver and cuff are applied to the right leg, and auscultation is carried out as described in the preceding chapter.

The training period evolves into two phases:(35)

(a) The phase of objective stabilization. This is the phase in which the dog has learned the procedure, and lays very calmly on the table. To all outward appearances, he has become adapted to his new pattern. The blood pressure readings tell quite a different story, however. Readings are high, and daily fluctuations may be extremely bizarre. This is evidence of an apprehension or emotional tension. The dog: evidently is not yet
ready to place his whole trust in the procedure. To the observer, however, the dog appears quiet and relaxed.

(b) The phase of subjective stabilization. During this phase, the blood pressure readings gradually fall till they reach a stable level. Fluctuations which previously had been bizarre and spiking settle down to a pattern of gentle undulations. This pattern is characteristic for the trained dog.

The length of time it takes to train a dog may vary from weeks to months. Not all dogs stand up under the training; indeed, some have to be discarded for one reason or another, even though they may have good tones.

Again, emphasis must be placed on the importance of routinizing the procedure. In the following paragraphs, we shall see why this is so.

It has been mentioned previously that blood pressure studies have been going on in this laboratory for about four years. All of the dogs have been in use for over a year. In fact, four of the dogs have been under observation for over three years. During this time, daily blood pressure determinations have been carried out, and since extreme care has always been taken to ritualize the procedure, the dogs have all attained a high degree of conditioning.

It was quite by accident one day that an incident
happened which was to lead to a series of planned experiments on the effects of emotions on the blood pressure. Between two and three years ago when Dr. Wilhelmj and Dr. Waldmann were working together, one of them (Dr. Wilhelmj) was just completing his usual ten daily readings on a dog, when there occurred a knock on the door. The door was unlocked, and the visitor was admitted, while in the meantime, the dog remained prepared on the rack. During the ensuing conversation, the dog lay quietly, apparently oblivious to the goings on. After a few minutes, the visitor left, and as Dr. Wilhelmj was getting ready to remove the dog, he decided instead to take a few more readings. The results were astounding. The readings which had been in the vicinity of 148 systolic and 81 diastolic were now in the vicinity of 171 systolic and 106 diastolic. After taking the readings, the dog was returned to his cage. Later in the afternoon, the dog was again brought into the laboratory, and another set of readings was taken. This last set was in good agreement with the original set of readings. During the ensuing months, this was repeated several times in the form of an experiment. The results substantiated the original observation.(35)

Another experiment along the same lines was the effect of changing experimenters. The usual observer,
after finishing his set of readings, slipped out of the room, and a new observer slipped in, being careful not to be seen by the dog. The new observer then took a set of readings which were found to be in close agreement with the first set. Then, the new observer made his presence known to the dog. The dog looked surprised, but did not seem afraid, nor did he try to get off the table. The new observer then took a third set of readings, and these were significantly higher than the first two sets.(35)

One day, the kennels were in an uproar because new dogs were being brought in, and because there were strange carpenters making some repairs on the premises. At the height of the uproar, it was decided to take some readings on one of the trained dogs to see what effect the disturbance had on the blood pressure. The dog was prepared in the usual manner, and after being allowed some time to rest, a set of readings was taken. This set was considerably higher than what was customary for the dog. Later in the afternoon, after things had quieted down, the dog was again prepared, and another set of readings was taken. This set was within the range of the dog’s normal values.(35)

The next experiment is similar to those just described, but illustrates the extreme care which must be
given to small (and seemingly insignificant) details in the procedure. The dog used was a small, highly sensitive collie type, that had been in use for over a year. Dr. Wilhelmj took the ten standard readings one day, and they were in close agreement with the dog's normal values. After taking the readings, he transcribed them into the permanent records, then crumpled up the scratch paper and threw it into the wastebasket. This was the customary procedure, and his next step was to take the dog off the table. Instead of doing this, a second set of readings were taken. The mean of the first ten readings was 127 systolic, and 64 diastolic, whereas the mean of the second ten readings was 172 systolic, and 100 diastolic. Later, this experiment was repeated several times, with nearly the same results, but the difference showed a tendency to diminish if the experiment was repeated too often—evidence that it was being incorporated into the conditioning. When this experiment was tried on other dogs, the results were not so striking; in fact, most dogs showed no response. The emotional stratum of the dog was the determining factor. Those that were overly sensitive and high-strung responded, while the more phlegmatic types did not. (35)

