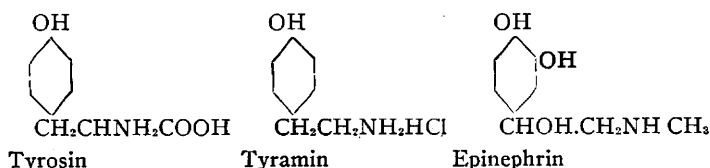


THE ACTION OF TYRAMIN ON THE CIRCULATION OF MAN *

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Tyramin is a hydrochloric acid salt of parahydroxyphenylethylamin. The latter is the most active blood pressure raising constituent in watery extracts of ergot.¹ It has been isolated from putrid meat² and from other decomposing organic substances. Here it appears to be formed by the action of bacterial ferments on tyrosin, one of the common amino-acid building stones of the protein molecule. The structural relationship of tyramin to tyrosin and to the physiologically related epinephrin is shown in the following structural formula:



The action of tyramin on the circulation of animals was studied by Dale and Dixon,³ who found that the intravenous injection of 1 mg. into the cat or into other laboratory animals was followed by a sudden and marked rise of arterial blood pressure, reminiscent of that produced by epinephrin. As compared with the latter, however, the blood pressure changes showed a longer latent period, the rise to the maximum was less sudden and the decline to the original level was more gradual. Cardiometer tracings taken by these authors showed that the rise of blood pressure was associated with an increase in the amplitude of the ventricular beats. This occurred even when the slowing of the heart was eliminated by section of the vagus nerves or by their functional exclusion with atropin. Apparently, therefore, the heightened blood pressure was due in part to an increased output from the heart.

Dale and Dixon also found that tyramin constricted the systemic blood vessels. Volume tracings from the dog's ear, from a loop of

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1. Barger, G., and Dale, H. H.: The Water-Soluble Active Principles of Ergot, *Proc. Physiol. Soc.*, May 15, 1909; *Jour. Physiol.*, 1909, **38**, 77.

2. Barger, G., and Wampole, G. S.: Isolation of the Pressor Principles of Putrid Meat, *Jour. Physiol.*, 1909, **38**, 343.

3. Dale, H. H., and Dixon, W. E.: The Action of Pressor Amines Produced by Putrefaction, *Jour. Physiol.*, 1909, **39**, 25.

the cat's intestine and from the hind extremity showed a shrinkage of these organs when the drug was injected. Furthermore, the addition of tyramin to the fluid used in perfusing the cat's hind limb and the dog's small intestine caused a marked slowing of the flow through these organs. The pulmonary vessels, on the other hand, were not constricted by tyramin. From these observations it would appear that the rise of blood pressure produced by the intravenous injection of tyramin into laboratory animals was due not only to an increased output from the heart, but also to a constriction of the peripheral blood vessels.

Tyramin, like epinephrin, appears to act only on such muscle fibers and gland cells as receive a sympathetic nerve supply. According to Dale and Dixon, the effects produced on these structures, whether stimulating or inhibiting, are comparable to those produced by excitation of the sympathetic nerves themselves. Although the action of tyramin resembles that of epinephrin in this particular, the two actions are not identical. Not only is tyramin much less active, being about one twentieth as powerful when judged by its pressor effects, but qualitative differences between the two drugs also exist. Thus Baehr and Pick⁴ found that while epinephrin caused a dilatation of the bronchi, tyramin caused a constriction. With respect to the blood vessels, it has been noted that epinephrin produces a much greater local effect. Thus Sollmann and Pilcher⁵ found that the application of epinephrin to slight cutaneous abrasions caused marked local pallor, whereas tyramin was without effect. Furthermore, tyramin has no value as a local hemostatic. The constriction of the blood vessels about subcutaneous or intramuscular injections of epinephrin interfere with its absorption into the general circulation, and this is believed to account for the fact that such injections rarely produce the marked rises of blood pressure that follow intravenous administration of epinephrin. On the other hand, tyramin with its less marked local effect, usually causes a striking elevation of the blood pressure when injected subcutaneously.

