SOME OBSERVATIONS on the ACTION of ADRENALIN.

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for
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by
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A great deal of the material included below has already appeared in the following papers:-

SOME STUDIES on the ACTION of ADRENALIN.

Chapter I.

The Reaction to Adrenalin in Man.

The Object, Scope, and Method of the Experiments.

During the course of some investigations on the carbohydrate metabolism, the rise in the blood sugar concentration following injection of adrenalin, was studied. The curves of adrenalin hypoglycaemia presented some unusual features, and in order to interpret them it seemed desirable to examine some of the other reactions produced by the drug. For this purpose a large number of observations were made on a series of individuals. The subjects chosen for this purpose include a few patients in whom no abnormality of the ductless glands was present, a number of diabetics and asthmatics, and several cases with thyroid involvement.

Great care was taken to get the subjects into a satisfactory state before the examination was begun. The patients, having fasted for fifteen hours, were put at rest in a quiet room. Preliminary estimations /
estimations of blood-pressure, pulse-rate, and respiration-rate were made occasionally. A Rosling or a Haldane face-mask was then adjusted, and when the circulatory phenomena had quietened down and the readings had fallen to a constant level, a 10-minute sample of expired air was taken in a Douglas bag for the estimation of the basal metabolic rate. The preliminary observations usually lasted from thirty minutes to an hour.

After this, adrenalin was injected subcutaneously on the outer aspect of the forearm, about two inches below the elbow. The dose employed was usually from 0.5 - 1.0 cc. of 1:1,000 solution of adrenalin chloride (P.D. & Co.), but smaller amounts have also been given. Following the injection, samples of expired air were collected over 10-minute periods for an hour, and a final sample was taken after a further interval of 30 minutes. The carbon dioxide and oxygen percentages in these samples were estimated by the Haldane gas-analysis apparatus. During the whole of the experiment, records of the systolic and diastolic blood-pressures together with the pulse-rate and the respiration-rate, were taken every two minutes. The data have been examined in various ways, and some of the results are presented below.

Every precaution was taken to avoid sources
of fallacy, but difficulties were sometimes met with. The needle puncture seldom caused sufficient pain to disturb the results, though occasionally the pulse-rate momentarily increased 5 - 20 beats, returning to normal before the next observation (cf. Clough (13)). More rarely there was also a rise of about 5 mm. in the systolic blood-pressure. In two cases frequent samples of venous blood were taken at the same time as the other examination was being made, and it was noticed that if pain were caused by the needle a secondary rise of metabolic rate, pressure, &c., soon followed, while an unusual increase in the blood-sugar occurred about 20 minutes later. When difficulty was experienced in getting the mask to fit closely there was a temptation to adjust it very tightly. For a time no discomfort would be felt, but later, pain developed at the points of pressure and caused the patient to worry and fidget. Another important cause of restlessness in the subject was the discomfort produced by lying motionless for such a long time. These sensations gave rise to occasional sighs or definite over-ventilation, resulting in an increase in carbon dioxide output, and such reactions could be recognized easily in the graphic records by the presence of a later secondary rise in the metabolic rate. No corresponding increase took place in the circulatory curves in these cases.

When the patient was highly emotional, a
very irregular series of respiratory quotients would be obtained, but even in these circumstances the readings of the total metabolism might show a fairly uniform movement. In very unstable subjects a sudden loud noise or the appearance of a stranger would cause a slight temporary disturbance, which usually showed itself as a rise in pulse-rate, or less often as an increase of about 5 mm. in the blood-pressure.

Another difficulty sometimes met with was that the initial levels of the readings remained high apparently from continued excitement. In one case, for example, when the patient's blood-pressure was taken in the general ward it was about 155 mm. Hg, but when she was prepared for examination in the special chamber the systolic pressure would rise to 200, and even a prolonged rest failed to reduce it below 190.

Description of Results.

The administration of adrenalin is followed by a local reaction, and by a general reaction which involves especially the vasomotor system and the general metabolism.

Local reaction: A short time after the hypodermic injection is given there appears a small pale area just proximal to the needle mark. This patch increases /
increases in size for an hour or so, and may still be visible three or four hours later. It has a rough goose-skin surface, is perfectly blanched, and is usually surrounded by a narrow zone of congestion. In a number of subjects long root-like projections spread from the pale area centripetally on the upper arm. Some of these pale streaks may follow the superficial veins, while others suggest lymphatic paths. The local pallor is obviously due to occlusion of capillaries and small vessels in the area, and absorption by these routes is out of the question. Yet in the majority of cases a great proportion of the adrenalin soon leaves the point of inoculation, and is probably carried by lymphatic channels to be poured into the general circulation at some point. Clinical evidence of rapid absorption is seen in cases of asthma, where relief from dyspnoea occurs a few moments after a minute dose of adrenalin has been given.

Certain phenomena follow absorption. The commonest symptom and one usually most pronounced is palpitation. This begins early and lasts throughout the height of the reaction, passing off as the blood-pressure returns towards normal again. It is present in practically all cases, and may be slight or very severe and distressing. The apex-beat becomes more powerful and can be seen over a larger area, and sometimes the violent cardiac action visibly shakes the whole praecordia. The accompanying subjective sensations may be a vague discomfort /
discomfort, a feeling of distress, or an actual praecordial pain. A beating headache or a throbbing in the head and the great vessels was frequently complained of. Exaggerated pulsations were often seen in the vessels of the neck, and sometimes even in the brachial and radial arteries. Extra-systoles were seldom noted.

In the vast majority of the subjects a fine tremor was present in the fingers and hands during a considerable part of the reaction. Occasionally there was observed a much more general shaking involving other parts of the body as well as the extremities.

The breathing became deeper and often more irregular in character. The other phenomena were less constant. Circumoral pallor might follow a large dose, but in cases of exophthalmic goitre there occurred a general flushing and an increased moistness of the skin. Profuse sweating took place in one case during a curious spell of hyperpnoea. Increased salivation was sometimes noticed. The pupillary changes were not definite and no lachrymation was encountered. Increased desire for micturition was only found in one patient.

The subjective sensations experienced during the reaction were variously described as a feeling of nervousness, excitement, agitation, apprehension, expectation, or of being "on edge". One person likened his condition to that state of tension/
tension experienced when one suddenly wakens in the night and listens intently for some expected sound.

Of the other general phenomena examined, it is interesting to note that several of them run closely similar courses, rising and falling together and reaching their highest (or lowest) points at practically the same time. (see Charts 1-3). This is true of systolic blood-pressure, "mean B.P.", pulse-pressure, oxygen consumption, carbon dioxide output, respiratory quotient, ventilation-rate, and metabolic rate, all of which increase, and also of diastolic pressure and the percentage of oxygen in expired air, which diminish. Three other curves are quite different from this general type. The percentage of carbon dioxide in the expired air remains practically constant throughout the experiment; the acceleration of the heart-rate occurs late in the reaction; and the apex of the wave of hyperglycaemia in the venous blood appears when most of the other actions are subsiding. So closely do the first group correspond with each other that it would be possible to look upon the fairly continuous systolic pressure-curve as an index of the general reaction.

Types of reaction. Clough, in his examination of the circulatory response to adrenalin, classifies his results into four groups according to the severity of the reaction. In the following table /
table the percentage of the subjects examined who fell into the various groups, is compared with the numbers given by Clough.

<table>
<thead>
<tr>
<th>Blood-pressure rise</th>
<th>Clough's present series</th>
<th>Percentage of type in cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative or insigni-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>f - up to 15 mm. Hg.</td>
<td>30 %</td>
<td>32%</td>
</tr>
<tr>
<td>Moderate</td>
<td>15 - 30 &quot;</td>
<td>50 %</td>
</tr>
<tr>
<td>Marked</td>
<td>30 - 50 &quot;</td>
<td>12.5 %</td>
</tr>
<tr>
<td>Very marked</td>
<td>50 - 100 &quot;</td>
<td>7.5 %</td>
</tr>
</tbody>
</table>

A classification of this sort is not as useful as it would appear at first sight, for it must be obvious that a rise of 15 mm. commencing from 200 would be of much greater significance than a similar increase from 105 to 120, and again such an arrangement would only be satisfactory if care was taken that the blood-pressure had reached a basal level before the adrenalin was given. It is true for adrenalin that the effect of the drug is modified by the condition of the individual, equal doses producing varying effects as the initial blood-pressure level is altered (see page 30). To express the increases as percentages of the original pressures is also unsatisfactory and only serves to make matters worse. Another fallacy in this classification is that cases of both sexes and of widely different ages may be grouped together, and that the standard /
standard dose is employed regardless of size, weight, or body surface.

It seems impossible, however, at the present time to devise a better grouping, but the shortcomings of the method should be recognized.

Adrenalin acts on the junctional tissue between the sympathetic nerve-ending and the organ innervated. It is rapidly destroyed and is used up quantitatively in producing its effects. The record of these effects should therefore give an indication of the rate at which the substance becomes available for the tissues, and from this curve can also be estimated the rate of absorption of the drug and the amount of it present in the circulation at any moment (see page 38).

The responses to adrenalin in different individuals vary not only in degree but also in speed and in form. The reaction might occur with startling rapidity, live a short time, and subside quickly; or the process might be a long-drawn-out affair. The moderate response shows its maximum in the second 10-minute period, and has a fairly gradual rise and fall of pressure, &c. The exaggerated reaction is usually also an early one which reaches its acme in the first few minutes; while on the other hand, slight responses might occur in ordinary time or might be greatly delayed.
The Individual Reactions.

1. Systolic blood-pressure. All the subjects examined showed some rise of blood-pressure after administration of adrenalin, even when only 0.1 cc. was given. In three cases a slight fall of pressure immediately followed the injection, but only lasted about a minute. A secondary fall of pressure below the original level took place in two patients who received doses of under 0.3 cc. This fall of pressure apparently results from indirect stimulation of the vagus, and is commonly seen in experimental animals unless the vagi have been previously resected.

The character of the blood-pressure curve varies greatly from case to case, and even in the same patient under different circumstances. In some, the pressure commences to rise within a few seconds of the injection, while in others four or five minutes may elapse before any effect is noticeable (cf. Clough (13)). The highest point may be reached as early as six minutes or may be delayed for thirty minutes or more. In nearly half the cases the maximum occurred in the second ten minutes, and in the others the highest point usually appeared in either the third or first periods. Occasionally a much greater delay was seen, and in these subjects the late maximum was probably really a secondary rise due to irritation from increasing discomfort.
The amount of the increase ranged from 5 mm. (rising from 115 to 120) to 65 mm. Hg (115 - 180), and in only three was it less than Goetsch's critical 10 points. (18). When the rise was slow and of only a slight degree the maximum level was maintained for a long time, but where a great and sudden increase took place the pressure rapidly fell again. In the majority of cases the reaction had practically passed off at the end of an hour and a half. The rise in the systolic blood-pressure probably depends upon the augmented cardiac output per minute, and also on increased peripheral resistance in a large part of the circulation (principally in the splanchnic area, where in experimental animals all the vessels appear to be occluded).

2. **Diastolic pressure** is recognized to depend on the state of the peripheral blood-vessels; it represents the dead load of pressure that the heart must overcome at each beat before the cardiac action becomes effective in circulating the blood. We have seen that the systolic pressure is always raised by adrenalin, and it is known that the drug contracts most vessels. It is surprising then to find that in the great majority of instances a **fall** in diastolic blood-pressure follows the giving of adrenalin. This must mean that there is a relaxation of the peripheral vessels in the limb where the blood pressure estimation is made, that the stream bed is increased, and that the blood flow is facilitated and augmented. These /
These are the conditions which favour action, as is pointed out by Cannon. (12). von Anrep has noted that the volume of the limbs increases during the rise of blood-pressure following adrenalin. (41).

In the cases examined, four types of response by the "diastolic pressure" have been found: (a) A rise and subsequent fall of pressure takes place, the greatest increase coinciding with the maximum of the systolic reading, but being very much less in extent (16 per cent of cases). (b) A primary short-lived rise of 5 - 10 points, followed later by a fall below the initial level (22 per cent). (c) The commonest reaction is an immediate fall of pressure with a later recovery. In this type the lowest point is reached when the systolic pressure touches its maximum, so that the dip may suggest a mirror image of the systolic curve, though usually less in degree. (d) In a few subjects the diastolic readings remain practically steady within 5 mm. of the basal level. The greatest reduction in diastolic pressure met with was 35 mm. (from 95 to 60).

In a sense this fall in diastolic pressure might be looked upon as a protective mechanism, a sort of safety-valve action to reduce a pressure which threatens to become too high and perhaps damage the vessels. Though the maximum intravascular pressure is considerably raised, it is so only during
during one phase of the cardiac cycle, and this great increase may be largely compensated for by the fall to a low level during the opposite phase. A close approximation to the total pressure or the heart’s activity during the whole cycle may be got by taking the arithmetical mean of the diastolic and systolic readings. When this is done it is found that in many of the cases, owing to the concomitant fall in the diastolic pressure, the average pressure during the cardiac cycle is but little altered throughout the whole reaction. Where a rise occurs the maximum coincides with that of the systolic pressure. The increase is of course most marked where both systolic and diastolic figures increase together.