The last of this series of experiments was done to see the effect on a male dog's blood pressure when a
bitch in estrus was brought into the room. One of the males was prepared and the usual set of readings was taken. Then a bitch in estrus was taken into the room and held up so that the male dog could inspect the genitals. Readings were made. Then the bitch was taken out of the room, and another set of readings was made. There was a slight rise of both systolic and diastolic while the bitch was in the room, but both systolic and diastolic promptly returned to normal when she was removed from the room. This result, though disappointing, can be explained first because the dog was a highly phlegmatic type, and second because the dog had been without food for 29 days. The effect of fasting on diminishing the libido is well known, so undoubtedly this had a great deal to do with the dog’s poor response. (35)
CHAPTER III

FASTING

Fasting provides a means of bringing an animal to a definite nutritional level, and it was for this reason that it has been utilized in our work. Since our dogs were originally mongrel street dogs, their nutritional levels varied quite considerably, and it was for the purpose of bringing them all to the same relative nutritional status that fasting was used.

There is quite an extensive literature on the subject of the effects of fasting on animals and man, and it is not our purpose to review it here. However, it will be advantageous to examine some of the effects of fasting on the animal organism. Keys made an extensive study of the effects of fasting on humans. He found that after caloric intake was abolished, the desire for food disappeared after about the third or fourth day, and that this was followed by complete indifference to, and later repulsion to the thought of food.\(^{(36)}\)

Fasting produces little change in mentality and emotions except that states of euphoria are frequent.\(^{(36)}\) Contrast this with the mental and emotional changes brought about by prolonged low-caloric undernutrition. These individuals become mentally depressed, introverted,
irritable, and shy away from social contacts. They are constantly thinking of food and may express this desire subconsciously by developing interests in farming, agricultural science, etc.; and following realimentation they may hoard food for months in spite of ample food stores. (36)

If one word could sum up the response of the animal organism to fasting, that word would be conservation. The intensity of metabolism during fasting is decreased tremendously, as is the amount of active metabolizing tissue. (37) Less essential tissues such as fat, muscle, and liver undergo large losses during starvation, whereas more essential tissues such as nervous tissue and plasma proteins remain practically unchanged. (37) There is a total reduction in the activity of the individual. Blood pressure and heart rate are considerably reduced. (36, 37, 38) Muscle strength tests of single effort are reduced about 30 per cent, and of endurance are reduced about 85 per cent during fasting. (36) The individual assumes a posture which is most conducive to energy conservation. The posture is one of dependence—the head hangs down upon the chest, and the back and shoulders are stooped forward. Movements such as walking are slow and kept to a minimum. (39)
Another effect of fasting has been brought forth by Selye. Fasting is an alarming-stimulus and as such causes stimulation of the pituitary-adrenal mechanism. When fasting elicits an alarm reaction, this alarm reaction greatly increases the stressor effect of other alarming stimuli which may be superadded.

My co-workers during the past few years made daily blood pressure, heart rate, and body weight determinations on trained healthy dogs; and then began fasting these dogs—allowing only water ad libitum. The daily fluctuations of blood pressure were increased at the start of the fast, then the pressure (both systolic and diastolic) and heart rate slowly began to fall in a see-saw manner. After an indefinite period of time systolic and diastolic pressure and heart rate reached a stable level. This stable level was marked by small daily fluctuations, and has been called the stable fasting blood pressure level. The length of time that it takes for the blood pressure to reach the stable fasting level is dependent on the previous nutritional level. Dogs that were on a low maintenance diet before the fast took 1-7 days to reach the stable fasting level, while dogs that were on twice the low maintenance diet before the fast took considerably longer (longest, 65 days). The stable fasting level is independent of the previous
nutritional level. It is of considerable interest that the stable fasting levels for a given dog are remarkably constant following repeated realimentation with various diets, and subsequent fasts. (34, 42)

The fact that the length of time it takes for the blood pressure to reach the stable fasting level is dependent upon the previous nutritional level, plus the fact that the stable fasting level is remarkably constant despite the previous nutritional status led to the following proposed working hypothesis: when the blood pressure reaches the stable fasting level, the animal has depleted all of its labile food stores. (44) The nutritional level at the stable fasting blood pressure level shall, for the sake of convenience, be referred to as nutritional zero in the following pages and chapters. Also, as a working hypothesis, it was felt that after an animal had depleted his food stores and was then realimented on an unbalanced diet high in either protein or carbohydrate, there initially would be a very high utilization of the predominating foodstuff. (43)