EFFECT ON THE BLOOD PRESSURE AND PULSE RATE OF MAN

The effect of tyramin on the circulation of man was tested by Dale and Dixon, one of whom took 10 mg. of the drug by mouth. The moderate rise of systolic pressure which was observed in this experiment was probably due to some cause other than the drug given; for

4. Baehr, G., and Pick, E. P.: *Pharmakologische Studien an der Bronchialmuskulatur der überlebenden Meerschweinchenlunge*, Arch. f. exper. Path. u. Pharmakol., 1913, **74**, 41.

5. Sollmann, T., and Pilcher, J. D.: *Endermic Reactions*, Jour. Pharm. and Exper. Therap., 1917, **9**, 309.

Clark⁶ showed subsequently that much larger doses — up to 200 mg. within forty minutes — when given by mouth, produced no striking effect on the blood pressure. If, however, tyramin were injected into man subcutaneously, it produced, in most instances, unmistakable circulatory effects. Clark,⁶ Hoyt,⁷ and Watson,⁸ each of whom studied the effect of subcutaneous injections on the blood pressure of man, found that tyramin usually caused a marked elevation of the systolic blood pressure. This rise usually began within a few (two to ten) minutes, proceeded rapidly to its maximum and then fell somewhat more slowly to the original level. The whole reaction occupied a period of fifteen to thirty minutes or more. In order to produce an appreciable rise of pressure, 20 mg. must ordinarily be injected. Larger doses (60 to 80 mg.) may cause very considerable elevations of pressure. Watson,⁸ who recorded the diastolic as well as the systolic pressure, found that the former was not affected by the drug, the heightened systolic pressure being due entirely to an increase in the pressure amplitude or pulse pressure. When the systolic blood pressure rose, the pulse rate usually fell, presumably because the heightened blood pressure caused a vagus inhibition of the heart.

In the present series of observations tyramin was administered subcutaneously in doses of from 40 to 80 mg., the usual dose being 60 mg. The resultant changes in the systolic blood pressure and the pulse rate were similar to those described by the authors just cited. In most instances the injection was followed within a few minutes by a striking rise in the systolic blood pressure and by a slowing of the pulse. Illustrative curves are shown in Figure 1. From this figure it may be seen that the rise in systolic pressure began within five minutes after the injection, that the maximum elevation usually occurred within ten minutes after the injection, and that the blood pressure had usually returned to the normal in from twenty to thirty minutes. Although Watson stated that the diastolic pressure was not affected by the drug, our observations indicate that in the doses given there was usually a slight but definite rise in the diastolic pressure. This, however, was very much less than the rise in systolic blood pressure, so that there was a marked increase in the pulse pressure. It is noteworthy also that the vascular sounds heard during the auscultatory determinations of blood pressure became much louder at the height of the tyramin action.

6. Clark, A.: The Clinical Application of Ergotamine, *Biochem. Jour.*, 1910-1911, **5**, 236.

7. Hoyt, D. M.: The Therapeutic Application of P. Hydroxyphenylethylamin (Tyramine); an Active Principle of Ergot, *Am. Jour. Med. Sc.*, 1912, **144**, 76.

8. Watson, A.: Observations on the Value of Drugs as Blood Pressure Elevators, *Practitioner*, London, 1915, **94**, 566.

The foregoing changes in the systolic blood pressure occurred in almost every instance when tyramin was injected in doses of 40 mg. or more (Tables 1 and 2). Yet no very definite relation existed between the rise of pressure and the dose of drug administered. In two persons, indeed, no rise of systolic pressure was observed. The cause of such variations in the effect of the drug is not certain. Aside from variations in individual susceptibility, the rate of absorption from the site of injection probably played a considerable rôle in