3. **pulse-pressure** is believed to represent the effective force of the heart, and great importance is now being attached to this figure. Addis (1) has claimed that by its use he can estimate thyroid activity and so dispense with further estimations of basal metabolic rate in an individual whose basal metabolic rate has once been examined. Several observers (38) have noticed that adrenalin causes an increase in pulse-pressure, and the same has been found in all cases examined in this series. The maximum increase is reached at the same time as the greatest rise in the systolic pressure. Some individuals showed a very striking difference in pulse-pressure before and during the reaction. In one /
one the increase amounted to 325 per cent, the range
in points being from 20 to 85. These alterations
in pulse-pressure are also obvious on palpating or
on auscultating the vessel. Sometimes at first
in the resting state the sounds over the radial are
soft and indistinct, but under adrenalin they become
progressively sharper and clearer, and later become
softer again. Similar changes can be recognised by
the finger.

4. Pulse-rate. Adrenalin is believed to have a
direct accelerating action on the heart, but this is
evidently of less consequence than the augmentor and
pressor effects. The heart-rate is ordinarily auto-
matically regulated by a reflex control from the pres-
sure on the walls of the aorta. The rise in intra-
arterial pressure produced by adrenalin will stimulate
this reflex and, acting through the vagus, will tend
to slow the heart. This reflex inhibition is anta-
gonized by the direct action of adrenalin on the
sympathetic accelerator nerve-endings in the heart,
and the pulse-rate observed is the product of these
two forces. The vagal inhibition must also be look-
ed upon as a salutary mechanism preventing undue
strain on the vascular system.

The graph of the pulse-rate is quite dif-
ferent from those of the other reactions. It is much
less regular in character and far more easily influ-
enced than /
than any other by outside conditions. A sudden loud noise or the approach of a stranger may, in a sensitive individual, cause an increase of 10 - 25 beats per minute over a short period, though the pressure and metabolism remain unaffected. Such rapid changes must arise directly from psychic stimuli, and probably do not depend on secretion of a small extra amount of adrenalin by the subject, as has been suggested.

In the patients investigated, cardiac acceleration always occurred after adrenalin, and in only four was the increase less than 10 points. It begins usually at once, but after increasing a few beats becomes arrested for a time, and then later continues to rise as the other phenomena are subsiding. Often the increase appears to occur in two definite phases - an early sharp rise which lasts about 10 minutes, to be followed for a time by a slight fall (vagus) and later by a greater and more persistent rise. The subsequent return to normal is much slower than in the case of the other disturbances. This would suggest either that the accelerating mechanism is much more sensitive to adrenalin than is the pressor mechanism, and still continues to respond to a much smaller dose when the vessels have ceased to do so, or that the effect of the stimulation on the heart persists longer.

The /
The greatest increase in rate was 85 per cent (from 65 to 120 beats per minute), and this occurred in a case of hypothyroidism.

5. Cardiac output and circulation-rate. No direct evidence of an increased output by the heart has been obtained. The violent cardiac action and the accompanying phenomena would suggest that the volume of blood driven into the circulation in unit time would be considerably increased. Von Anrep, however, thought that in animal experiments the increased blood-pressure in the early stages was accompanied by a dilatation of the heart and a diminished outflow of blood. (41). Indirect evidence of the increase in circulation-rate is found in the arterialized state of the venous blood during the height of the post-adrenalin reaction, a state of affairs also found in cases of exophthalmic goitre, when routine samples of blood are taken for Wassermann examination &c.

Metabolic Responses.

One of the invariable reactions to the administration of adrenalin is an increase in the general metabolism. This metabolic response appears to be even more sensitive to adrenalin than the circulatory mechanism is, for Sandiford found that in man these changes might occur irrespective of any action on the arterial pressure. (38). Nice, Rock, and /
and Courtright report that the metabolism is increased in animals even when the dose of adrenalin is small enough to cause a fall of the blood-pressure. (33). The heightened metabolic activity is shown in the increased volume of air breathed and in alterations in the gaseous exchange.

6. Oxygen consumption. A marked increase in the quantity of oxygen consumed per minute is regularly found. The average excess over the basal level lies between 20 per cent. and 40 per cent., but much wider extremes are seen. The greatest percentage increase was got in a case of hypothyroidism, the preliminary value of 115 c.c. of oxygen per minute giving place to a maximum of 221 c.c. (92 per cent. increase). The slightest reaction occurred in a diabetic who had been practically fasting for some days. In this case the increase was only 6 per cent. (173 to 183 c.c. per minute). The greatest oxygen consumption usually occurred in the second or third 10-minute period, corresponding closely in time to the maximum of the circulatory disturbance.

7. The alteration in the output of carbon dioxide per minute follows the general reaction, and especially the oxygen consumption. The curve of carbon dioxide excretion is always a little lower than the corresponding oxygen value, but the actual percentile increase is greater, so that the respiratory quotient is
is raised during the reaction. Most of the subjects examined showed 30 per cent. to 50 per cent. increase in the carbon dioxide output. The extreme figures were 20 per cent. (from 173 to 207 c.c.) and 101 per cent. (from 102 to 205 cc.).

8. A very different state of affairs is shown by the percentages of these gases in the samples of expired air. The concentration of carbon dioxide in the first specimen may be high or low, but this level is usually maintained with remarkable constancy in the subsequent samples. Sometimes immediately after the injection of adrenalin the carbon dioxide percentage touches a new figure slightly higher or lower than the original one, and this new value is maintained throughout the rest of the reaction - see the last three cases in Table I. This uniformity in percentage in spite of wide alterations in the volume expired is a remarkable confirmation of the importance of this gas in regulating respiration. A selection of carbon dioxide readings is given in the accompanying table.

Table I. Carbon dioxide percentages /
9. In the samples of expired air examined after the giving of adrenalin the percentage of oxygen falls at first and later recovers although at the same time the total volume of the gas consumed is greatly increased. The change begins at once and the minimum value is seen at the same time as the other maxima, so that the curve of oxygen percentage is inverted. The smallest drop was from 4.27 per cent. to 4.16 per cent. in a case of diabetes, the most marked reduction in those suffering from asthma - e.g. from 4.47 per cent. to 3.01 per cent.
### Table II. Oxygen Percentages.

<table>
<thead>
<tr>
<th>Before Injection</th>
<th>After Adrenalin</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.48</td>
<td></td>
<td>3.99</td>
<td>3.96</td>
<td>4.16</td>
<td>4.18</td>
<td>4.31</td>
<td>4.39</td>
<td>-</td>
</tr>
<tr>
<td>4.20</td>
<td></td>
<td>3.65</td>
<td>3.66</td>
<td>4.12</td>
<td>4.39</td>
<td>4.32</td>
<td>-</td>
<td>4.35</td>
</tr>
<tr>
<td>3.41</td>
<td>3.01</td>
<td>3.10</td>
<td>3.16</td>
<td>3.24</td>
<td>3.23</td>
<td>3.33</td>
<td>3.62</td>
<td></td>
</tr>
<tr>
<td>4.09</td>
<td>3.02</td>
<td>3.16</td>
<td>3.22</td>
<td>3.38</td>
<td>3.54</td>
<td>3.78</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>3.44</td>
<td>2.48</td>
<td>2.62</td>
<td>2.70</td>
<td>2.76</td>
<td>2.80</td>
<td>2.81</td>
<td>2.84</td>
<td></td>
</tr>
<tr>
<td>4.18</td>
<td>3.57</td>
<td>3.35</td>
<td>3.84</td>
<td>3.95</td>
<td>2.87</td>
<td>3.80</td>
<td>4.26</td>
<td></td>
</tr>
<tr>
<td>3.84</td>
<td>3.52</td>
<td>2.87</td>
<td>2.88</td>
<td>3.11</td>
<td>3.83</td>
<td>3.37</td>
<td>3.99</td>
<td></td>
</tr>
</tbody>
</table>

The minimum values are underlined.

10. The curious relationship between these gases explains the changes in the respiratory quotient. An increase in the respiratory quotient is an invariable feature of the response to adrenalin. The curve expressing the rise and fall of the respiratory quotient is a very regular one, much more uniform than the graphs of the metabolic rate or of the air expired, since these latter values are more readily influenced by outside disturbances. A metabolic reading must be considerably displaced (e.g. by over-ventilation, &c.) before the corresponding respiratory quotient figure falls out of line. In nearly all cases the maximum respiratory quotient occurs in either the first or second 10-minute
10-minute period. In about 40 per cent. of the tests
the rise of the respiratory quotient anticipated the
metabolic increase (cf. Tomkins, Sturgis, and
Wearn (40)). Sometimes the administration of
adrenalin appears to be at once followed by a marked
alteration in the ratio between oxygen consumption
and carbon dioxide output, so that a very high respir-
atory quotient is produced in the first 10 minutes.
The more rapid the whole general reaction, the higher
goes the respiratory quotient, and the highest read-
ings are always found in period 1. Of the 15 cases
having the respiratory quotient summit in this period
no less than six reach or exceed unity, and five
others are over 0.95, whereas in all the other groups
only three respiratory quotients reached 0.95. These
very high readings are difficult to account for. The
accompanying phenomena do not suggest that they are
due to an abnormal type of ventilation, for the res-
piratory quotient falls step by step as in other cases,
and there is no succeeding period of compensatory low
respiratory quotient such as follows a spell of over-
ventilation. It is difficult to see how the regular
series of changes in the respiratory quotient extend-
ing over an hour and a half could be explained except
as a specific effect of adrenalin on the metabolism
of the cell. The altered respiratory quotient
indicates that a greater proportion of carbohydrate
is being utilized by the cell, but this consumption
of carbohydrate does not passively follow an increased mobilization of glucose from the liver. (II). If Cannon's emergency theory of the action of adrenalin is sound - and there is much to support it - an increased utilization of sugar by the cell is to be expected, for it is much more easily and rapidly made use of than fats. Lusk and Riche (30) have shown that a dose of adrenalin has little or no influence on nitrogen excretion, so the metabolic and circulatory activities which occur are probably almost entirely performed at the expense of carbohydrate. An idea of the respiratory quotient changes is got from Table III.

Table III. Respiratory quotients.

<table>
<thead>
<tr>
<th>Before Adrenalin</th>
<th>After Adrenalin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>0.774</td>
<td>1.03</td>
</tr>
<tr>
<td>0.785</td>
<td>0.866</td>
</tr>
<tr>
<td>0.767</td>
<td>0.871</td>
</tr>
<tr>
<td>0.850</td>
<td>0.899</td>
</tr>
<tr>
<td>0.841</td>
<td>0.916</td>
</tr>
<tr>
<td>0.850</td>
<td>0.904</td>
</tr>
<tr>
<td>0.765</td>
<td>0.857</td>
</tr>
<tr>
<td>0.776</td>
<td>0.973</td>
</tr>
<tr>
<td>0.790</td>
<td>1.05</td>
</tr>
<tr>
<td>0.725</td>
<td>0.881</td>
</tr>
<tr>
<td>0.817</td>
<td>0.931</td>
</tr>
</tbody>
</table>

The maximum value is underlined in the above table.
11. Respiration. In practically all cases the rate of breathing is hardly altered throughout the whole period of investigation. A few subjects show an increase of two to six respirations per minute. On the other hand, considerable irregularity in the breathing is sometimes found. Tomkins, Sturgis, and Wearm (40) note that the augmented volume of air breathed per minute may be accompanied by an increased rate or depth of respiration, and that often only one of these factors responds. In the present series of cases any marked increase of rate has seldom been noticed, but in one case of asthma a curious reaction was found. For six minutes after the injection the patient breathed at the same rate as she had previously done, then without warning the rate increased to 30 per minute and the respirations became very shallow. This phase lasted for half an hour and then subsided as quickly as it came on. (see case No. 46).

12. The most notable effect of adrenalin on respiration is an increase in the depth of each inspiration so that the ventilation-rate may be greatly augmented. The volume of air expired may be raised by as much as 60 per cent. over the resting level.

The distribution of the maximum values is similar to that of the others already studied, the majority appearing in the second 10 minutes and about
equal numbers in periods 1 and 3. Between the volume of air expired and the metabolic rate a very close parallelism exists, so that if the basal metabolic rate has been calculated in an individual and compared with the accompanying ventilation-rate, the subsequent alterations in the volume of air expired would almost accurately express the changes in metabolism. But in two different individuals the ventilation-rate would be of little value in comparing their respective metabolisms.

Few of the subjects were aware of the change in their breathing, but the deeper and easier ventilation after adrenalin was a great pleasure to the asthmatic patients, who felt the change almost immediately after the drug was injected. Minute doses of adrenalin suffice to give this relief, and it is known that dilatation of contracted bronchioles may occur independently of any rise in the blood-pressure. \(15+24\). The action on the bronchial muscle is a specific attribute of adrenalin, but the ventilation changes are essentially secondary to the increased general metabolism.

13. **Metabolic rate.** The details already presented will indicate the changes to be expected in the rate of the general metabolism. Augmentation occurred in all cases; the degree might be great or small and the reaction rapid or slow.

The character of the metabolic responses must /
must depend on the rate of the absorption of the adrenalin, the rate at which it is presented to the tissues, and the sensitiveness of the reacting structures to the stimulus applied. These questions have been more fully discussed elsewhere (p.38).
14. **Adrenalin hyperglycaemia.** The known influence of adrenalin and of splanchnic stimulation in causing a rapid glycogenolysis and the flooding of the blood with sugar from the liver would lead one to expect to find this reaction in line with the other responses to adrenalin. Cannon's emergency theory of the action of adrenalin would demand that the liberated sugar should be immediately available. It is curious to find, as Hamman and Hirshman have already pointed out, that the blood-sugar curve is delayed and in no way parallels the rise in systolic pressure. (20).

The relationship has been investigated in a number of cases. As painful venipuncture may cause over-ventilation, the sugar examinations had to be made on another day, but under similar conditions. In these cases doses of 1.0 c.c. of adrenalin were employed in order to secure a considerable rise in the blood-sugar. As the hyperglycaemia produced is of short duration, samples of venous blood were taken at intervals of 10 minutes. Examined in this fashion the curve of hyperglycaemia appears to differ from all the other curves. The sugar in the blood increases slowly, the maximum occurs late when the other reactions have nearly passed off, and the subsequent decline of the wave is also very gradual.