In the following chapters, we shall deal with various types of diets and their effects. It will be well to bear in mind that these diets will all be started from a nutritional zero. Using nutritional zero as a
baseline allows a legitimate comparison of the effects of the various diets. It will also be well to keep in mind that fasting produces an alarm reaction which sensitizes the organism to a subsequent alarming-stimulus. (41)
When blood pressure studies were begun in this laboratory four years ago, the basic hypothesis was this: Americans as a people are plagued with hypertension to a degree much more common than in other peoples. It has also been observed that Americans are gregarious eaters, consuming especially, large amounts of carbohydrates. Is there a correlation between these two observations? If so, could hypertension be produced in the dog by dietary means?

In endeavoring to find an answer to these questions, the diet immediately assumes a paramount role. It is essential to establish what, and how much is to be fed; and certain standards must be defined which can be applied to all the dogs.

In this work, we have used two standards of caloric intake. The first of these is the maintenance level, and the second is the luxus consumption level.

The maintenance level is defined as that diet which provides sufficient calories to maintain the body weight constant. When a dog reaches the stable fasting blood pressure level, a diet is calculated which will just maintain body weight, e.g., if a dog weighs 12 kg.
at the beginning of the stable fasting level, calories are provided to the extent of maintaining body weight at 12 kg. indefinitely; and this diet is called the low-maintenance level of caloric intake for this particular dog (high-maintenance levels are those that are maintenance when the animal is of normal weight or somewhat overweight).

In calculating the maintenance level of caloric intake, 40 C/m²/hr was used as the basal metabolic rate of the dog. Since the dogs were leading a sedentary cage life, another 50 per cent or 20 C/m²/hr was added. These figures, when combined, give a maintenance level of 60 C/m²/hr. In calculating the body surface area in square meters, Meeh's formula is used.¹ The maintenance level has been found to be satisfactory for our work when calculated in this manner.

The second standard of caloric intake—the luxus consumption level—is by definition twice the low-maintenance level.

Also to be considered, when calculating these diets, is the Specific Dynamic Action (S.D.A.) of the primary foodstuffs. Since this work has been in progress, we have endeavored to restrict the diets to one or

¹Meeh's Formula: \( m = 0.112 \sqrt{Bd. \text{ Wt.}^2} \text{(Kilo)} \)
another of the primary foodstuffs, so that we can get an idea of how they act specifically. So far, only protein and carbohydrate have been investigated—the fats remain for future work. In calculating caloric levels, 30 per cent extra should be added for the S.D.A. of protein, and 5 per cent more should be added for the S.D.A. of carbohydrate. The 5 per cent for carbohydrate may be effectively dropped, because it is such a small amount. Our methods of calculating the levels of caloric intake are not sufficiently accurate to make necessary the inclusion of the 5 per cent. However, it is necessary, when making up protein diets, to add the 30 per cent extra in order that they may be relatively isocaloric to the carbohydrate diets.

There have been five diets which have been investigated extensively during the past four years: (a) maintenance level of protein (M-P); (b) maintenance level of carbohydrate (M-C); (c) luxus consumption level of protein (L-P); (d) luxus consumption level of carbohydrate (L-C); (e) luxus consumption consisting of one-half protein and one-half carbohydrate (L½P½C). It will be noted that this last diet consists of (M-P) plus a (M-C).
CHAPTER V

THE EFFECT OF MAINTENANCE AND LUXUS CONSUMPTION LEVELS OF PROTEIN AND CARBOHYDRATE

In the chapter on fasting it was shown that blood pressure and heart rate fall, and reach a stable level during the fast, and that this stable fasting level would be used as a baseline for subsequent dietary regimens.

It was also shown (in the chapter on special diets) that the dietary regimens which have been used are:

(a) maintenance carbohydrate (M-C)
(b) maintenance protein (M-P)
(c) luxus consumption protein (L-P)
(d) luxus consumption half protein half carbohydrate (L\frac{1}{2}P\frac{1}{2}C)
(e) luxus consumption carbohydrate (L-C)

These regimens have been tried many times on various dogs, but for purposes of comparison, three dogs have been selected on which all five diets have been tried. The range of time on each diet for the three dogs is as follows:

(a) M-C 28-58 days
(b) M-P 12-17 days
(c) L-P 60-94 days
(d) L²P₂C 75-89 days
(e) L-C 90-95 days

All of the diets were started after the dogs were brought to their stable fasting blood pressure level.

