

## THE ABSORPTION OF ADRENALIN.

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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 (1). It has been shown (2) 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 as 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 (3).

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 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. 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 (4-6). 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 has been given, is in itself evidence that absorption by this route is rapid and satisfactory.

When adrenalin is administered hypodermically there develops in the neighbourhood of the needle puncture a white zone which increases in size and persists for a long time. In many cases irregular white lines can be traced for some distance centrally from this area. These lines do not correspond to blood vessels but resemble in distribution the red streaks of inflamed lymphatics which appear in cases of cellulitis. It is 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 (7), 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  $z$  also follows Wilhelmy's law. 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 (8).

The absorption and utilisation of adrenalin are an example of consecutive reactions, the first 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 Text-fig. 2). 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 affect 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.  
 $x_1$  = the amount of adrenalin remaining unabsorbed at any time after the reaction has started.  
 $z$  = the amount of adrenalin destroyed by the tissues.  
 $y$  = the quantity of adrenalin in the circulating blood.  
 $t$  = the time which has elapsed since the beginning of the reaction.  
 $r$  and  $s$  = constants which express the rapidity of the two reactions.  
 $e$  = 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

$$(1) \quad \frac{dx}{dt} = rx_0$$

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

$$(2) \quad \frac{dz}{dt} = sy$$

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

$$(3) \quad \frac{dy}{dt} = \frac{dx}{dt} - \frac{dz}{dt} = rx_0 - sy$$

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.

$$(4) \quad x_1 = x_0 e^{-rt} \text{ gives adrenalin still unabsorbed,}$$

$$(5) \quad z = \frac{x_0 r s}{s - r} \left( \frac{1 - e^{-rt}}{r} - \frac{1 - e^{-st}}{s} \right) \text{ the amount already destroyed,}$$

$$(6) \quad y = \frac{x_0 r}{s - r} \left( e^{-rt} - e^{-st} \right) \text{ the quantity of adrenalin in the circulating blood.}$$

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.

$$(7) \quad \frac{dz}{dt} = sy, \text{ or giving } y \text{ its value,}$$

$$= s \frac{x_0 e^{-rt}}{s - r} (e^{-rt} - e^{-st})$$

that is, the rate of transference of adrenalin to the tissues  $\left(\frac{dz}{dt}\right)$  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  $e$  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:

$$F = e^{-(r+s)p} = \frac{BD - C^2}{AC - B^2} \quad \text{If } A = 0,$$

$$G = e^{-rp} + e^{-sp} = \frac{AD - BC}{AC - B^2} \quad F = \frac{C^2 - BD}{B^2}$$

$$H = e^{-rp} - e^{-sp} = \sqrt{G^2 - 4F} \quad G = \frac{C}{B}$$

$$2e^{-rp} = G + H \quad 2e^{-sp} = G - H$$

$$e^{-rp} = \frac{1}{2}(G + H) \quad e^{-sp} = \frac{1}{2}(G - H)$$

$$rp = w \quad sp = v$$

$$r = \frac{w}{p} \quad s = \frac{v}{p}$$

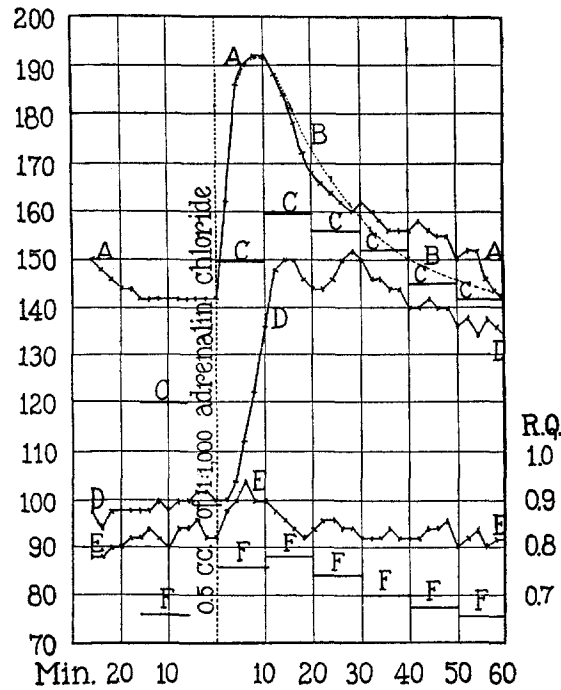
$w$  and  $v$  can be obtained from tables of exponentials. With these newly found constants the blood pressure curve can be reconstructed and compared with the observed figures, the value of the expression  $s \frac{x_0 e^{-rt}}{s-r}$  being obtained from