Tomkins, Sturgis, and Wearn (40) suggested that
that the general metabolic rise might be due to the hyperglycaemia, and Sandiford (38), supporting this theory, compared the post-adrenalin metabolism curve with the changes described by Lusk (29) as following carbohydrate plethora. But the fact that the two reactions do not coincide in time must negative this idea. Boothby and Sandiford (11) regard the sugar mobilization as an 'interesting compensatory mechanism'. If this be so, why should the compensation overshoot the mark? On the other hand, if the hyperglycaemia is part of a general reaction it is difficult to see why it should be only slowly developing as the main reaction is subsiding.

The amount of sugar in the blood at any moment is the result of the interaction of two factors - the rate at which the sugar is being supplied to the blood and the rate at which it is being removed from the blood. We have here an example of 'consecutive reactions'. What takes place is probably as follows. Some of the adrenalin having reached the blood-stream is carried to the liver. Here, as in other tissues, it acts quickly and directly, increasing the rate of conversion of glycogen into glucose. This ought to raise the percentage of sugar in the circulation, but several factors obscure this effect. The rate of blood-flow is increased during the height of the adrenalin reaction, and if the portal system shares in this acceleration - as seems likely - a very considerably increased output /
output of glucose could be hidden in the blood, provided the blood reaching the liver has no more than the usual concentration of sugar. This would require that the tissues removed sugar from the systemic circulation at a greater rate than normal. This also seems highly probable, for the heightened respiratory quotient shows that the heart and other activated tissues are utilizing a higher ratio of carbohydrate, and in consequence they will make a correspondingly greater demand upon the sugar of the blood. It is suggested, therefore, that the curve of the rate of discharge of sugar from the liver conforms to the general type (i.e. resembles the blood-pressure graph), but that the greatly increased call of the tissues for carbohydrate causes a rapid removal of sugar from the circulation, so that the increased glycogenolysis is masked during the most active period of the reaction, and only becomes evident in the venous blood when the demand of the tissues lessens. As the tissue activity subsides the rate of removal of the blood-sugar diminishes, and the percentage of the circulating sugar increases. The greatest increase of sugar in the venous blood appears when the reaction is nearly over, and at about the same time as the pulse-rate reaches its highest level. This prolonged effect, as in the case of the heart acceleration, possibly indicates that the glycogenolytic response is more sensitive than the circulatory reactions. The increased circulation-rate /
circulation-rate may also aid in the removal of sugar from the blood, as well as in the addition of sugar to it.

15. Glycosuria resulted in a considerable proportion of the patients who received 1 cc. of adrenalin. This waste of sugar is of short duration and never amounts to much. It resembles the transient glycosurias which occur as the result of excitement, anger, or worry in people with a low carbohydrate tolerance - for example, in cases of exophthalmic goitre and in treated diabetics whose margin of safety is narrow.

Chapter 2.

Experimental Investigations as to the Relationship between size of dose and the amount of reaction produced.
Experimental Investigations as to the Relationship between size of dose and the amount of reaction produced.

It has frequently been noted in pharmacological work, that when increasing quantities of a substance are employed, the responses to the higher doses fall short of expectation. This relationship between cause and effect, although not a simple ratio, is probably not a haphazard affair, but must follow some definite law. The apparent shortage found in such experiments recalls the case of the special senses where, as the stimuli are increased arithmetically the effects only increase logarithmically (Weber's Law).

The same failure in response to higher doses was remarked in the case of adrenalin by Hunt (22), who shewed that whereas 0.000083 mgm. per kilogram body weight produced a rise of 5 mm. Hg in the blood pressure, 0.005 mgm. only raised the pressure 66 mm. Varying doses produce varying results, but Baylac (6) found that in animals the same dose of adrenalin repeated many times always produced the same effect. Elliot (16), who re-examined the question, suggested that after frequent repetition of /
of the drug the threshold of stimulation might be raised.

The following experiments were undertaken in order to see whether Weber's Law was in operation in the case of the pressor reaction to adrenalin. The case seemed a favourable one for testing whether the Law could be applied outside the field of psychology, for the drug acts quickly, its effects can be readily recorded and most of the factors can be controlled.

As subjects, cats were selected. The animals were anaesthetized with ether, decerebrated in order to cut off any impulses from the higher centres, and artificial respiration was continued with the Brodie pump. The records of blood pressure changes were taken from the carotid artery. The nerves in both carotid sheaths were divided and both femoral veins were exposed to facilitate administration of the drug. Adrenalin chloride (Parke, Davis & Co.) was employed in these experiments, the actual strength of the fluid being chosen so as to give a blood pressure reaction of suitable size. Dilutions of from 1:1000 to 1:20,000 have been used, and of the solution chosen, a series of intravenous injections was given, the doses ranging from 0.05 to 1 ccm.

Adrenalin is believed to act quantitatively, being /
being used up as it produces its effect in the tissues \(^{(24)}\). The effect recorded (blood pressure readings) should therefore indicate how much of the substance is being destroyed at any given moment, and the rate of this destruction is doubtless proportional to the concentration of adrenalin in the circulating blood (Mass Action Law).

The intravenous injection of adrenalin solution is followed after a short interval by a rapid rise in the blood pressure, the height reached and the duration of the reaction depending on the amount of the drug given. During the latent period the injected material is passing from the femoral vein through the heart to the arterial system. As the adrenalin begins to act on the arteries its effect appears and the pressure rises rapidly until all the drug is in the circulation. At this moment the maximum increase is evident. The constrictor action of adrenalin is short-lived and, as the material is used up, the blood pressure falls. During the short first phase of the decline the curve is convex upwards. In the second phase the curve becomes concave upwards, the rate of the fall increasing for the time and then becoming ever more slowed as the pressure approaches the original level. The second phase of the blood pressure decline resembles the familiar exponential "die-away" curve. In the earlier records the curves were /
were frequently deformed by a secondary depression which might appear on the rise or the fall or might obliterate the apex altogether. This depression no longer occurred in those cases where the vagi were previously cut.

Some difficulty has been experienced in measuring the records. To gauge the effect of a dose it would seem best to measure the height of the rise of pressure above the level of blood pressure in the resting state immediately preceding the injection. It was soon found that, as the experiment advanced, the resting level of the blood pressure tended gradually to sink to a lower plane, and this led to alterations in the degree of response (vide infra)

Better results could be obtained by measuring the maxima from the average resting level, or, what amounts to the same thing, from zero. In several cases both procedures have been employed and the results are similar though a closer agreement is given by the second method. To make a strict comparison between the reactions to various doses it would be necessary to have the resting level of the blood pressure uniform between each observation, but although this ideal has not been attainable, except over very short periods, the results are sufficiently accurate for our purpose.
Ordinates give blood pressure in millimeters of mercury, the abscissae, dosage in fractions of a cubic centimeter of a 1:10,000 solution of adrenalin chloride. Line A is the logarithmic curve calculated from the formula $E = 21.43 \log S + 91.83$. The points on line B are the observed maxima of a series of blood pressure rises. At the foot of the figure under each maximum point, is shown the level from which the reaction started. At point D a clot had to be removed from the cannula in the carotid.
The method of investigation was to take an animal prepared as above and inject successive small quantities of adrenalin of different values into the circulation, allowing each reaction to subside completely and the blood pressure to return to the normal base line before the next dose was given.

A number of animals have been examined and in each subject several series of observations have been made. All the results point in the same direction. When the data are plotted out so that the abscissa shows dosage and the ordinates pressure in millimeters of mercury, the maximum points of blood pressure will be found to lie in a curve which rises steeply at first and then flattens out. This type of curve suggests a logarithmic relationship. If it is assumed that the Weber-Fechner Law holds good, the formula expressing this relationship will be: "The effect is proportional to the natural logarithm of the stimulus," or \[ E = N \log_e S + C, \]
where \( E \) = effect, i.e., blood pressure rise, \( N \) = a constant which expresses the sensitiveness of the reacting mechanism, \( S \) = the amount of adrenalin employed, and \( C \) is an added constant which will not alter the form of the curve but merely controls its distance above zero.

Figure 1. is from subject 12. On it are plotted out the maxima of a series of curves which have been measured from zero and not from the resting level.
Fig. 2. Blood Pressure Tracing

Showing that the response to a uniform dose of adrenalin chloride varies with the height at which the blood pressure stands when the drug comes into action. Curve A followed 1 cc. 1:1000 solution; rises B, C, D, E, F, G all followed doses of 0.2 cc. 1:10,000 adrenalin.
level of the blood pressure. The resting level of blood pressure present immediately before the injection is also shown in the chart below each maximum reading. The continuous line A has been obtained from the observed figures by the method of least squares and corresponds to the formula -

\[ E = 21.43 \log e S + 91.83. \]

The observed and the calculated figures coincide so closely that it may be said that the blood pressure response to adrenalin obeys Weber's Law. This is an extremely important fact for it infers that the drug does not produce uniform results under varying conditions. For example, in the case recorded in figure the increase of the dose from 0.1 to 0.2 cc. causes an extra rise of 15 mm. Hg (141 to 156) whereas an increase of similar magnitude (0.1 cc.), between 0.9 to 1 cc., raises the pressure only 3 points (187 to 190), and to cause an increase of 15 points at this level (187 to 202) would require a dose of adrenalin very much greater than that which suffices to produce the same increase at 141 mm. Hg.

This varying value has been illustrated in another way. A large dose of adrenalin (1 cc. 1 : 1000 solution) was given in order to raise the blood pressure to a considerable height and produce a slowly diminishing curve. At various points on this falling curve small doses (0.2 /
<table>
<thead>
<tr>
<th>Height</th>
<th>Main curve</th>
<th>Secondary curves</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beginning</td>
<td>94</td>
<td>246 217 197 180 160 136</td>
</tr>
<tr>
<td>Maximum</td>
<td>260</td>
<td>264 248 239 227 215 199</td>
</tr>
<tr>
<td>Wave</td>
<td>166</td>
<td>18 31 42 47 55 63</td>
</tr>
<tr>
<td>Dose</td>
<td>1 cc. 1:1000</td>
<td>0.2 cc. 1:10,000</td>
</tr>
</tbody>
</table>
(0.2 cc. 1 : 10,000 solution) were injected. These produced a series of secondary waves (fig. 2.). At a glance it will be seen that the responses to a uniform dose depend on the level from which they commence the disturbances varying from 18 mm. at 246, to 63 mm. when the initial pressure has fallen to 136 mm. Hg.

The accompanying table gives the actual measurements. During the latent period after the secondary injections the main curve continues to fall, then at a definite point the fall gives place to a rise. At this point it might be confidently assumed that the newly added adrenalin has come into action. This point has been taken as the base in the measurements rather than the level actually corresponding to the time of injection. The height of the wave of disturbance caused by the small dose of adrenalin is measured from this point to the maximum of the secondary curve. It should be noticed, however, that as the base line (the large curve) is constantly falling the true magnitude of the disturbance should be somewhat greater. In the table no account of this has been taken because of the difficulty of determining the exact position of the main curve at the point corresponding to the maximum of the secondary one. These results have been confirmed in several similar experiments.

From these experiments it would appear that:

(1) /
Fig. 4.—Ordinates millimetres of blood pressure, abscissae doses of adrenalin employed in fractions of a cubic centimetre 1:10,000 solution. The points on the curve show the height to which the blood pressure rose as the result of giving the dose indicated on the base line. Notice the great diminution of additional effect as the dose increases by equal amounts.
(1). Repeated doses of a uniform amount of adrenalin chloride solution produce the same increase in blood pressure only if the resting level of the pressure immediately preceding the injection is the same in each case.

(2). When the resting levels differ, the blood pressure responses to uniform doses of adrenalin vary, the magnitude of the disturbance diminishing as the resting level rises. In other words, a much larger dose is required to produce the same effect at a higher level.

(3). When the amount of adrenalin administered is increased arithmetically, the resultant blood pressure rises do not follow suit but bear logarithmic relationship to the stimulus.

Chapter III.

The Absorption of Adrenalin.
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The Absorption of Adrenalin.

Adrenalin, the most powerful of the sympathomimetic amines, acts locally on the terminal mechanism of the sympathetic nerves in the organs and also produces the same response as the sympathetic itself, whether that be stimulation or inhibition. It has been shown (14) that the reaction to adrenalin is proportional to the amount of the drug present in the blood at the time, and that the response only continues so long as an excess remains in the blood. Adrenalin disappears rapidly from the circulation and from the tissues, apparently undergoing immediate destruction, and none of it can be discovered in the blood after the reaction is finished (16).

The mode of administration has an important bearing on the character of the response to adrenalin, for its action depends on the rate at which
which it reaches the tissues, and this varies with the path of absorption. Given intravenously in animals adrenalin causes a rapid rise and fall of systolic pressure, the whole disturbance lasting only a few minutes. (see chapter II.). with intramuscular injection, the response is still considerable but is slower and lasts somewhat longer. The impression seems to be widely prevalent that adrenalin, given subcutaneously, causes little general effect, and its action is quite uncertain (q ) (1q). This view is probably based on the blanching of the skin which is seen around the site of injection, and on the fact that adrenalin causes vasoconstriction of some vessels. But the spectacular relief from distressing symptoms that occurs in asthmatics within a few minutes after a hypodermic injection of a minute dose of adrenalin is in itself evidence that absorption by this route is rapid and satisfactory.