If a maintenance level of either carbohydrate or protein is given after a dog has reached the stable fasting level, the response is a slight rise in systolic and diastolic pressure and in the heart rate. The changes brought about by protein and carbohydrate at the maintenance level are of the same magnitude (Fig. 2), and are statistically insignificant.

When a luxus consumption level of protein is given, the response is about the same as for maintenance levels of protein or carbohydrate (Fig. 2), and the differences between them are not statistically significant.

On the other hand, when a luxus consumption carbohydrate diet is given, there is a sudden, spectacular elevation in heart rate followed by a highly significant rise in systolic pressure and a moderate elevation of diastolic pressure. (Figs. 2, 3, 4, and Tables 6, 7)

When a luxus consumption half protein and half carbohydrate diet is given, there is a moderate elevation of systolic and diastolic pressure and heart
Fig. 2.—A Comparison of the Fast, Maintenance Carbohydrate, Maintenance Protein, Luxus Consumption Protein, Luxus Consumption Half Protein Half Carbohydrate, and Luxus Consumption Carbohydrate.
Fig. 3.--The Degree Rise of Luxus Consumption Carbohydrate over the Fast--Millie and Shad.
Fig. 4.—The Degree Rise of Luxus Consumption Carbohydrate over the Fast—Boris and Brownie.
TABLE 6
A COMPARISON OF THE FAST, MAINTENANCE CARBOHYDRATE, MAINTENANCE PROTEIN, LUXUS CONSUMPTION PROTEIN, LUXUS CONSUMPTION HALF PROTEIN HALF CARBOHYDRATE, AND LUXUS CONSUMPTION CARBOHYDRATE

<table>
<thead>
<tr>
<th>DOG</th>
<th>F</th>
<th>M-C</th>
<th>2.4</th>
<th>L-P</th>
<th>L-P/L-H</th>
<th>L-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>NELL</td>
<td>87±2.97 (8 fasts)</td>
<td>109±10.6</td>
<td>106±2.4</td>
<td>108±13.3</td>
<td>119±7.8</td>
<td>156±10.9</td>
</tr>
<tr>
<td>BESS</td>
<td>77±13 (4 fasts)</td>
<td>89±6.1</td>
<td>87±7.9</td>
<td>98±6.9</td>
<td>115±8.9</td>
<td>135±8.2</td>
</tr>
<tr>
<td>BLACKIE</td>
<td>88±4.5 (6 fasts)</td>
<td>94±5.3</td>
<td>103±3.5</td>
<td>107±5.0</td>
<td>107±12.0</td>
<td>143±15.1</td>
</tr>
<tr>
<td>NELL</td>
<td>38±7.1</td>
<td>50±7.1</td>
<td>44±2.5</td>
<td>51±8.3</td>
<td>49±8.6</td>
<td>54±7.2</td>
</tr>
<tr>
<td>BESS</td>
<td>43±4.5</td>
<td>55±5.7</td>
<td>59±9.2</td>
<td>54±6.4</td>
<td>63±7.0</td>
<td>64±8.2</td>
</tr>
<tr>
<td>BLACKIE</td>
<td>52±4.1</td>
<td>55±4.4</td>
<td>57±2.3</td>
<td>54±4.5</td>
<td>64±10.0</td>
<td>70±8.6</td>
</tr>
<tr>
<td>NELL</td>
<td>51±1.4</td>
<td>70±6.4</td>
<td>57±5.1</td>
<td>67±11.5</td>
<td>72±9.9</td>
<td>96±10.2</td>
</tr>
<tr>
<td>BESS</td>
<td>56±11.5</td>
<td>51±7.4</td>
<td>56±10.5</td>
<td>93±8.6</td>
<td>97±10.4</td>
<td>91±10.6</td>
</tr>
</tbody>
</table>
| BLACKIE | 54±13.5 | 69±10.8 | 54±8.9 | 103±11.4 | 89±16.6 | 104±17.0 | 92.6%
## Table 7
A Comparison of Luxus Consumption Carbohydrate and Luxus Consumption Protein Each Started From a Fast