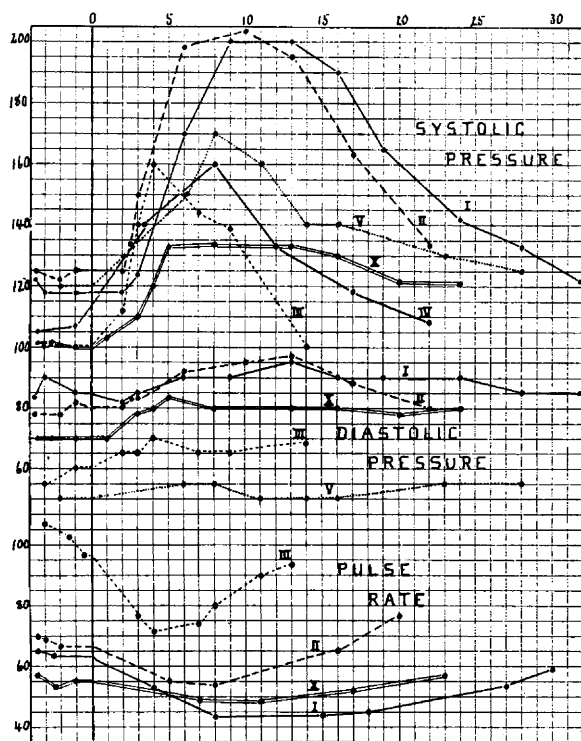


Fig. 1.—Chart showing the effect of tyramin on the systolic and diastolic blood pressure and on the pulse rate. The Roman numerals correspond to the cases in Table 1.

determining the intensity of the reaction. Clark stated that when injections were given into the arm or forearm little general reaction followed, and he recommended that injections be given into the loose tissues about the clavicles. In one of our tests without reaction a lump formed at the site of the injection in the forearm. Following Clark's suggestion, therefore, most of the remaining injections were given into the loose subcutaneous tissues beneath the clavicle.

Any marked rise of pressure was, as a rule, accompanied by a slowing of the pulse similar to that reported by others who have studied the clinical effects of the drug. From Dale and Dixon's animal experiments this appears to result from vagus stimulation by the heightened blood pressure. In two instances the pulse rate increased during the action of the drug. One of these patients (No. 13) had exophthalmic goiter and the pulse rate increased from 75 to a maxi-

TABLE 1.—EFFECT OF TYRAMIN ON BLOOD PRESSURE, PULSE RATE AND VOLUME PULSE

Case	Hospital Number		Dose, Gm.	Blood Pressure			Pulse Rate	Volume Pulse	Sustained Quality
				Sys-tolic	Dias-tolic	Pulse			
1	59747	Before	0.06	118	85	33	64	0.39	Increased
		After		200	92	108	44	0.68	
2	59947	Before	0.065	125	79	46	68	0.65	No change
		After		203	95	108	54	0.70	
3	60120	Before	0.06	100	57	43	100	0.90	Increased
		After		160	70	90	72	1.2	
4	57928	Before	0.06	106	0.55	Increased
		After		160	1.0	
5	58322	Before	0.08	120	50	70	..	1.20	No change
		After		170	52	118	..	1.48	
6	57788	Before	0.04	120	72	48	..	0.55	Increased
		After		170	83	87	..	0.69	
7	57676	Before	0.05	131	80	51	..	0.85	No change
		After		180	84	96	..	1.25	
8	59876	Before	0.06	120	82	38	57	0.47	No change
		After		165	90	75	45	0.60	
9	58061	Before	0.05	115	85	30	..	0.88	Increased
		After		155	90	65	..	1.05	
10	59732	Before	0.06	100	70	30	55	1.10	No change
		After		134	80	54	48	0.90	
11	59732	Before	0.06	113	86	27	56	0.92	No change
		After		134	90	44	52	0.95	
12	59856	Before	0.05	155	85	70	107	0.72	No change
		After		180	85	95	94	0.87	

mum of 84. The other patient (No. 16) showed extrasystoles before the administration. This irregularity became more pronounced and at the same time the sinus rate was accelerated (Fig. 6). In the remaining tests any marked rise of systolic pressure was accompanied by a definite slowing of the heart rate, which disappeared as the pressure fell to normal.

EFFECT ON THE VOLUME PULSE IN THE ARM

In twelve experiments the volume pulse of the forearm and lower arm was recorded by using a plethysmograph which was connected with a Frank capsule by air transmission. Calibration was made in

each experiment by introducing into or withdrawing from the plethysmograph 2 c.c. of air while the arm was in place. The average change on the records produced by several such tests was taken to indicate the effect resulting from a 2 c.c. change in arm volume.