On page 5 it was suggested that absorption
of adrenalin can take place freely by lymphatic channels.

A large number of reactions in the body, e.g. the action of enzymes, obey the law of mass action, according to which the rate of change is proportional to the concentration of the reacting substance. If a certain quantity of a substance $x$ is being converted into another substance $y$, the process is rapid at first but becomes slower and slower as the amount of $x$ diminishes.

When the change takes place in two stages (consecutive reactions) the conditions are not so simple. Let $x$ be converted into $y$, which in turn becomes $z$. The transference of $x$ into $y$ takes place as above and the conversion of $y$ into $z$ follows Wilhelmy's Law of Mass Action. In this case, however, the rate of formation of $z$ is proportional to the concentration of $y$ in the system at different times, and the quantity of $y$ present at any moment depends on the relative rates of the processes $x \rightarrow y$ and $y \rightarrow z$. The concentration of $y$ starts from zero and increases until a point is reached at which its rate of formation is balanced by the rate of its conversion, after which it again diminishes in amount. (32).

The absorption and utilization of adrenalin form an example of consecutive reactions, the first stage /
Fig. 3.—Curves showing distribution of adrenalin between original focus of injection (x), the bloodstream (y) and the assimilating tissues (z). The ordinates indicate fractions of the original 0.5 c.c. adrenalin administered, the abscissae show minutes. The transference of adrenalin from the blood to the tissues, and consequently the rate at which the drug becomes available is proportionate to the curve (y).
stage \((x \rightarrow y)\) is the introduction of the drug into the circulation, the second \((y \rightarrow z)\) its removal from the blood stream into the reacting tissues. The quantity of adrenalin absorbed in unit time is greatest at the beginning of the process and becomes less as the local concentration of the drug diminishes. (see Curve X in figure 3). From the site of inoculation the adrenalin is transferred by lymphatic channels to be discharged at some point into the blood stream. A latent period will be required for its passage between these two points, but this will not effect the character of the reaction, and the rate of the appearance of adrenalin in the circulation will be the same as the rate of its removal from the subcutaneous area.

The quantity of adrenalin available for the tissues at any moment depends on the varying concentration of the drug in the blood stream.

Methods Employed in Interpreting the Records.

If it be assumed that the rate of absorption of adrenalin and the rate of its destruction obey the law of mass action, and that the changes in blood pressure following administration of the drug are proportionate to the changes in concentration of the substance in the circulating blood, an analysis of the blood pressure curves should yield...
a good deal of information regarding the processes of absorption and utilisation of the adrenalin.

Let \( x_0 \) = the original amount of adrenalin injected.

\[ x_1 = \text{the amount of adrenalin remaining unabsorbed at any time before the reaction has started.} \]

\( z = \text{the amount of adrenalin destroyed by the tissues.} \)

\( y = \text{the quantity of adrenalin in the circulating blood.} \)

\( t = \text{the time which has elapsed since the beginning of the reaction.} \)

\( r \) and \( s \) = constants which express the rapidity of the two reactions.

\( e = \text{the mathematical constant } 2.7182. \)

From the law of mass action the rate of transference of adrenalin from the site of injection into the blood stream is given by the differential equation

\[ \frac{dx}{dt} = rx \]

The rate of utilisation of the adrenalin by the tissues is expressed by

\[ \frac{dz}{dt} = sy \]

and the difference between these two processes, absorption and destruction, shows the rate of accumulation of adrenalin in the circulating blood.

\[ \frac{dy}{dt} = \frac{dx}{dt} - \frac{dz}{dt} = rx_0 - sy \]

By /
Fig. 5.—A series of curves showing the effects of varying the reaction constants \((r, \text{ and } s)\) of the consecutive processes, absorption into the blood and removal to the tissues. The curves correspond to \((y)\) in Fig. 3, and indicate the quantity of adrenalin in the blood at successive points of time. The values of the constants are:

<table>
<thead>
<tr>
<th>Curve</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>0.08</td>
<td>0.03</td>
<td>0.08</td>
<td>0.14</td>
</tr>
<tr>
<td>S</td>
<td>0.16</td>
<td>0.05</td>
<td>0.01</td>
<td>0.16</td>
</tr>
</tbody>
</table>
By integration from these formulas can be found the actual distribution of the adrenalin between subcutaneous tissue, blood, and reacting tissues at any instant of time.

(4) $X_t = X_0 e^{-rt}$ gives adrenalin still unabsorbed.

(5) $Z = \frac{X_0 \gamma s}{s - r} \left( \frac{1 - e^{-rt}}{r} - \frac{1 - e^{-st}}{s} \right)$ gives the amount already destroyed.

(6) $Y = \frac{X_0 \gamma}{s - r} \left( e^{-rt} - e^{-st} \right)$ gives the quantity of adrenalin in the circulating blood.

Since the adrenalin is quantitatively used up in producing its effects, the blood pressure curve should follow the changes in the rate of destruction of the substance and should correspond to formula (2) given above.

(7) $\frac{dz}{dt} = SY$, or giving $Y$ its value,

" $\frac{dz}{dt} = \frac{X_0 \gamma}{s - r} \left( e^{-rt} - e^{-st} \right)$,

that is, the rate of transference of adrenalin to the tissues $\frac{dz}{dt}$ is proportional to the quantity of the drug in the circulating blood, and is simply this value $(Y)$ multiplied by the reaction constant $(s)$.

In equation (7) the figures for $X_0$, $t$, and $\gamma$
and e are already known and it only remains to discover values for the constants r and s. This can be done by an examination of the curve itself. Take readings of the curve at four points separated by equal intervals of time. Let the value of these points be represented by A, B, C, and D, and the time interval be p. (The calculation can be considerably shortened by taking A as the initial point in the reaction and giving it zero value.)

The constants r and s are found thus:

\[
\begin{align*}
F &= e^{-(r+s)p} = \frac{BD - C^2}{AC - B^2} \\
G &= e^{-rp} + e^{-sp} = \frac{AD - BC}{AC - B^2} \\
H &= e^{-rp} - e^{-sp} = \sqrt{G^2 - 4F} \\
2e^{-rp} &= G + H \\
e^{-rp} &= \frac{G + H}{2} \\
r &= \frac{w}{p} \\
2e^{-sp} &= G - H \\
e^{-sp} &= \frac{G - H}{2} \\
s &= \frac{v}{p} \\
\end{align*}
\]

w and v can be obtained from tables of exponentials.

With these newly found constants the blood pressure curve /
A = B.P. values observed.
B = " " calculated
C = Metabolic Rate.
D = Pulse Rate.
E = Diastolic B.P. readings.
F = Respiratory Quotients.

Fig. 6
\[ T a b l e \ 5 \]

<table>
<thead>
<tr>
<th>( t )</th>
<th>0</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
<th>24</th>
<th>28</th>
<th>32</th>
<th>36</th>
<th>40</th>
</tr>
</thead>
<tbody>
<tr>
<td>( x )</td>
<td>0.5</td>
<td>0.363</td>
<td>0.264</td>
<td>0.191</td>
<td>0.139</td>
<td>0.101</td>
<td>0.073</td>
<td>0.053</td>
<td>0.038</td>
<td>0.028</td>
<td>0.018</td>
</tr>
<tr>
<td>( y )</td>
<td>0</td>
<td>0.099</td>
<td>0.124</td>
<td>0.113</td>
<td>0.100</td>
<td>0.081</td>
<td>0.063</td>
<td>0.048</td>
<td>0.036</td>
<td>0.026</td>
<td>0.017</td>
</tr>
<tr>
<td>( z )</td>
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<td>0.038</td>
<td>0.112</td>
<td>0.191</td>
<td>0.261</td>
<td>0.318</td>
<td>0.364</td>
<td>0.399</td>
<td>0.426</td>
<td>0.446</td>
<td>0.465</td>
</tr>
<tr>
<td>( x_0 - x_1 )</td>
<td>0</td>
<td>0.137</td>
<td>0.236</td>
<td>0.309</td>
<td>0.361</td>
<td>0.399</td>
<td>0.427</td>
<td>0.447</td>
<td>0.462</td>
<td>0.472</td>
<td>0.482</td>
</tr>
<tr>
<td>( s y )</td>
<td>0</td>
<td>0.016</td>
<td>0.020</td>
<td>0.019</td>
<td>0.016</td>
<td>0.013</td>
<td>0.010</td>
<td>0.008</td>
<td>0.006</td>
<td>0.004</td>
<td>0.003</td>
</tr>
</tbody>
</table>

\( t \) = time in minutes; \( x \), adrenalin remaining unabsorbed; \\
\( y \), adrenalin in the circulation; \( z \), adrenalin destroyed \\
in the tissues; \( x_0 - x_1 \), amount absorbed; and \\
\( s y \), quantity in action at the moment.
curve can be reconstructed and compared with the observed figures, the value of the expression $s \frac{x_{0}r}{s-r}$ being obtained from

$$\frac{B - A \left( \frac{G - H}{2} \right)}{H}, \quad \text{or when} \quad A = 0, \quad \text{from} \quad \frac{B}{H}.$$  

If the calculated and the observed figures correspond closely the values of $s$ and $r$ are satisfactory and they may be employed in formulas (1) to (9).

Figure 6. is shown as an example of the blood pressure readings which follow the administration of adrenalin. Curve A is fairly smooth for the first 28 minutes but after this it becomes irregular. The constants extracted by the four point method from the regular part of the curve have the values 0.08 for $r$ and 0.16 for $s$. From these figures the curves of $x$, $y$, $z$, and $sy$ have been calculated (Table 5) and these are shown graphically in figure 7. It will be observed that $x$ declines at first much more rapidly than $z$ rises, so that the amount of adrenalin in the circulation increases for 8 minutes. At this point the rates of the absorption and of the removal of adrenalin from the blood equal each other and the drug ceases to accumulate in the blood. At the maximum point, 25 percent of the original dose of adrenalin is being carried in the circulating blood, but the amount transferred to the tissues at the same time, and available /
TEXT-FIG. 7. Graphs from Case C in which $r = 0.08$ and $s = 0.16$. These lines show the distribution of adrenalin during 40 minutes following its administration subcutaneously. $x =$ adrenalin subcutaneously; $y =$ adrenalin in the blood stream; $z =$ adrenalin destroyed in reacting tissues; and $sy =$ adrenalin passing from blood to tissues.  

Case C = 29. 30.
available for producing an effect there, is only 4 per cent. The removal of the adrenalin from the site of inoculation is very rapid; after 9 minutes only 50 per cent remains locally, at 20 minutes 20 per cent, and by 40 minutes less than 4 per cent is left unabsorbed. Individual cases show wide differences in their behaviour to adrenalin and the records vary considerably in character, notably in regard to the rate of onset, the magnitude of the reaction, and its duration.

In the majority of cases the rise of the blood pressure commenced within 2 minutes after the hypodermic injection, but occasionally the increase was not evident for several minutes; in one instance a latent period of 10 minutes elapsed (vide infra). The increase of pressure may occur quickly or slowly so that the highest point is often reached in 6 to 10 minutes or may be delayed for nearly 40 minutes. If the process of absorption is rapid a greater quantity of the drug can come into action at one time and consequently the apex of the curve is high. This high level does not persist for long and a speedy fall of pressure usually follows. A sustained maximum and a slow decline characterise those cases in whom the onset is more gradual.

Two patients suffering from diabetes mellitus offered a great contrast. Both were young men; the /
the one, (case 55), was an excitable individual who was at the beginning of his course of treatment, the other (case 70), was of plethoric temperament and had been sugar-free for a year. In the former the reaction took place with startling rapidity, the pressure mounting at once and the maximum increase (52 mm. Hg) occurring at 10 minutes. The decline was almost equally speedy and within 24 minutes the reaction was practically over. The other subject, showed a very different type of response. Following the injection of adrenalin there was a latent period of 10 minutes during which the blood pressure remained steady. A quite insignificant rise then took place (10 mm. Hg) and persisted for some time. A clue to the cause of the difference between the responses was obtained from the pulse rate. Case 70 had a habitual bradycardia (48 beats per minute) while in case 55 the heart usually ran about 80.

An investigation, by Professor Meakins, of the blood flow in these two subjects gave similar information. While the circulation rate in case 70 was less than normal, case 55 had an accelerated blood flow. It would seem from this that the rate of absorption of the substance from the subcutaneous tissues into the blood was dependent on the rate of the blood flow. The effect of a rapid circulation rate on the rate of absorption would also serve to explain the exaggerated reactions to adrenalin which are obtained in
**Table 6.**

Adrenalin absorbed = \( x_0 - x_g \), or \( y+z \)

<table>
<thead>
<tr>
<th>Case</th>
<th>0 min.</th>
<th>10 min.</th>
<th>20 min.</th>
<th>30 min.</th>
<th>40 min.</th>
<th>50 min.</th>
<th>60 min.</th>
<th>( r )</th>
<th>( s )</th>
<th>Time of maximum elevation</th>
<th>Diagnosis</th>
<th>B.M.R. per cent.</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>cc.</td>
<td>cc.</td>
<td>cc.</td>
<td>cc.</td>
<td>cc.</td>
<td>cc.</td>
<td>cc.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Myxoedema</td>
<td>- 36</td>
</tr>
<tr>
<td>E</td>
<td>-</td>
<td>0.07</td>
<td>0.13</td>
<td>0.18</td>
<td>0.23</td>
<td>0.26</td>
<td>0.28</td>
<td>0.015</td>
<td>0.15</td>
<td>25</td>
<td>Diabetes</td>
<td>- 15</td>
</tr>
<tr>
<td>F</td>
<td>-</td>
<td>0.12</td>
<td>0.21</td>
<td>0.28</td>
<td>0.33</td>
<td>0.37</td>
<td>0.40</td>
<td>0.027</td>
<td>0.12</td>
<td>16</td>
<td>Asthma</td>
<td>+ 7</td>
</tr>
<tr>
<td>G</td>
<td>-</td>
<td>0.20</td>
<td>0.32</td>
<td>0.39</td>
<td>0.43</td>
<td>0.46</td>
<td>0.48</td>
<td>0.050</td>
<td>0.30</td>
<td>14</td>
<td>Cancer</td>
<td>+ 8</td>
</tr>
<tr>
<td>c</td>
<td>-</td>
<td>0.23</td>
<td>0.35</td>
<td>0.42</td>
<td>0.45</td>
<td>0.48</td>
<td>0.49</td>
<td>0.060</td>
<td>0.10</td>
<td>13</td>
<td>Hyperthyroidiam</td>
<td>+ 20</td>
</tr>
</tbody>
</table>
the subjects of exophthalmic goitre, without raising the question of any hypersensitiveness of the tissues to adrenalin in such cases. A similar view has been put forward by Kendall. (15).