<table>
<thead>
<tr>
<th>DOG</th>
<th>Luxus Consumption Carbohydrate</th>
<th>Luxus Consumption Protein</th>
<th>Difference</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S</td>
<td>D</td>
<td>P</td>
<td>S</td>
</tr>
<tr>
<td>Nell CM</td>
<td>156âte11</td>
<td>54ête72</td>
<td>96ête102</td>
<td>108ête1</td>
</tr>
<tr>
<td>Rice</td>
<td>147ête13.8</td>
<td>67ête11.6</td>
<td>89ête11.5</td>
<td>133ête1</td>
</tr>
<tr>
<td>BeSS CM</td>
<td>135ête6.2</td>
<td>64ête8.2</td>
<td>91ête9.6</td>
<td>98ête7.0</td>
</tr>
<tr>
<td>C M + 25gmSalt/day</td>
<td>150ête16.8</td>
<td>72ête7.1</td>
<td>87ête8.7</td>
<td>70ête7.0</td>
</tr>
<tr>
<td>Blackie</td>
<td>143ête15.1</td>
<td>70ête8.6</td>
<td>104ête17.1</td>
<td>107ête5.0</td>
</tr>
<tr>
<td>The Hound</td>
<td>149ête101</td>
<td>57ête6.8</td>
<td>104ête11.7</td>
<td>127ête9.7</td>
</tr>
</tbody>
</table>
rate. These values tend to fall between luxus consumption protein and luxus consumption carbohydrate values (Fig. 2, Table 6).
CHAPTER VI

THE EFFECT OF LUXUS CONSUMPTION PROTEIN FOLLOWING LUXUS CONSUMPTION CARBOHYDRATE WITHOUT AN INTERVENING FAST

In Chapter V, it was shown that a luxus consumption level of carbohydrate following a sufficient fast produced definite cardiovascular defects; viz., highly significant elevations of heart rate and systolic pressure, and significant (although not so spectacular) elevations of diastolic pressure. It was also shown that these effects could apparently be maintained indefinitely (longest, 108 days) so long as the luxus consumption carbohydrate was given.

In the present chapter we shall deal with the effects of changing from luxus consumption carbohydrate (after the blood pressure and pulse rises have been definitely established) to a luxus consumption protein diet. For this study, five dogs were used. All were fasted to their stable fasting blood pressure level, and then re-alimented on a luxus consumption level of carbohydrate. Four of the dogs received luxus consumption carbohydrate alone (three were on cracker meal, and the other on rice). The other dog was given cracker meal plus 25 gm NaCl/day.
All the dogs were carried on this regimen for periods ranging from 75-92 days. Then they were all switched to a luxus consumption protein diet consisting of horsemeat (to which an extra 30 per cent was added to compensate for the S.D.A. of protein). The dog that had been receiving 25 gm salt/day was continued on the same amount of salt while on the luxus consumption protein diet. Four of the dogs were kept on luxus consumption protein for 80 days.

Results.—The dog which was on luxus consumption protein plus 25 gm salt/day (Bess) was on this regimen for only a little while and then switched to kennel diet. The time period on this dog was too short to warrant statistical analysis; however, the spectacular fall in pressure can be seen in Figure 5. Of the other four dogs, there was a prompt, highly significant fall in systolic pressure in all cases. The diastolic pressures were higher in two cases and lower in the other two. Heart rates were significantly lower in all four dogs (Table 8, Figs. 6, 7, 8, 9).
Fig. 5.—Luxus Consumption Protein following Luxus Consumption Carbohydrate—Bess.
### Table 8

A Comparison of Luxus Consumption Protein Following Luxus Consumption Carbohydrate Without an Intervening Fast