Table 1 shows that in nine of the twelve experiments a distinct increase (over 0.1 c.c.) in the size of the volume pulse in the arm

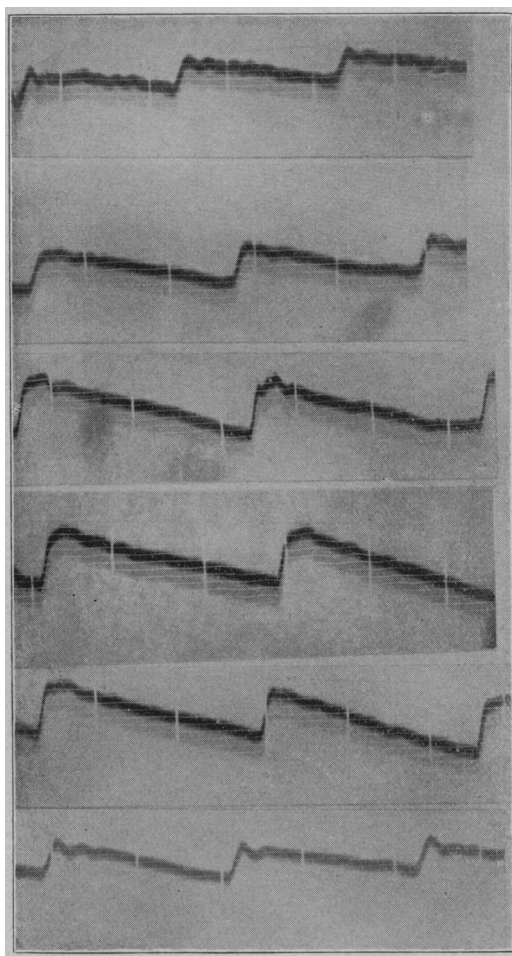


Fig. 2.—The volume pulse in the arm after tyramin. (Case 1 of Table 1 and Figure 1.) First record taken before, second 4 minutes after, third 8 minutes after, fourth 15 minutes after, fifth 18 minutes after and last 30 minutes after the injection of 0.06 gm. tyramin. The changes in the size and form of the pulse waves were most marked in the third and fourth records.

occurred at the height of the tyramin action; in two instances the recorded increase was so slight as to be doubtful, while in one instance the volume pulse was distinctly lessened. This increase in the volume

of the arm pulse was, as we shall see, presumably due to a larger output of blood at each cardiac systole.

The form of the volume pulse was altered in five of the twelve experiments, and in each case this alteration was in the direction of a more sustained pulse. In Figure 2, for example, the primary pulse wave was followed by an anacrotic plateau at the height of the tyramin effect. In Figure 3 from a patient with typhoid fever, the collapsing quality of the febrile pulse became less marked. Such changes were not constant, however, and in many instances no definite alteration in the form of the arm pulse was noted during the heightened systolic pressure and slow pulse produced by the tyramin injection.

In four instances satisfactory records of the blood flow in the arm were obtained. These showed no marked and constant alteration. In

TABLE 2.—EFFECT OF TYRAMIN ON THE ELECTROCARDIOGRAM

Case	Hos- pital Number		Dose, Gm.	Systolic Pres- sure	Pulse Rate	Lead I			Lead II			Lead III		
						P	R	T	P	R	T	P	R	T
13	56167	Before	0.06	110	75	1.0	6.0	1.0	1.2	18.0	0.5	0.5	15	0.0
		After		162	82	0.0	6.5	4.0	1.5	20.0	5.0	1.8	17	1.5
14	57676	Before	0.05	113	85	0.2	3.0	1.7	2.5	9.0	2.0	2.2	7	0.5
		After		140	80	0.2	3.0	2.0	2.5	9.0	5.2	2.5	6	2.5
15	58845	Before	0.06	135	90*	0.8	5.5	1.7	2.0	12.0	1.3	1.0	7	0.0
		After		160	106*	0.3	4.5	2.7	2.3	11.0	2.5	2.0	7	0.5
16	57928	Before	0.06	102	84	1.0	9.5	3.0	0.7	16.0	2.5	0.5	8	
		After		130	73	0.7	8.0	5.0	0.7	15.0	4.8	0.3	9	
17	Before	0.06	135	63	No change								
		After		122	60									

* Sinus rate. Numerous ventricular extrasystoles occurred (Fig. 6).

one case no change occurred, in a second there was a slight increase during the heightened blood pressure, with a slight diminution when the pressure fell, while in the remaining two there was a gradual increase in the rate of flow, which continued after the pressure fell. Whatever may have been the cause of this gradual increase, it was not definitely related to the variations in the blood pressure.