In Table 6 are set out figures showing the rate of absorption of adrenalin in five cases. The absorption constants (r) range from 0.015 to 0.08 but, with the exception of Case F, the constants (s) controlling the second reaction lie closer together. It will be seen too that the time at which the maximum elevation is reached also depends on the r constant. When this is small the rise is slow, and conversely. Case D was an untreated case of myxoedema whose bodily activities were sluggish. This may account for the slow absorption and the comparatively small response to the drug. The results in Table 6 are graphically shown in figure 8.
TEXT-FIG. 8. Rate of absorption of adrenalin in five cases (Table II). The curves, which show the rate of removal of adrenalin from the site of injection, have been calculated from 

\[ x_t = x_0 e^{-rt} \]

The values of the constant \( r \) are as follows: Case D = 0.015; Case E = 0.027; Case F = 0.05; Case G = 0.06; and Case C = 0.08.
In the above discussion on the absorption of adrenalin it has been assumed that the drug acts in a strictly quantitative fashion in producing its effects. It has been shown, however, in Chapter II that this view must be modified, since the relationship between the size of the dose and the magnitude of the effect is a logarithmic one corresponding to the formula \( E = N \log e S + C \) (see page 34).

When this fact is taken into account, some revision of the above views is necessary.

Since large amounts of adrenalin produce apparently proportionately less responses than smaller doses, the quantity of the drug in action at the maximum of the curve must be even greater, and the rate of its absorption will be faster, than the simple case allows for.

In order to make this logarithmic correction for each subject it would be necessary to know the value of the constant of reactivity \( N \). To obtain this constant, the responses to at least two different amounts of adrenalin must be studied. The figure for \( N \) can then be extracted from the following formula -

\[
N = \frac{E_2 - E_1}{\log e S_2 - \log e S_1}
\]

\( S_1 \) and \( S_2 \) represent the two doses employed, and \( E_1 \) and \( E_2 \) are the maximum values of the responses to these doses.
It seems highly probable that the value of the Reactivity Constant \( R \) would give a better index of the sensitiveness of an individual to adrenalin than Goetsch's rather crude clinical test.

The method has been tried out in several persons but does not prove as valuable in practice as in theory. The blood pressure in a normal individual is not kept absolutely steady but varies spontaneously from minute to minute 5 or 10 mm. Hg up or down. This variability is unfortunately about as great as the effects produced by small doses of adrenalin 0.1 - 0.3 cc. Investigations along these lines are still being carried out.

In this connection compare charts 14 and 37.

The principles discussed in Chapters II and III appear to be of considerable importance in the science of therapeutics, and have formed the basis of a paper on "Some factors which influence dosage."


Chapter IV.

The Character of the Reaction as influenced by the subject's state of health.
Chapter 4.

The Character of the Reaction as influenced by the subject's state of Health.

Group 1. Cases showing no evidence of endocrine disturbance. (Graphs 1 - 16).

The subjects in this group gave a wide variety of responses, so that no single type could be pointed to as the normal. Amongst the reactions obtained, some are slow others rapid, some slight in degree others exaggerated. Those patients clinically recognised as "nervous" or excitable usually shewed a very active response, but a similar rapid and marked reaction might be given by a subject who presented no such clinical evidence of hypertonus.

Group II. Cases showing disturbance of thyroid function.

The results obtained from this group are of special interest because of the fact that Goetsch has made use of adrenalin for testing the functional capacity of the thyroid. A close relationship is known to exist between the thyroid and the suprarenals, and the state of activity of the thyroid is believed to influence the character and degree of the response of the body to adrenalin. Removal of the /
the thyroid (in animal experiments) lessens the response to a subsequent injection of adrenalin, while conversely the administration of thyroid products, enhances the adrenalin reaction \((2, 3, 4, 8)\).

Stimulation of the cervical sympathetic, by causing active secretion from the thyroid, produces increased responses \((13)\). The explanation usually given is that the thyroid hormone sensitises sympathetic nerve endings to the action of adrenalin. Several observers have shown that a similar relationship obtains in man also. A great deal of attention has been paid to this subject and the question is by no means settled.

Plummer \((36)\) believes that thyroxin controls the rate of cellular metabolism, but he has pointed out that the supposed relationship between thyroid and adrenals can be explained on grounds involving the rate of blood flow alone, entirely apart from any other action. This view is in keeping with the observation quoted on page 46, where a rapid exaggerated reaction was seen to correspond to a quick circulation rate, while a slow moderate response accompanied a sluggish blood flow.

\(15\)

Kendall takes a similar position when he states that "if viewed purely from a consideration of the physics involved, the injection of adrenalin into a subject with a normal basal metabolic rate will be necessarily different from injection of the same".
same quantity into a subject with a metabolic rate
30% above normal." Ãub also rejects the theory of specific sensitisation and decides that the thyroid is not an essential factor in the action of epinephrin and that the effects of thyroxin and epinephrin are distinct and not interdependent. It is interesting to note that Marine & Lenhart (31) continued to get an increase in metabolic rate after administration of adrenalin to rabbits after these had been deprived of their thyroid glands.

The question has also been investigated in the human subject. Sandiford (38) found no relation between the intensity of the adrenalin reaction and the condition of the thyroid in her patients, and she doubts if there is any sound physiological foundation for the belief that such a relationship exists.

Other observers report that Goetsch's test may frequently be positive in non-goitrous subjects. Thus Wagenen (42) found a positive response in 20% of physically fit, symptomless students; and Tomkins, Sturgis & Wearn (40) obtained 65% of positives in cases of irritable heart (in which condition the B.M.R. is normal).

Herring in his review of the subject, sums up the position thus - "The specific action of the thyroid in sensitising tissues amenable to adrenalin, though not improbable, is not yet proved." (21)
Goetsch's test consists of giving a standard dose of 0.5 ccm. of 1:1000 adrenalin subcutaneously and noting the changes produced in the blood pressure and the pulse rate. The typical positive reaction he states is "a rise of about 10 points in pulse or in systolic pressure or in both, together with certain clearcut subjective and objective symptoms (palpitation, tremor, apprehension &c)" (18). The present view of the value of the test appears to be that a negative finding is valuable in definitely excluding hyperthyroidism, whereas a positive result is of less significance, since it is frequently got in cases where no evidence of an over-acting thyroid exists.

The thyroid cases examined naturally fall into two groups - (A) those with deficient action (B) those showing symptoms of overaction.

(A) Cases of Hypothyroidism (graphs 17 to 24).

Untreated patients of this class give blood pressure changes of slight degree and short duration. The increase in systolic pressure following adrenalin was usually only from 5 - 15 mm. Hg and the maximum point was reached about 12 or 15 minutes. The metabolic reaction was of somewhat the same form, but on the whole was rather more active than the vascular response. The very slight rise in arterial pressure seemed to avoid the necessity for the vagal inhibition of /
of the heart rate seen in most other experiments, so that an early and moderately extensive increase in pulse rate might take place (25 - 30 beats). This augmentation did not last for long, and the pulse rate returned to the resting level in about 20 minutes. In normal subjects, it will be recalled, the increase often persisted for over 1½ hours.

After the hypothyroid cases had been for some time on thyroid treatment, the reactions to a similar dose of adrenalin became considerably enhanced. The blood pressure rise and the metabolic increase now reached a higher level and persisted for a longer time, and, although the primary rise in pulse rate was still prominent a secondary and more extensive acceleration followed as in normal subjects.

It is interesting to notice that several of these cases though far from being hyperthyroid, are positive to Goetsch's test since they shew an increase of over 10 points in pulse rate or blood pressure. (see graphs 17 + 18)

(B) Cases of Hyperthyroidism. In this group very active responses to adrenalin are to be expected. Some are certainly exaggerated, others are surprisingly mild. Although all the hyperthyroid subjects investigated surpassed the critical 10 points increase of Goetsch, a wide range of type of response is found in them. The data obtained have been particularly examined /
examined with a view to discovering whether there was a close correspondence between the activity of the thyroid, as measured by the basal metabolic rate, and the other reactions to adrenalin. On the whole, some such relationship appears to exist. When the B.M.R. is high—above plus 40, the response is of exaggerated type; when it is below plus 20, the blood pressure rise may be slow in onset, slight in degree, and rather persistent. Graph 15 illustrates a case who had a B.M.R. of plus 54; in him the systolic pressure rose 44 mm. Hg to its maximum within three minutes. The other extreme is seen in graph 33 where the subject, although showing marked exophthalmos, had only a B.M.R. of plus 22. In this case there was a gradual rise of 20 mm. Hg to a maximum 25 minutes after the injection, the systolic readings then remained practically steady at the maximum figure of 160 for 40 minutes and only returned to normal at the end of two hours.

In some of the exophthalmic subjects the giving of adrenalin was followed by a rise in the diastolic pressure instead of the more usual drop, and in others the diastolic values remained practically constant throughout the whole reaction neither falling nor rising. This failure to produce the usual fall in diastolic pressure may indicate that the peripheral channels in the arm were already greatly dilated. In many of the cases, however, the diastolic readings obtained in the resting state were not lower than usual, in a few the figures could not /
not be obtained with absolute certainty as sounds could still be heard over the vessels when the sphygmomanometric pressure had fallen almost to zero.

A very prominent feature of the hyperthyroid cases, was the very unstable character of the pulse. Wide differences in rate would sometimes suddenly occur from minute to minute, apparently on little or no outward provocation, and a transient rise or fall of 20 or 40 beats was quite often seen during the reaction. The accelerator effect in the most severe cases was very marked, and in these patients an abrupt increase in pulse rate might be seen in the first 10 minute period. Thereafter, still further elevation might occur, or at least the pulse rate would remain very rapid throughout the whole of the reaction.

The metabolic responses also appeared to depend on the activity of the thyroid (the value of the B.M.R.) but the correspondence is not absolute. The greatest effects are to be found in the middle ranges. When the metabolic rate is just a little above normal the reaction is moderate in degree. Very considerable increases in metabolism follow adrenalin administration, in those cases where the B.M.R. is plus 30 to plus 40, but where the resting level is still higher, plus 50 or over, the amount of metabolic augmentation falls short of expectation. For example, a patient with a B.M.R. of plus 12 gave a rise of 28 points; another with a basal level of 40 above
In order to facilitate comparison the figures normal is taken as 100 and the figures found are

<table>
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<th>Diagnosis</th>
<th>Bas.</th>
<th>Inc.</th>
<th>Max.</th>
<th>Metabolic Rate</th>
<th>Pulse</th>
<th>Blood Pressure</th>
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</tr>
<tr>
<td>Asthma</td>
<td>16</td>
<td>94</td>
<td>78</td>
<td>5</td>
<td>150</td>
<td>115</td>
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<td>11</td>
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<td>125</td>
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<tr>
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<td>46</td>
<td>146</td>
<td>105</td>
<td>33</td>
<td>136</td>
<td>123</td>
</tr>
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</table>

Table 8

Comparison of Cases Showing Similar Basal Metabolic Rates.
above normal increased by 60 points; while a third subject, starting from plus 54 only added 38 points. These results suggest the application of the logarithmic law (see page 30).

The influence of the state of the thyroid on the character of the response to adrenalin can be investigated in two ways: (a) by comparing the reactions in different subjects, and (b) by examining the same individuals on more than one occasion.

(a). **Comparison of Reactions in Different Individuals.** When viewed as a whole, these show only a slight relation to the activity of the thyroid as determined by the basal metabolic rate. A large cardio-vascular response may be present in a patient with a low metabolism and vice versa. The lack of uniformity can best be shown by a comparison of patients with approximately similar basal metabolic rates. Two groups are recorded in the accompanying table. Even when allowance is made for size, body-weight, age and sex (as is done in computing the B.M.R.) no better results are obtained.

(b). **Reactions in the same subject.** If it be true that thyroxin sensitizes the body to the action of adrenalin the effect should be evident when the amount of the thyroid hormone in the patient is varies. Table 9. gives the results of the examinations of four subjects before and after the administration /
<table>
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<th>Date</th>
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<td>115</td>
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<td>135</td>
<td>157</td>
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<td>150</td>
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<td></td>
<td></td>
<td>142</td>
<td>165</td>
<td>192</td>
<td>225</td>
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</table>
administration of thyroid extract. Two of the patients were cases of myxoedema with very low metabolic rates; the other two suffered from asthma. Of the latter, no. 45 showed rather high basal figures, while no. 43 was normal. The effect of the thyroid in raising the general activity of the body is evident in the increase of basal metabolic rate, basal pulse rate, and basal systolic pressure readings, while in those observations made after the giving of thyroid extract its sensitizing effect is shown in the great increase in the pulse and the pressure seen in all instances except one.