$$\frac{B - A \frac{1}{2}(G - H)}{H} \text{ or when } A = 0, \text{ from } \frac{B}{H}$$

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 (7).

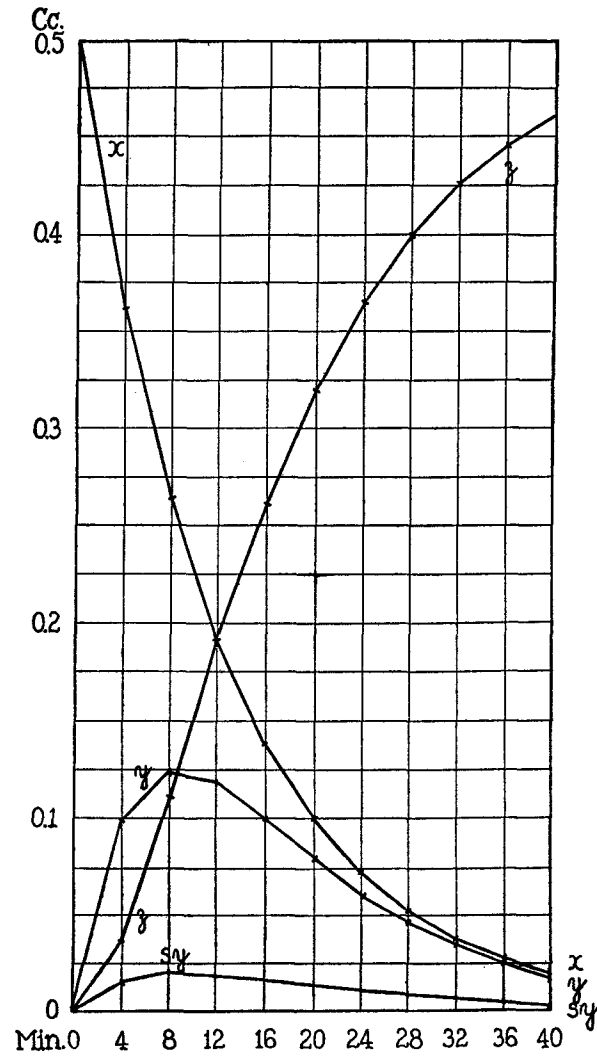
The response to hypodermic injection of adrenalin has been investigated in about 50 patients. Records of the pulse rate, systolic and diastolic blood pressure readings, and the basal metabolic rate

were first made with the usual precautions. The subject was then given in the forearm a subcutaneous injection of 0.5 cc. of adrenalin chloride 1:1,000 solution (Parke, Davis and Company). Following this, observations were made every 2 minutes for an hour on the blood pressure, the pulse, and respiration rates and 10 minute samples of



TEXT-FIG. 1. Graphic record of Case C. The abscissæ give time in minutes, the ordinates refer to Curves A, B, C, D, and E. The respiratory quotient values are shown on the right. Curve A is the observed systolic blood pressure in mm. Hg; Curve B, values obtained by calculation; Curve C, metabolic rates; Curve D, pulse rate; Curve E, diastolic blood pressure; and Curve F, values of respiratory quotient.

expired air were collected over the same period. The effects of the drug included a rise and subsequent fall in the volume of expired air, the oxygen consumption, the carbonic acid output, the metabolic rate, the respiratory quotient, and the systolic blood pressure. The movements of these readings coincide closely and the record of the



TEXT-FIG. 2. 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.

systolic pressure changes may be taken as expressing the general reaction.