EFFECT OF TYRAMIN ON THE ELECTROCARDIOGRAM

In five patients electrocardiograms were taken before the administration of tyramin and again at the height of the rise of blood pressure. The instrument was carefully adjusted before each record with the patient in circuit so that a deflection of 10 mm. should correspond to a current of 1 milliamper. Of these five patients, one showed no rise of blood pressure after the injection and no change in the electrocardiogram. In the remaining four patients the change in blood

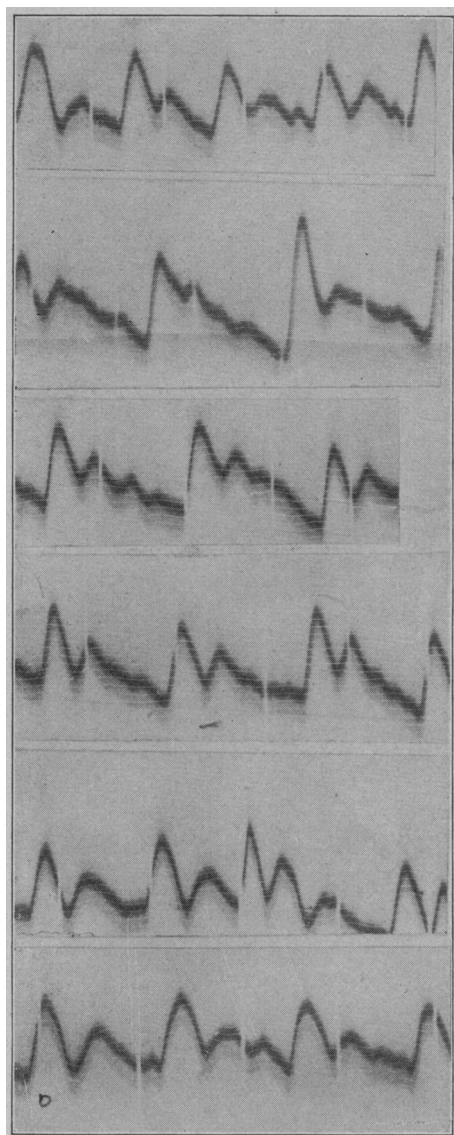


Fig. 3.—The volume pulse in the arm after tyramin (Case 3 of Table 1 and Figure 1), a patient with typhoid fever. First record before, second 4 minutes after, third 7 minutes after, fourth 8 minutes after, fifth 11 minutes after and last 13 minutes after the injection of 0.06 gm. tyramin. The change in size and form of the pulse was most marked in the second and third records. In this patient the maximum effect occurred unusually early. A premature beat is seen in next to the last record.

pressure was accompanied by definite alterations in the form of the electrocardiogram. These may be seen by referring to Table 2 and to Figures 4, 5 and 6. The most constant of these changes was an increase in the size of T. This occurred in every instance in which T was originally upright. In one patient where T was originally small and diphasic in Lead III (Figure 5), it became somewhat more definite after tyramin, but the diphasic character of the wave did not permit of expressing the change numerically. In another patient, not included in Table 2 because the instrument had not been carefully calibrated before each record, T was negative in Lead III before the injection and it apparently became more so under the influence of tyramin.

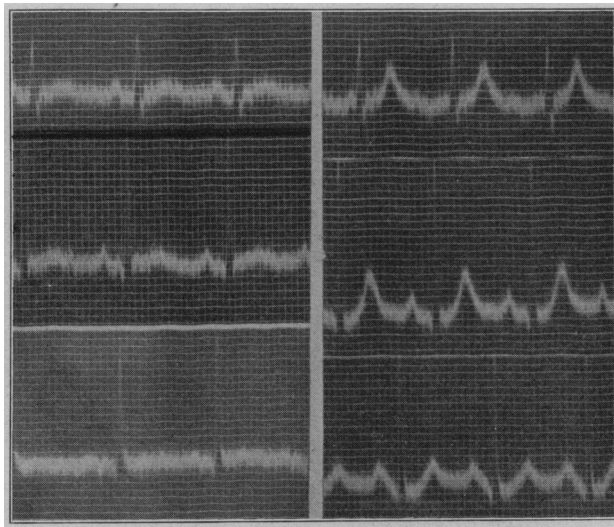


Fig 4.—Electrocardiograms taken before (left) and after (right) the injection of 0.06 gm. tyramin. (Case 13, Table 2.) T became larger in all leads; P became smaller in Lead I and larger in Lead III.