Confirmation of the influence of the thyroid would be expected in cases of exophthalmic goitre examined at different phases of the disease. The results shown in Table 10. at first sight seem contradictory. The cases were first examined shortly after admission to hospital and were re-examined when the clinical condition had improved. On the subsequent occasions the basal metabolic rates had fallen greatly and the slowing of the pulse was even more marked, the reduction in the case of the basal systolic blood pressure being less evident. In case no. 19 the reactions to adrenalin agreed very closely on two occasions when the basal metabolic rate stood at 120. On the third examination, though the basal levels were much reduced, the post-adrenalin increases in metabolic rate and in pulse rate were practically the same as before treatment. Cases 33 and 27 showed
<table>
<thead>
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<th>Pulse</th>
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<tr>
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<td></td>
<td>Aug. 30</td>
<td>125</td>
<td>160</td>
<td>141</td>
</tr>
</tbody>
</table>
showed a definite reduction in metabolic response, but in both patients the post-adrenalin blood pressure rise was greater and the pulse acceleration was little affected. Such results would suggest that the thyroid controls only the basal levels, while the reaction to adrenalin depends on some other independent mechanism.

When the logarithmic law is applied to Table q. this principle will have the effect of magnifying the increases actually obtained after the administration of thyroid; and in the case of Table 10. the apparent anomaly will diminish if not disappear, since the relatively large responses from a low basal level are of less value than if from higher basal level. Even when this allowance has been made, the differences in Table 10. fall far short of those in Table q. suggesting that the adrenalin sensitive mechanism still remains hypersensitive when the thyroid activity diminishes. (This might lend support to the view that the thyroid changes in exophthalmic goitre are merely secondary to a hypertonus of the sympathetic system) If the two mechanisms are entirely independent, as Aub (3) believes, an increase in thyroid activity would merely raise the basal levels and the adrenalin effect superimposed on these would have the same value whatever level the reaction started from. This does not fit the facts. The thyroid certainly does control the resting levels of pulse rate, metabolic rate, and /
and systolic pressure. It may also sensitise the tissues to the action of adrenalin. On the other hand the response to the injection of adrenalin may reflect principally the state of tonus of the sympathetic system, which may or may not depend on the condition of the thyroid. In discussing this question consideration must also be given to the acceleration of the circulation which probably leads to more rapid absorption of adrenalin.

Some of the points mentioned above may help to explain the comparative failure of Goetsch's reaction as a clinical test. It would seem too, that the criteria accepted are too low, since so many apparently normal persons give positive reactions.

Group III. Cases of Asthma.

Hyperthyroid patients are, of course, typical examples of sympathicotonia (Eppinger & Hess (17)) where the sympathetic side of the autonomic system is in a hypertonic state. Asthmatic subjects are vagotonic and should offer a sharp contrast to the exophthalmic cases. Three cases of this class have been investigated. The responses are certainly much less active than usual, but in each case the systolic pressure and the pulse rate increase by more than the 10 points of Goetsch's Test. Although not breathing with difficulty before the adrenalin was given, all three patients remarked on the greater respiratory comfort /
comfort that followed the injection.

In asthma the pivotal factor is a hypertonus of the pulmonary vagus. Normally, it is believed that vagus and true sympathetic tend to balance each other, so that an overaction on the part of one calls forth an increased activity of the other. The distressing symptoms of asthma probably result when the patient's sympathetic-adrenal system is unable to counteract the vagal stimulation. Acting on this hypothesis, thyroid extract has been given in several asthmatic patients, in the hope that this might enhance the value of their own adrenalin.

Striking success has apparently attended this treatment in several cases, notably in no. 45. Graphs 46, 47, and 48, are for data obtained after a course of thyroid.

In subject/45/ the great height of the initial level of the blood pressure will be noticed. This was undoubtedly an artificial level due to excitement or apprehension, for blood pressure estimations made in the ward were very much lower. Adrenalin given to this case produced comparatively little alteration, for the reason that the starting point was high. This is comparable to the slight rise in pressure obtained at the extreme right of the logarithmic curve (see fig. 4 page 37) in animal experiments. Doubtless had it been possible to have made a start from a lower initial point more reaction would have appeared. The responses are greater in the /
the results obtained after a course of thyroid although they commence from about the same high point.

Group IV. Cases of Diabetes Mellitus.

Clinical experience has shown that some diabetics, apparently very severe cases when first seen, may make a remarkable recovery, while others, although they can be controlled by diet and insulin, never regain any functional power. The former group have been regarded as suffering from a temporary functional incapacity of the mechanism regulating carbohydrate metabolism, the latter as cases of organic destruction of islet tissue. In the functional cases the sympathetic system often seems to play a large part. Our present diagnostic powers do not permit us to distinguish the two groups and hence a prognosis must be delayed until the patient has been watched for a long time. It was hoped that the use of adrenalin might serve to indicate those cases in whom the sympathetic system was most active, but other factors play such a large part in determining the character of the response that a clear differentiation has not been possible.

In this series of patients the dose of adrenalin employed was 1 cc. of 1 : 1000, in order that a marked hyperglycaemia and a glycosuria might be produced.

Many /
Many different types of reaction are represented in this group, and some offer extreme contrasts to each other. Several of the patients were examined on more than one occasion, and it was seen that the character of the response to adrenalin depended to a great extent on the stage of treatment that has been reached. When a case of diabetes is first admitted to hospital it is usual to put him on a standard "mixed" diet containing ordinary carbohydrates, for a few days in order to estimate the waste of sugar and get an idea of the severity of the disease. This phase is followed by a few days fasting or semistarvation. When the adrenalin is administered in either of these periods the basal metabolic rate and the respiratory quotient are low and the metabolic disturbances following the injection are slight in degree. Curiously enough the corresponding vascular reactions may still be considerable at these times. During the preliminary period when the patient is on ordinary diet, he is really being undernourished for comparatively little of the carbohydrate ingested can be made use of. In this stage and on the days of actual fasting the stores of glycogen are probably very low and little is available for conversion into glucose on emergency. The increased activity of the adrenalin emergency is largely paid for, of course, by sugar combustion as in shewn by the rise in R.Q. in all experiments. On the other hand, note the very slight post-adrenalin increase /
increase in R.Q. in graph 57 when the test day followed two days on which the patient took in food to the value of 2140 calories. This increase in the degree of the responses as the diet improves, suggests that the reaction depends in some way on the amount of stored carbohydrate available for use.

In nearly all cases the basal metabolic rates are lower than the normal, the poorest values being found where undernutrition was most obvious. Improvement in food intake increases the rate of the metabolic processes during rest. The amount of metabolic augmentation after adrenalin varies very greatly from case to case. In one subject the change was only 5 points (from -15 to -10) while at the other extreme an increase of 44 points was found (-20 to +22).

A very interesting observation in this series of cases was the extremely low level of the R.Q. which was generally in the lower seventies. In several cases the figure actually obtained was below 70. Similar low readings have been recorded, by other observers, but no completely satisfactory explanation is forthcoming. No uniformity in type of pressor response to adrenalin was found. Sudden or slow reactions occurred, the maximum point being reached within 5 minutes in the quickest, and being delayed for 35 minutes in the slowest. The actual rise in pressure in millimeters of mercury varied from /
from 10 points (120 - 130) to 75 points (105 - 180).
In nearly all cases the injection of adrenalin was
followed by quite a marked cardiac acceleration, the
maximum appearing late and the increase in rate
being maintained for a long time.

Further remarks on individual reactions
will be found in the notes on the cases
below.

Notes on Cases Examined.

Group I.

Graph 1. H.J. aged 29. Height 167.6 cm., weight
53.5 kilo. Convalescent.

Given 1 cc. Adrenalin. Rather gradual rise and
fall. Note that metabolic rate and ventilation rate
in periods 4 and 5 are out of place owing to rest-
lessness, the corresponding R.Q. values however are
very nearly in line. Pulse acceleration slight.
Respiratory rate constant except during restless
phase.

Graph 2. /
Graph 2. F.L. aged 53. Height 160 cm., weight 56 kilo. Retroperitoneal sarcoma. Shortly after admission to hospital and while still in good condition.

Given 1 cc. Adrenalin. Rapid rise of 64 mm. Hg after short latent interval of 4 minutes. Apex slightly sustained. Regular fall. Pulse shews immediate rise of 10 points followed by a phase of depression which in time passes into a more gradual acceleration. Note that pulse remains very rapid until end of observation.


Dose 0.5 cc. Adrenalin. Note high initial B.P. value and rapid decline in preliminary resting period. Metabolic values rise more quickly than pressure, but maxima almost correspond. Diastolic response is peculiar — depression, temporary elevation, depression and gradual recovery. Pulse acceleration comparatively slight — two isolated rises occur due to outside stimuli. Patient clinically was a highly nervous individual.

Graph 4. Same case as 3. Patient given Atropin sulph. 1/33 grain (Marais' typhoid test) in order to compare effects on metabolism, circulation, &c. with those produced by adrenalin. The metabolic to each other and and systolic pressure curves are closely similar of very slight degree. The characteristic atropin effect is seen in the pulse. The immediate temporary rise is connected with the administration of the drug.
The main increase begins after 10 minutes and approaches its maximum after 20.

Graph 5. Same subject as 3 and 4. Patient when in fasting state was given 100 grams of glucose in 400 cc. water in order to observe the effect on metabolism. The circulatory phenomena are insignificant - the variations being such as occur normally without special cause.

The metabolic response is a slow increase to a maximum an hour after ingestion of the sugar, followed by a slow decline. These curves are quite different from the changes produced by adrenalin.

Graph 6. A.H. aged 69. Height 164 cm. Weight 55.3 kilo. Dyspepsia.

Received 0.5 cc. Adrenalin. High initial systolic pressure may be due to excitement - patient was only observed for 25 minutes before commencement of test. Adrenalin administered because the levels shewed no sign of coming down. Curious initial temporary depression of B.P. reminiscent of that seen in experimental animals. The effect on the pulse rate appears very slight in comparison with changes in pressure and in metabolism.

Blood sugar curve typical - the height being reached as the other curves return to normal.

Graph 7. H. O'D. (female) aged 25. Height 159 cm. Weight 41.3 kilo. Gastric Neurosis.

Adrenalin /
Adrenalin 0.5 cc. Initial pressure readings much too high for female of this age. Post adrenalin increase therefore slight. The final B.P. value is probably the correct resting level.

Fasting metabolic value probably not unduly elevated and adrenalin effect on metabolism appears greater than that on blood pressure.

Pulse rate comparatively steady for a person of excitable temperament.


Dose 0.5 Adrenalin. This record is very similar to the last except as regards the pulse rate. The pulse in the preliminary period falls from 118 to 96, then rises early and remains up, showing wide changes when a stranger approaches.


Adrenalin 0.5 cc. The curves show a slow steady rise and decline. The diastolic B.P. after a slight fall, rises above the resting level. The pulse shows a well marked secondary increase.

Graph 10. Mrs J.F. (female) aged 53. Height 170 cm. Weight 80 kilo.

An example of a rather mild reaction. The increased metabolic values in the last 3 periods are due to discomfort. Note the uniformity of the percentage of carbon dioxide in the earlier samples.
Group I - continued.


The record shews circulatory and blood sugar changed only. Dose of Adrenalin 1 cc. Note sudden great increase of systolic pressure to 190 followed by a dip which resembles the vagal inhibition of animal experiments. The pulse rate shews a marked preliminary rise which gives place to an unusually prolonged depression. The pulse fall and the pressure reduction take place simultaneously and are both probably vagal in origin.

Graph 12. M.G. aged 24. Height 163 cm. Weight 58.5 kilo. Convalescent influenza case.

An early record to see relation of post adrenalin hyperglycaemia to the pressure effect.


Incomplete record shewing comparatively slight circulatory effect of 1 cc. Adrenalin. 155 mm. Hg is a rather high systolic level for this age.


Circulatory disturbances produced by the different doses of adrenalin. Black marks - data from dose of 0.1 cc. Red curves from 0.5 cc. The resting level in each case was the same — 130. The curves are not quite smooth and this introduces a difficulty in deciding what point to take as maximum. Some of the /
Group I - continued.

the waves are due to other factors. This record gives
the value of the constant \( N \), as \( 3.75 \).

Graph 15. C.G. aged 53. Height 165 cm. Weight 68.5
kilo. Arterio sclerosis.

1 cc. Adrenalin given. Chart is principally to
shew the time of maximum of adrenalin hyperglycaemia.
In this case an hour after the injection.

Graph 16. M.G. aged 22. Height 159 cm. Weight
77.5 kilo. Obesity.

Record taken principally for sugar curve. This
has a slow increase for 30 minutes, followed by a
period during which the high level is kept practically
constant. The circulatory changes are almost over
when the sugar reaches its maximum.

Group II. Thyroid Cases.

(a). Hypothyroids.

Graph 17. M.L. (female) aged 17. Height 134.7 cm.
Weight 40.4 kilos. Post-operative myxoedema.

When about 13 years old patient had an enlarged
thyroid. A large portion was removed surgically
under the impression that it was too big. Since that
time the patient has remained practically stationary
and has now the appearance and development of 13. The
skin and facies, however, shew the usual signs of
myxoedema.