<table>
<thead>
<tr>
<th>DOG</th>
<th>LC-CHO Systolic</th>
<th>LC-CHO Diastolic</th>
<th>LC-CHO Pulse</th>
<th>LC-PROT Systolic</th>
<th>LC-PROT Diastolic</th>
<th>LC-PROT Pulse</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>MILLIE 554-99</td>
<td>154±8.89</td>
<td>67±7.44</td>
<td>111±15.08</td>
<td>12.3±12.06</td>
<td>59±8.81</td>
<td>98±17.27</td>
<td>&lt;.01 &lt;.01 &lt;.01</td>
</tr>
<tr>
<td>SHAD 730-107</td>
<td>162±11.15</td>
<td>65±7.27</td>
<td>98±13.59</td>
<td>129±9.92</td>
<td>62±6.53</td>
<td>81±21.43</td>
<td>&lt;.01 &lt;.05 &lt;.01</td>
</tr>
<tr>
<td>BORIS 577-108</td>
<td>140±8.26</td>
<td>56±6.20</td>
<td>94±16.36</td>
<td>122±9.02</td>
<td>58±7.11</td>
<td>86±14.74</td>
<td>&lt;.01 &gt;.05 &lt;.05</td>
</tr>
<tr>
<td>BROWNIE 362-106</td>
<td>152±1002</td>
<td>52±7.71</td>
<td>75±8.39</td>
<td>120±11.77</td>
<td>57±8.99</td>
<td>70±11.98</td>
<td>&lt;.01 &lt;.01 &lt;.05</td>
</tr>
</tbody>
</table>
Fig. 6.—Luxus Consumption Protein following Luxus Consumption Carbohydrate—Millie.
Fig. 7.—Luxus Consumption Protein following Luxus Consumption Carbohydrate—Shad.
Fig. 8.—Luxus Consumption Protein Following Luxus Consumption Carbohydrate—Boris.
Fig. 9.—Luxus Consumption Protein Following Luxus Consumption Carbohydrate—Brownie.
Discussion, Speculations and Conclusions

Discussion

As has already been mentioned in Chapter III, fasting elicits an alarm reaction which sensitizes the organism to a following alarming-stimulus. The fact that carbohydrate in sufficient quantities can act as an alarming-stimulus is shown by the fact that fasting dogs re-alimented on a luxus consumption carbohydrate diet invariably develop signs of the shock phase of the alarm-reaction. Tachycardia, diarrhea, and muscular weakness are common; and vomiting, tarry stools, and hypoglycemic convulsions sometimes occur.(43)

There is also an ample literature to show that carbohydrate is an alarming-stimulus. Glucose given orally or parenterally causes a fall in circulatory lymphocytes and eosinophiles in humans and laboratory animals.(44,45,46,47,48) This response does not occur in the absence of the adrenal glands.(44,48) Adrenal cholesterol and ascorbic acid levels also fall following glucose administration.(49,50) Carbohydrate is effective, as is adrenal cortical extract, in prolonging the survival time of animals exposed to hypoxia.(51,52)

Since carbohydrate is an alarming-stimulus and under the proper conditions is able to engender quite
severe signs of shock, we may speculate that the elevation of blood pressure is a countershock phenomenon, and is a result, in some manner, of a hyperactive pituitary-adrenal system which is operating to relieve the stress which is acting in the animal organism. However, there is a discrepancy which manifests itself in this line of reasoning. Selye and others, in their work on the alarm-reaction, have found that if an alarming-stimulus is repeated, the intensity of the response is progressively diminished, so that, if the alarming-stimulus is repeated often enough, there may be no response and the organism is said to be in a state of adaptation to the stress in question. On repeated fasts and realimentations with luxus consumption carbohydrate diets, the animal has always shown the same shock pattern at first, and later the same elevation of blood pressure. There has never been any evidence of adaptation. The stable fasting blood pressure level remains the same, the luxus consumption carbohydrate blood pressure level remains the same, and the severity of the shock remains unchanged. Maybe this regime has not been repeated often enough to show whether or not adaptation can occur. At any rate, the possibility that the elevated blood pressure during luxus consumption carbohydrate is due to a stimulated pituitary-adrenal system is worthy of serious future investigation.
Another intriguing concept as to the underlying mechanism of the elevated blood pressure during luxus carbohydrate consumption is the VKM-VDM mechanism of Shorr and co-workers; but before going into this, we shall show why we consider it to be a possible correlation.