Text-fig. 1 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 I) and these are shown graphically in Text-fig. 2. 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 ad-

TABLE I.

Case C. *r* = 0.08; *s* = 0.16.

<i>t</i> .....	0	4	8	12	16	20	24	28	32	36	40
<i>x</i>	0.5	0.363	0.264	0.191	0.139	0.101	0.073	0.053	0.038	0.028	0.018
<i>y</i>	0	0.099	0.124	0.118	0.100	0.081	0.063	0.048	0.036	0.026	0.017
<i>z</i>	0	0.038	0.112	0.191	0.261	0.318	0.364	0.399	0.426	0.446	0.465
<i>x</i> <sub>0</sub> - <i>x</i> <sub>1</sub>	0	0.137	0.236	0.309	0.361	0.399	0.427	0.447	0.462	0.472	0.482
<i>sy</i>	0	0.016	0.020	0.019	0.016	0.013	0.010	0.008	0.006	0.004	0.003

*t* = time in minutes; *x*, adrenalin remaining unabsorbed; *y*, adrenalin in the circulation; *z*, adrenalin destroyed in the tissues; *x*<sub>0</sub> - *x*<sub>1</sub>, amount absorbed; and *sy*, quantity in action at the moment.

renalin from the blood equal each other and the drug ceases to accumulate in the blood. At the maximum point, 25 per cent 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 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 behavior 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 characterize those cases in whom the onset is more gradual.

TABLE II.

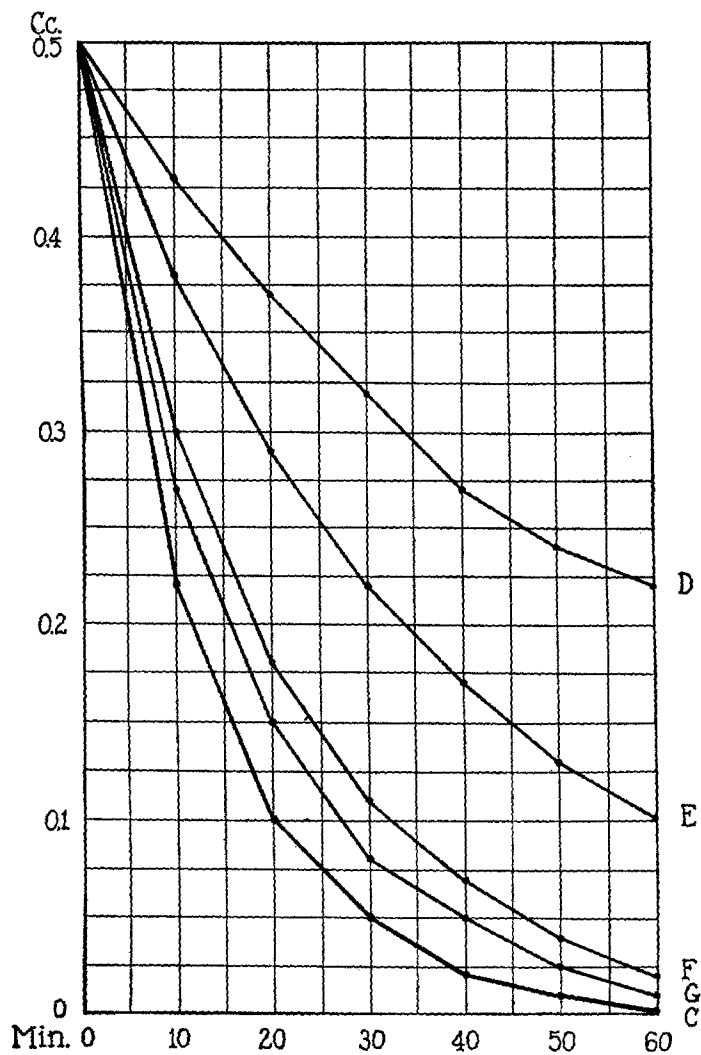
Adrenalin absorbed =  $x_0 - x_1$ , or  $y + z$ .