This /
This record was taken a few days after the patient was admitted to hospital and before any thyroid had been given. The dose of adrenalin employed was 0.5 cc. - a relatively large amount considering the size of the subject. In spite of this, however, there is very little response to the drug. The systolic blood pressure increases only 5 points for a short time, while the diastolic pressure remains constant throughout. The most active response is the primary cardiac acceleration - a rise in pulse rate of 22 occurring immediately after the injection, but a return to normal takes place within 15 minutes. The basal metabolic level is very low, - 37, but the adrenalin raises it to - 22. It was very noticeable that practically no local reaction appeared in the forearm in the neighbourhood of the injection. Although the other responses were so slight, a very marked rise in blood sugar is seen to take place.

Graph 18. From the same case as no. 17; a month later. During this interval thyroid had been administered regularly and the clinical improvement was enormous. The patient was now very active and bright. The same dose of adrenalin, 0.5 cc. was employed and the responses are much more like those of a normal person that on the previous occasion. The basal metabolic rate is now plus 20 and the post adrenalin increase is considerable. The figure for the 4th period is rather too high, but.
but if this reading be discounted a great resemblance
will be noticed between the metabolic graph and the
curve of the systolic pressure. The diastolic pres-
sure increased slightly when the mask was adjusted
for the estimation of the preliminary basal exchange.
After the adrenalin a further slight increase
occurred and this was followed by a period of depres-
sion. The pulse changes are of the same character
as on the former occasion, but the response is more
marked. Early acceleration of this type is seldom
seen in other cases. The carbon dioxide percentages
are fairly uniform throughout except for period four
where overventilation obviously was present. The
curve of the respiratory quotient is very regular.

It is very interesting to notice that the blood
sugar levels are now much more like those of a nor-
mal subject.

Also myxoedematous! Height 151 cm.
Weight 43.5 kilo.

As in the previous case the state of develop-
ment is only that of 13 or 14 years of age. This
patient has for a long time been receiving small
doses of thyroid, so the record more closely
resembles no. 18 than no. 17. The B.M.R. is at
present plus 7. The only point worthy of special
notice here is the pulse curve — a marked early
rise followed by slight arrest and later further
advance.
Graph 20. MRS. A.S. aged 56. Height 152 cm. Weight 72 kilo. Adult myxoedema.

B.M.R. - 15%

The dose of adrenalin employed was 0.5 cc. and to this there was very little reaction. Blood pressures and pulse rate are scarcely affected. The great irregularity in the R.Q. values indicates that the breathing was not satisfactory. The later metabolic figures are therefore not to be relied on.


Owing to patient's small size only 0.25 cc. adrenalin was given. The vascular reactions are slight, the metabolic ones somewhat greater. Notice the rapid and irregular respiration - a condition not unusual in children.

Graph 22. E.S. (female) aged 30. Height Weight. Myxoedema.

This was a case of considerable interest. The patient developed hoarseness 10 years ago. The condition became extremely severe and the surgeon decided to remove the cause - a swelling at the back of the tongue. This mass proved to be a lingual thyroid rest. The thyroid tissue in the usual situation was insufficient for normal needs and myxoedema developed. The symptoms were marked at the time of the first examination. B.M.R. - 36%.

Adrenalin 0.5 cc. given. Pressure reactions slow, slight in degree and very soon over. Diastolic pressure rose after the injection. The pulse shows the early acceleration seen also in chart 17 no secondary /
secondary rise taking place. In spite of the very low resting level of the metabolism a very marked rise took place after the adrenalin - the rate becoming almost doubled during the second 10 minute period.

Graph 23, from same case as no. 22. Record taken a fortnight later, the patient having received 2½ grains thyroid extract daily in the interval. The B.M.R. is now plus 5%. The blood pressure reaction is of the same slow character, but is greater and of longer duration. The diastolic curve is now an inverted image of the systolic one, so that the mean pressure values are nearly constant throughout the whole period. The readings of the respiratory quotient shew a satisfactory rise and fall, so that the irregular values for metabolism must depend on faulty measurement of the air expired. (Trouble was being experienced with the meter at this time). The pulse still shows the early rise, but about 20 minutes after the reaction commenced a secondary rise occurred.

Graph 24. A.G. (female) aged 9½. Height 141 cm. Weight 46 kilo. Extremely adipose and very precocious. For two years patient has been increasing rapidly in weight and also in height until now she is as large as a girl of 12. Her intelligence is above the average and she competes in school with girls of 12 - 14.
According to Du Bois the number of calories per hour consumed by a normal child of age 9 is 54. Using this figure in the calculation the B.M.R. works out at - 40%. There is probably a fallacy in using this figure in a case of this type and if the readings were compared with those of girls of her own size - aged about 12 - a nearer approach to normality would be obtained. This factor, however, does not impair the comparison between the figures for the resting period and those obtained after adrenalin. Adrenalin 0.5 cc. employed.

Some reaction accompanied the first employment of the mask. Abrupt changes immediately follow the adrenalin.

The most striking feature of the chart is the pulse. Acceleration occurs in two phases, the early rise fairly considerable and lasting 20 minutes, the secondary rise being even much more marked and persisting for a long time.

(b). Cases with Hyperthyroidism.

Graph 25. J.A. (male) aged 22. Height 176.5 cm. Weight 55 kilos. Exophthalmic goitre.

Dose of adrenalin 0.5 only. The reactions are very marked. Systolic blood pressure quite steady before adrenalin, mounts precipitously 45 points within four minutes. Tremor and palpitation became very marked almost at once. A primary rise in diastolic pressure also occurs.
Group II - continued.

This phase is apparently followed by inhibition for a time and as this wears off the pressures rise once more. The pulse is characteristic of the disease. An early rise in rate takes place and a wide oscillation then occurs at a high level. Cardiac irregularity (extra systoles) was present for a time. Respiration rapid throughout - the breathing being jerky and irregular now and again.

Blood sugar estimations made a few days later showed a curve of moderate extent.

Graph 26. H. McC. (female) aged 33. Height 161.5 Weight 54.5 kilos. Exophthalmic goitre of 4 years duration. B.M.R. + 40%.

0.5 cc. adrenalin employed. Reaction of much slower type, the maxima appearing in second 10 minute period. Metabolism values and pressure curves correspond closely. Diastolic readings above resting levels. Pulse shows same unstable characters.

Graph 27. R.I. (male) aged 31. Height 174.6 cm. Weight 52.5 kilos. Exophthalmic goitre.

Has complained of "nervousness" for three years. B.M.R. + 40%. Adrenalin 0.5 cc. The systolic pressure in the resting state is rather high for a man of this age, but despite this the adrenalin has produced a very marked further increase - the maximum reaching 198 mm. Hg. The reaction, however, is slow considering its severity.

Metabolic /
Group II - continued.

Metabolic curves conform to pressure changes. The pulse in this case is exceptional for an exophthalmic subject. The resting rate of heart is absolutely steady and adrenalin produces a slow acceleration which subsides entirely within an hour.

Graph 28. From same subject as 27 - taken a month later when the clinical picture had greatly improved and the B.M.R. had fallen to +25.

The responses, however, are of the same type and practically of the same extent as those on the former occasions, but occur at slightly lower levels. Note the very constant values for CO₂ percentage.

Graph 29. J.J. (female) aged 17. Height 170 cm. Weight 50 kilos. Hyperthyroidism.

Some months ago patient came to hospital with an adolescent goitre, the basal metabolism being then normal. She was given a prescription for iodine of potassium in small doses and returned to her home in the country. The drug was kept up longer than was intended and the patient reappeared with undoubted symptoms of thyroid overaction. The data in chart 29 were taken at this point.

B.M.R. now +20%. The graph represents the reaction to 0.5 cc. adrenalin.

The responses are of the rapid exaggerated type. Systolic pressure rises precipitously and after remaining up for a short time only falls fairly quickly. An early rise in diastolic pressure also occurs. Metabolism changes in much the same way.
Group II - continued.

The pulse shows both a marked early rise and secondary increase as well. Wide variations in rate occurring within a few seconds.

Graph 30. From same patient as 29 - three weeks later.

During this interval the condition remained stationary, the B.M.R. being still recorded as + 20%. The remarkable thing about this record is its close similarity to No. 29. The figures rise from about the same resting levels to about the same extent after the injection. The primary pulse rise is considerable but the inhibiting phase separating it from the secondary rise is very slight. The unstable character of the pulse has also disappeared. The smooth contour of the pressure curve in this chart suggested the idea of mathematical analysis (see chapter 3).

Graph 31. From subject 29. Taken four days after No. 30. The curves represent reaction of blood pressure, pulse rate and respiration rate to a dose of 1/100 grains Atropine sulphate. The blood pressure and respiration are unaffected. The pulse rate unfortunately starts from an unusually high level and this probably obscures the real response. The maximum attained corresponds closely to the highest level seen in charts 29 and 30.

Graph 32. Also from subject 29. Taken three months after No. 29. During the interval
the patient had continued to rest and the phenomena of hyperactivity had quite disappeared. The conditions of examination were exactly similar to those obtaining in 29 and 30, but the B.M.R. was now +2%, i.e. normal.

The resting systolic readings are almost the same as on previous occasions, but the post-adrenalin reaction is insignificant in this examination. The metabolic response though greater than the pressure one, is much less than formerly and the maximum appears late.

The pulse rate starting from a very much lower plane allows practically the same increase - about 50 points.

Graph 33. J.S. (female) aged 19. Height
Weight
Exophthalmic goitre - of 8 months duration. B.M.R. + 22%.

Adrenalin 0.5 cc. given. In this subject, though the B.M.R. is almost identical with that in the last case, the reactions are of quite a different type. The pressure increase occurs slowly, and only amounts to 22 mm. Hg, but persists for nearly two hours. The metabolic rise, too, is slow and the effect persistent. The pulse rate shows a slow acceleration, the primary phase passing into the second without a period of inhibition. A record of this type suggests slow absorption of the drug.

Graph 34. Also from subject 33. Shows practically the same characters though taken five weeks /
weeks later. The initial values and therefore the following curves are at a slightly lower level.

Graph 35. J.R. (female) aged 27. Height 158 cm. Weight 50.5 kilos. Exophthalmic goitre. B.M.R. + 40%.

The record shows a reaction of only moderate extent considering the level of the B.M.R. The responses are prompt and rather sustained. During the fourth period trouble was experienced with the mask and it was therefore removed. The remaining data indicate sufficiently the direction of the change.

Graph 36. From same case as 35. Shows reaction of heart to 1/100 grains of Atropine. The slow onset of the effect as compared with the rapid acceleration following adrenalin, speaks to the involvement of an entirely different mechanism.

Graph 37. Also from subject 35. Shows the ex reaction of this exophthalmic patient to two doses of adrenalin - the larger 0.5 cc. - the smaller 0.1 cc. The constant of reactivity (sensitiveness of the patient) is N = 15. Compare this with graph 14.

Graph 38. J.J. (female) aged 42. Height 164 cm. Weight 52.5 kilos. Exophthalmic goitre.

The record was taken at a time when the B.M.R. was only + 12%. The resting levels, including the pulse rate, are practically those of a normal person. The reaction is very slight, the disturbances increasing /
increasing slowly until the fourth period and then subsiding. Notice the slight variations of O₂ percentage, R.Q., and volume of expired air.

**Graph 39.** E.R. (female) aged 33. Height 163 cm. Weight 52.5 kilos. Exophthalmic goitre. A very marked long-standing case who was being prepared for surgical treatment. This patient did not make a good subject for investigation. Notice the great irregularity in the figures during the preliminary period of examination; the levels of pulse rate and blood pressure rising after the face mask was adjusted. Two separate estimations of B.M.R. correspond fairly closely. In periods 2 and 3 the mask caused pain and this led to over-ventilation; these figures must therefore be discounted. The systolic pressure rise is abrupt and is accompanied by a diastolic increase. The heart rate varies greatly in characteristic fashion.

**Graph 40.** F.B. (male) aged 54. Height 175 cm. Weight 59.5 kilos. Hyperthyroidism with auricular fibrillation. A history of indefinite weakness extending over seven months. The patient was very excitable and apprehensive. B.M.R. + 16%. Given 0.5 cc. adrenalin. Following the injection marked changes took place and during the second ten minutes great distress and fear were complained of. Within an hour the figures had returned to the original values.
Group III. Asthmatic subjects (vagotonia?).

Graph 41. J.S. (female) aged 19. Height 152.5 cm. Weight 44.2 kilos. Severe asthma since childhood.

Given 0.7 cc. adrenalin. The patient had been prepared for examination in the usual way, but shortly before it was due she had an attack. This may help to explain the curious character of some of the responses. The circulatory disturbances are very slight.

Graph 42. Same case as 41 - a fortnight later.

For about a week before the present record was taken the patient was given Tr. Belladonna to physiological limits to endeavour to overcome the vagal hypertonus. The reaction in general is of same type as No. 41, except that the metabolic values are higher. Some difficulty was experienced with the fitting of the mask.

Graph 43. Mrs. F.D. aged 33. Height 162.5 cm. Weight 55. kilos. Asthmatic attacks for 12 years.

The patient was a thin, rather nervous type. When the examination was begun, the patient was wheezing slightly, but this disappeared as soon as the adrenalin was given. The reactions here are of moderate degree but fairly rapid in onset. The pulse rate shows both primary and secondary rises very well.

Graph 44. Same subject as 43. Record taken 9 days later. During this period the patient received /
received 9 grains of thyroid extract daily. This raised the B.M.R. from +7 to +18. In consequence a slightly larger metabolic reaction was obtained at the second examination. The circulatory changes, however, are very much the same as on the first occasion.

**Graph 45.** Mrs. J.R., aged 56. Height 155 cm. Weight 52.3 Chronic Asthma associated with much emphysema and some arteriosclerosis.

This chart is compiled from data obtained in the general ward, and shows practically no reaction. The variations present might quite well occur from other causes than the adrenalin. The patient was a severe case and was accustomed to frequent large doses of adrenalin.