There is evidence from the literature that during fasting fat accumulates in the liver, and that during feedings with diets deficient in lipotrophic factors, there is also accumulation of fat in the liver. Also, under certain conditions, there may be renal changes when animals are given lipotrope-deficient diets. Mottram (53) showed that the fatty metamorphosis occurring in the liver during fasting was due to mobilization of fat from the depots, and not due to a fatty degeneration of the liver. Dible and Libman (54) later showed that the amount of fat mobilized to the liver during starvation was dependent upon the amount of fat in the depots. Best (55) describes two phases of fatty infiltration to the liver during fasting: the early phase—during which fat is mobilized from depots to liver—and a later phase—which occurs after depots have been exhausted and no more fat can come to the liver. During both of these phases liver fat is being utilized, although during the early phase, fatty infiltration exceeds fat utilization.
The fact that depancreatized-insulinized dogs fed lean meat and sucrose invariably develop tremendous fatty livers and die in hepatic failure, and that this could be prevented by adding raw pancreas to the diet, led to a group of researches which ultimately showed that choline was the factor which prevented the accumulation of fat in the liver (56, 57, 58, 59, 60) and that choline did so by phosphorylating fatty acids to phospholipids—thus preventing the accumulation of neutral fat. (61) It was later shown that thiamine and cystine tend to increase liver fat content (55, 62, 63) and that methionine, like choline, exerts a lipotropic effect on liver fat. (64)

An extremely interesting offshoot of the lipotropic effect of choline on liver fat is the work of Griffith and Wade and others on the effects of choline-deficient diets on young rats. Weanling rats that are placed on a choline-deficient diet die within 6-10 days, and the outstanding lesion is a peculiar hemorrhagic degeneration of the kidneys. The kidneys are enlarged about twice normal size, and there is tubular necrosis and hemorrhage. (64, 65, 66, 67) Those that survive for more than ten days generally will not succumb in spite of continued choline-free diet. The fact that adult rats do not develop the renal hemorrhagic-degenerative syndrome
prompted Handler to show that partially nephrectomized adult rats on choline-deficient diets will develop hemorrhagic degeneration in the remaining kidney during its period of hypertrophy, but not after hypertrophy is complete. Thus, it was shown that choline deficiency produces the lesion only at times of great metabolic activity—during growth, and during hypertrophy.

Since the kidneys are affected in weanling rats by choline-deficient diets, one might inquire about the status of the blood pressure in those that survived the lethal effects of the lesion. Sobin and Landis placed weanling Wistar rats on choline-deficient diets and the blood pressure of the experimental rats was not significantly different from the controls even after five months. Two years later, Hartroft and Best placed weanling Wistar rats on a choline-deficient diet for 5-7 days, and then realimented them on a normal diet. Six to seven months later, the entire group was hypertensive, and showed cardiac enlargement to nearly twice normal size.

In the light of what has been said in the preceding paragraphs, we may speculate that dogs fasted and then realimented on a high-caloric high-carbohydrate diet which is devoid of lipotrophic activity (as our cracker meal and rice diets are) develop fatty livers. Speculating again, we may say that the stress of fasting plus subsequent
high-carbohydrate realimentation engenders a state of great metabolic activity—leaving the kidneys susceptible to the effects of choline deficiency.

The fact that lipotrope-deficient diets can produce changes in liver and kidney, and that these organs are the site of formation of VEM and VDM leads to the hypothesis that the elevated blood pressures of dogs fasted and then realimented on luxus consumption carbohydrate may be due to changes in the VEM-VDM mechanism.

The sensitivity to adrenaline of the arterioles and pre-capillaries of the rat meso-appendix furnishes the test upon which the phenomenon of VEM-VDM activity has been worked out. Shorr et al.(71,72,73,74,75) found that in states of hemorrhagic shock in dogs there is a vaso-excitor material (VEM) of renal origin and a vaso-depressor material (VDM) of hepatic origin which are poured into the blood stream. During the early stage of hemorrhagic shock, there is a preponderance of VEM in the plasma; but during the later stage—the non-responsive stage (during which time the animal will not respond when transfused with a volume of blood equivalent to that which it has lost)—there is a preponderance of VDM in the plasma. (71,72) Plasmas that have a preponderance of VEM will augment the adrenaline-sensitivity of vessels of the rat meso-appendix; whereas plasmas that have a preponderance
of VDM will depress the sensitivity to adrenaline of these vessels.\(^{(71)}\) It was also shown that normal kidney and liver produce these substances anaerobically both \textit{in vivo} and \textit{in vitro} and that they inactivate their respective products under aerobic conditions both \textit{in vivo} and \textit{in vitro}.\(^{(71)}\)