Case.	Time.							r	s	Time of maximum elevation.	Diagnosis.	Basal metabolic rate.
	0 min.	10 min.	20 min.	30 min.	40 min.	50 min.	60 min.					
	cc.	cc.	cc.	cc.	cc.	cc.	cc.					
D	—	0.07	0.13	0.18	0.23	0.26	0.28	0.015	0.15	25	Myxedema.	—36
E	—	0.12	0.21	0.28	0.33	0.37	0.40	0.027	0.12	16	Diabetes.	—15
F	—	0.20	0.32	0.39	0.43	0.46	0.48	0.050	0.30	14	Asthma.	+ 7
G	—	0.23	0.35	0.42	0.45	0.48	0.49	0.060	0.10	13	Cancer.	+ 8
C	—	0.28	0.40	0.45	0.48	0.49	0.50	0.080	0.16	8	Hyperthyroidism.	+20

Two patients suffering from diabetes mellitus offered a great contrast. Both were young men; the one, A, was an excitable individual who was at the beginning of his course of treatment, the other, B, was of plethoric temperament and had been sugar-free for a year. In A 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, B, 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 of A and B was obtained from the pulse rate. B had a habitual bradycardia (48 beats per minute) while A's heart usually ran about 80. An investigation by Professor Meakins of the blood flow in these two subjects gave similar information. While B's circulation rate was less than normal, A had an accelerated blood flow. It would seem from these cases 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 rapid circulation rate on the rate of absorption would also serve to explain the exaggerated reactions to



adrenalin which are obtained in 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 (9).



TEXT-FIG. 3. 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  $x_1 = x_0 e^{-rt}$ . 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 Table II 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 myxedema whose bodily activities were sluggish. This may account for the slow absorption and the comparatively small response to the drug. The results in Table II are graphically shown in Text-fig. 3.

In the above discussion it has been assumed that adrenalin acts in a strictly quantitative fashion in producing its effects. This view, however, must be modified in the light of recent investigations (10). It is known that when the dose of adrenalin is increased by a certain amount, the resultant response is not increased in direct proportion but falls short of expectation. The relationship between the size of the dose and the magnitude of the effect is a logarithmic one corresponding to the formula

$$E = n \log_e s(+c)$$

$E =$  effect.  
 $s =$  dose of adrenalin.  
 $n =$  a constant which expresses the activity of the subject.  
 $c =$  an added constant.

This would modify the above conclusions to a certain extent. Since large doses produce apparently a proportionately less response than the smaller doses, the amount of adrenalin in action at the maximum of the curve must be even greater, and the rate of absorption of the drug will be faster, than the simple case allows for.

In order to make this logarithmic correction it would be necessary to know the value of the constant of reactivity  $n$ . To obtain this, 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.

$$n = \frac{E_2 - E_1}{\log_e s_2 - \log_e s_1}$$

when  $s_1$  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  $n$  would give a better idea of the sensitiveness of the individual to adrenalin than the method at present in general use (Goetsch's).

## SUMMARY.

1. Adrenalin solution given subcutaneously is usually rapidly absorbed, probably by lymphatic channels.
2. The speed of this process may be influenced by the circulation rate.
3. The relative amounts of adrenalin at any moment unabsorbed at the site of inoculation, carried in the circulating fluids, and taken up by the reacting tissues can be calculated from figures extracted from the curve of the blood pressure changes. The relative rates of transference of adrenalin into the blood and from the circulation into the tissues can also be estimated.
4. When absorption takes place rapidly a large quantity of the drug comes into action at once and the maximum occurs early, the curve of blood pressure reaches a considerable height, and subsides quickly. When absorption is slow the apex appears later and does not reach so high a level.
5. The response to adrenalin bears a logarithmic relationship to the dose employed and a method of allowing for this is indicated.

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