**Graph 46.** (Reduced to half size) From case 45.

The patient was placed in the metabolism chamber about 1½ hours before the adrenalin was given. Readings for the last 50 minutes of this period were constant at the levels shown for the preliminary test period. The very high systolic pressure made one hesitate before giving adrenalin, but in view of the fact that the patient was accustomed to the drug and often took it at times of great excitement, the administration was considered justifiable. Blood pressure and pulse rate show only slight changes. The most striking feature of the chart is the curious period of rapid breathing which /
which commenced suddenly and as quickly disappeared after persisting for 24 minutes. The effect of this over-ventilation on the composition of the expired air is interesting. The metabolic increase is fairly considerable.

**Graph 47.** (Reduced to half size) Also from case 45 - six weeks after no. 46. The patient had been receiving thyroid during this time in order to see if it would enable her to make more use of her own adrenalin. Clinical improvement appeared to be considerable.

The B.M.R. was now +30% and the reaction is greatly enlarged. The pulse is much more labile in character. The respirations are on a high plane all through, but there is no period of hyperpnoea as in the last chart. The sudden rise in blood pressure in period four is undoubtedly a secondary phenomena due to coughing.

**Graph 48.** From the same subject - no. 45.

(Chart half size). The reaction is of much the same character as in the previous chart. The final rise in metabolism is due to discomfort.

**Graphs 49, 50, & 51.** R.H. aged 45. Height 65 4 cm. Weight 122 kilos. Asthma of 10 years duration.

These charts show circulatory reactions to different doses of adrenalin. The slight character of the responses are to be noticed.

**Graphs /**
Group III - continued.

Graphs 52, 53, & 54. Are from T.R. aged 51, who has suffered from Asthma for 9 years. They show the reactions to 0.1, 0.5, 1.0 cc. adrenalin in the same patient. The reactions vary in degree according to the dose. It will be noticed that the smallest dose produces a slight rise in blood pressure followed by a period of depression such as is seen in animal experiments when small doses are employed.

Group IV. Cases of Diabetes.

All the subjects in this group, except the last two, received 1.0 cc. of adrenalin.

Graph 55. W.L. aged 16. Height 176.5 Weight 50 Kg. Diabetes recognised for 3 months.

Patient is a thin, excitable and nervous person. The first examination was made when the patient had been for six days on an ordinary mixed diet containing 180 grams of carbohydrate and yielding 2100 calories. On this occasion a breakfast of oatmeal and milk was given 2 hours before the test began so that the preliminary metabolic value is higher than the true B.M.R.

The reaction is a good example of the sudden exaggerated variety. The injection is followed by an immediate increase in the cardiac rate of nearly 50 beats which, however, drops within a minute or so to its original level. The blood pressure increase,
Group IV. - continued.

too, is alarming, but fortunately the symptoms soon pass off. The diastolic values rise for a few minutes then fall to a low level, recovering slowly. The early cardiac acceleration is almost entirely obliterated, but the secondary rise is considerable and reaches its upper limit about the time the blood pressure returns to normal. The blood sugar values are high because the patient was on ordinary diet. Glycosuria increased during the test.

Graph 56. Same subject a week later. The patient was now sugar free, having fasted for two days. The systolic and diastolic curves on this occasion were almost the same as in no. 55, except that the systolic blood pressure begins from a lower point. The metabolic reaction is greater on this occasion, and the blood sugar curve very much lower. No glycosuria occurred.

Graph 57. Taken from the same boy three weeks later. The patient was now well up the dietary ladder, having on the previous day reached a diet of 2100 calories again, this time without losing any sugar in the urine.

The reactions now more closely approach the average type. The circulatory reactions are somewhat less abrupt and less extensive. The respiratory quotients are considerably higher. The blood sugar curve is also a little greater than /
group IV. - continued.

than in the last examination.

Graph 58. W.A. aged 18. Height 65½ cm. Weight 109 kilos. Symptoms for 4 months. A youth of much the same type as case 55.

This chart shows reaction of blood pressure and blood sugar to adrenalin. As the patient was on an ordinary mixed diet of 1700 calories and was passing urine containing about 1% of sugar, the blood sugar curve is rather elevated. The blood pressure response is moderately rapid and fairly great. A rise in diastolic pressure is also seen. Pulse rate remains almost constant during the whole period of observation.

Graph 59. From case 58. The patient was now sugar free. Very similar results to those on previous examination. The blood sugar levels are slightly low and only traces of sugar appeared in the urine towards the end of the reaction.

Graph 60. Also from case 58. The record was taken a fortnight after no. 59 - the patient meantime remaining sugar free and putting on weight on a diet of 2100 calories. The reactions now are of the exaggerated precipitant type. Notice how the diastolic pressures have increased on each successive examination. It is curious to observe how stable the pulse rate is in this subject. The blood sugar curve is of same type and nearly the same size as last time. Glycosuria occurred /
Group IV. - continued.

occurred throughout.

Graph 61. J.M. aged 44. Height  Weight  Four years history of Diabetes.

A severe case with great emaciation and weakness. The record was made on the first fasting day, the diet for the preceding day having been 93 grams of carbohydrate (almost 400 calories), 36 grams of which the patient passed in his urine. Notice the low R.Q. values and low metabolic readings. The low resting level of the systolic pressure is also striking. The pressure response is moderate in amount but slow in onset and decline. The pulse shows small primary and moderately large secondary rise. Blood sugar curve high.

Graph 62. From the same subject (61) - a week later. The diet is still very poor, containing only 400 calories. No glycosuria now present. Bradycardia still present during resting period but blood pressure now more normal. The pulse changes are very slight and so are these of the blood pressure. The sudden rise from 130 - 155 occurring at 20 minutes was due to pain caused by vein-puncture. The smaller elevation at 35 minutes is from same cause. The later metabolic readings are disturbed because of this and the increasing discomfort of the mask. The cheeks are so hollowed out that the mask had to be tightly adjusted to be air tight.
Group IV — continued.

Graph 63. Also from case 61. Three weeks later than no. 62. The diet has improved considerably and yields 1500 calories. No glycosuria present. The type of reaction has quite altered and this response is one of the sudden explosive variety. The systolic readings show a great contrast to those of the previous two examinations. The pulse rate also shows a much greater disturbance, but the metabolic readings are only slightly greater. Respiratory quotients, however, are much higher. This series of observations suggests that the character of the response is influenced greatly by the diet — probably the amount of stored glycogen available for use is the determining factor.

Graph 64. Was taken from the same subject (61) — a year later. He had been in good health until three months before re-admission to hospital, but had broken down again as the result of influenza. For about a month before this test was made (64) the patient had been treated with insulin in order to build him up again. He now weighed 59.5 kilos — in place of 47.

The reactions are again rather slight. Some increase takes place in the systolic pressure and in the Respiratory quotient, but pulse rate and metabolic rate remain practically constant.
Group IV - continued.

Graph 65. W.D. aged 20. Height 169 cm. Weight 61.5 kilos. Recent onset of symptoms.

Pressure changes occur moderately rapidly and are maintained for a long time. The pulse acceleration takes place in the usual two phase manner. The metabolic increase is curiously delayed. Low initial Respiratory quotient values are to be observed. These reactions were obtained after 36 hours' starvation at the beginning of treatment.

Graph 66. Same case 14 days later. The diet scale had now risen to 1360 calories, but the patient had fasted on the day immediately preceding. The reaction commences in much the same fashion as on previous occasions but the pressure effects are shorter lived. The other responses are very similar to those of chart 65.

Graph 67. Mrs. M.P. aged 60. Height 159 cm. Weight 49.5 kilos. Longstanding case with 12 years history. Great emaciation and debility.

Record taken after five days convalescent diet at the beginning of treatment. The systolic pressure commencing from high level rises sharply and declines slowly. The pulse acceleration is only slight. Considerable increase is shown in the metabolic readings. The blood sugar values are also high.
Group IV - continued.

Graph 68. Same case five weeks later. The patient reacted very slowly to dieting, glycosuria recurring often and necessitating frequent fast days. This record was taken after 60 hours starving, and shows a state of affairs almost identical with those in chart 67.

Graph 69. T.R. aged 43. Height 165 cm. Weight 55 k Five years history of Diabetes - moderately severe.

The patient also suffered from duodenal ulcer. The data included in this figure were obtained two months after treatment began. The patient was now getting 2400 calories. A sudden and very considerable vascular reaction has taken place. The pulse shows an unusual primary depression, possibly a compensation for the greatly increased blood pressure, the secondary acceleration takes place in usual fashion as the pressure returns to normal.

Graphs 70, 71, 72, & 73. Are from a most interesting case of Diabetes with Xanthoma, an account of which has been published in the Edinburgh Medical Journal.

The patient J.R.M. was aged 27. Height 173 cm. Weight 64 kilos. He had been in hospital about a year previously and had gone on well until recently when traces of sugar returned. He was re-admitted and overhauled and an opportunity was taken to test his reaction to adrenalin. The first records were made when he was on 1600 calories. The most notable features of this case are the persistent bradycardia and /
and the latent interval of about 10 minutes before the reaction definitely commences.

**Graph 71.** Taken two days later shows the accelerator effect of atropine.

**Graph 72.** Was obtained five days after No. 70. The diet now had reached 2500 calories. At this level the resting phase systolic pressure had risen from 120 to 140 and the post-adrenalin curve reaches a higher point than on the previous occasion, though the actual augmentation in figures appears less, 25 instead of 45. The pressure is sustained for a much longer time too.

**Graph 73.** Taken ten days after No. 70. Shows the same slow onset and a reaction of much the same character as No. 72. The diet at this time was still 2500 calories.

**Graph 74.** D.G. aged 34. Height 70 cm. Weight 147 kilos. Six weeks history of Polyuria and thirst - a case of considerable severity.

The chart shown is one of the first observations made. It shows merely the difference between the pressure curves and the changes in blood sugar.

**Graphs 75 & 76.** From A.F. aged 26. Height 68 cm. Weight 141 kilos. A mild case of five months' duration.

No. 75 was taken at the beginning of treatment after the period of ordinary diet when glycosuria was still present. The pressure response is slight, the /
Group IV - continued.

the pulse acceleration practically nil, but the sugar wave reaches a high level.

No 76 taken ten days later when the diet was beginning to be built up again. The reactions are now much greater and the sugar curve at a lower level.


Record taken after five days on ordinary diet followed by restriction of fat and protein for two days.

Only 0.5 cc. adrenalin was employed on this occasion, and the reaction is quite considerable for such a dose.

An interesting point is the sudden change from a respiratory quotient of 0.78 in the preliminary period to one of 1.08 in the first ten minutes. The metabolism rises slowly and the reactions are rather sustained.

Graph 78. E.T.K. aged 35. Height 168 cm. Weight 55 kilos. Diabetes for 2 years, becoming latterly very severe.

Examined while on preliminary ordinary diet. Shows extremely low respiratory quotient values, and metabolism somewhat high. Mask caused discomfort and led to over-ventilation. Adrenalin 0.5 cc. employed.
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<tr>
<th>Reference</th>
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No. 4.

Atropin Effect.

![Graph showing Atropin Effect with various data points and lines for different measurements.]
No. 5
Effect of Glucose ingestion

[Graph with various lines and annotations, possibly representing different physiological parameters such as oxygen consumption (O2), respiratory rate (RQ), and systolic and diastolic blood pressure.]
\[ N = \frac{E_2 - E_1}{\log_2 S_2 - \log_2 S_1} \]

\[ = \frac{14 - 8}{1.6 - 0} \]

\[ = 3.75 \text{ constant expressing reactivity.} \]
Local reaction very slight.

No. 17.
No 20.

Systolic

MR

Diastolic

Litres

Pulse

Co2

O2

Co2

Co2

O2

O2

Adrenaline

0.5

O2
No. 26.

Very highly emotional.
Notice great irregularity of RQ, 
O₂ + CO₂ yet
The metabolism curve is fairly smooth.
No. 31.

Pulse

Systolic

Diastolic

Respirations

\(\text{Atropin}\)
No 36.

Pulse

NB: palpitation nor distress.
N = 15.

Constant of Reactivity.
No 42.

Systolic

MR

Pulse

Diastolic

Respiration

Adrenalin

CO₂

O₂

litres

0 10 20 30 40 50 60 70 80 90 100

CC
No 45.

Systolic

Diastolic

Pulse

Respiration

0.5 cc. Adrenalin.
No. 49.

Very excitable
Face flushed throughout.

Adrenalin

0.3 c.c.
No. 51.

 skeletal
disturb.

 Palsies of face.

 Profuse.

 Indolent.

 Tumour.

 Systolic

 Pulse

 Diastolic

 1 c.c. Adrenalin.
Saline: No effect.

- Tachycardia
- Tachycardia
- Tachycardia
- Tachycardia

Systolic

Diastolic

0.3 cc Saline
0.3 cc Adrenaline
No. 56.
No. 59.

Blood Sugar.

Pulse, Diastolic

Pulse, Systolic

Reptilatin
Thrombin
Thrombin
Injection

Adrenalin

Glycosuria

Glycosuria

Trace

0.1

0.2 %

% 10 20 30 40 50 60 70 80 90 100

10 cc
Mask hunting - Rashness
Sighing and
breathing deeply & irregularly.

Tremor
tremor gone

Pulsation

Adrenalin,
No 71.

Systolic

Diastolic

Pulse

O₂

CO₂

RQ

BMR
No 72.

Pulse: Too high.

Blood Sugar: No Glycosuria.

Adrenalin: 10 cc
No. 73.
No 74.