There is a definite correlation between experimental renal hypertension and VEM. Shorr and his co-workers have shown that within forty-eight hours after application of a Goldblatt clamp or gauze-collodion sac, the kidney is converted into an organ which elaborates VEM continuously—even under aerobic conditions.\(^{(76,77,78)}\) During the humoral (renin) phase of experimental renal hypertension there is pronounced VEM activity; whereas in the non-humoral phase there is no activity in the unfractionated plasma, but marked VEM activity in the fractionated (incubation aerobically in liver slices) plasma.\(^{(77)}\)

Of eleven human essential hypertensives examined, all showed no activity in the unfractionated sample, but showed pronounced VEM activity after the sample had been incubated in liver slices aerobically.\(^{(77)}\) Human normotensives showed neutral plasmas both before and after fractionation.\(^{(77)}\) This similarity between human essential hypertension and the non-humoral phase of experimental
renal hypertension is extremely interesting.

Shorr and co-workers have also shown that the adrenal cortex is intimately associated with the maintenance or alteration of the VEM-VDM mechanism. The kidneys of adrenalectomized rats progressively lose their power to form VEM until eventually no VEM-forming ability can be demonstrated.\(^{(79)}\) The VEM-forming ability of these kidneys can be restored by DCA but not with any of the glucocorticoids.\(^{(79)}\) Furthermore, these same workers were unable to produce a single case of renal hypertension in rats that had been previously adrenalectomized.\(^{(80)}\) This is of further interest in the light of Green's work. He was the first to cure a case of malignant hypertension in the human by employing bilateral adrenalectomy.\(^{(81)}\)

Certain nutritional regimes have been found which affect the VEM-VDM mechanism. Cirrhotic-like changes were produced in the livers and kidneys of rats by feeding low protein (10 per cent casein) diets with high cystine supplements. These animals developed a poor tolerance to surgery and other trauma--being prone to go into shock. Kidneys were found to have lost the ability to form VEM; while livers were found to have lost the ability to inactivate VDM.\(^{(82,83)}\) Fasting rats, on the other hand, show a progressive inability of the kidney to form VEM.\(^{(83)}\)
The possible role of adrenaline in the blood pressure elevations during luxus consumption carbohydrate alimentation following a fast is also intriguing. Selye (84) says that the elaboration of adrenaline is an integral part of the alarm reaction.

The cardiovascular effects of adrenaline have been well summarized in an excellent paper by Goldenberg and his co-workers (85). They show that adrenaline infusions in physiological dose ranges (0.15–0.30 micrograms/kg/min) produce marked increases in cardiac output together with decreases in Total Peripheral Resistance (TPR). The resultant effects on blood pressure and heart rate are: (a) marked rises in systolic pressure, (b) increases in heart rate, (c) non-specific changes in diastolic pressure. Barcroft and Konzett (86) reported essentially the same results when they repeated the experiment the following year.

The cardiovascular effects (on our dogs) during high carbohydrate alimentation following a fast is certainly compatible with an adrenaline effect. There is characteristically a marked elevation of heart rate and systolic pressure, and minimal elevations of diastolic pressure.
Speculations

1. The low blood pressure values during fasting are due to interference with the VEM-elaborating mechanism of the kidney subsequent to decreased adrenal cortical output.

2. The blood pressure and heart rate elevations during alimentation with luxus consumption carbohydrate following a fast are due to:
   a. Sensitization by fasting to a following alarming stimulus—enhancing the stressor effect of high carbohydrate.
   b. Augmentation of renal VEM production due to an increased elaboration of adrenal corticoids.
   c. Increased adrenal medullary output occurring as a part of the Alarm Reaction.
   d. Epinephrine effects augmented by VEM increase the cardiac rate and output—causing a rise in systolic pressure. The epinephrine effect on peripheral resistance is to lower it. The increase in systolic pressure and heart rate overcome the decrease in TPR so that the resultant is a slight rise in diastolic pressure.

3. The fall in blood pressure and heart rate when luxus consumption carbohydrate is changed to luxus consumption protein is due to:
a. Removal of the stressor (LC-CHO) which does away with the Alarm Reaction.
b. Decreased adrenal corticoids allow VEM production to return to normal.
c. Decreased VEM and epinephrine allow cardiac rate and output, and TPR to return to normal.

Conclusions

The elevated heart rate and systolic pressure of dogs alimented with luxus consumption levels of carbohydrate following an adequate fast are markedly decreased when the carbohydrate is changed to an isocaloric diet of protein. This phenomenon probably involves the pituitary adrenal axis, and the VEM-VDM mechanism.
REFERENCES