Changes in the other waves of the electrocardiogram, though present in certain instances, were not constant. The QRS complex was on the average unaffected. P showed a slight but not invariable tendency to be diminished in Lead I and increased in Lead III.

Augmentation of T has been described by Rothberger and Winterberg⁹ after accelerator stimulation, and by Lewis and Cotton¹⁰ and others following exercise. In these conditions, however, P also

9. Rothberger, J., and Winterberg, H.: Ueber die Beziehungen der Herznerven zur Form des Elektrokardiogramms, *Arch. f. d. ges. Physiol.*, 1910, **135**, 506.

10. Lewis, T., and Cotton, T. F.: The "P-R" Interval in Human Electrocardiograms and Its Relation to Exercise, *Proc. Physiol. Soc.*, June 28, 1913; *Jour. Physiol.*, 1913, **46**, 60.

increased in size, whereas this did not occur after tyramin injections, except in Lead III.

THE PRODUCTION OF EXTRASYSTOLES

On four or five occasions it was noted that extrasystoles, previously absent, occurred during the action of tyramin. Such a premature beat is seen in next to the last tracing of Figure 3. Before this fact was fully appreciated, a patient already showing occasional ventricular extrasystoles was given an injection of tyramin in order to determine if this might influence the irregularity in a favorable manner. In place

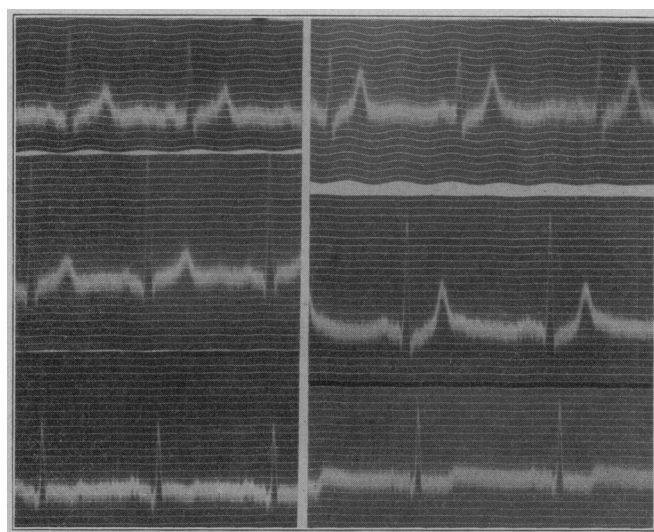


Fig. 5.—Electrocardiograms taken before (left) and after (right) the injection of 0.06 gm. tyramin. (Case 16, Table 2.)

of a favorable effect, there was an increase in the number and variety of abnormal ventricular contractions (Fig. 6).

Levy produced ventricular fibrillation in a cat under chloroform anesthesia by injecting tyramin.¹¹ Inasmuch as there is a close relationship between ventricular fibrillation and very numerous ventricular extrasystoles, it seems possible that under proper conditions tyramin might cause a dangerous or even fatal ventricular fibrillation in man. Caution is therefore urged in the use of this drug if ventricular extrasystoles are already present or if there is reason to suspect a condition

11. Levy, A. G.: The Genesis of Ventricular Extrasystoles Under Chloroform; with Special Reference to Consecutive Ventricular Fibrillation, *Heart*, 1913-1914, **4**, 299.

of increased irritability in the heart muscle such as seems to occur during chloroform anesthesia.

EFFECTS PRODUCED BY SUBCUTANEOUS INJECTIONS
OF EPINEPHRIN

In susceptible individuals, subcutaneous injections of epinephrin frequently produce symptoms and signs which resemble those of exophthalmic goiter. Within a few minutes the individual experiences

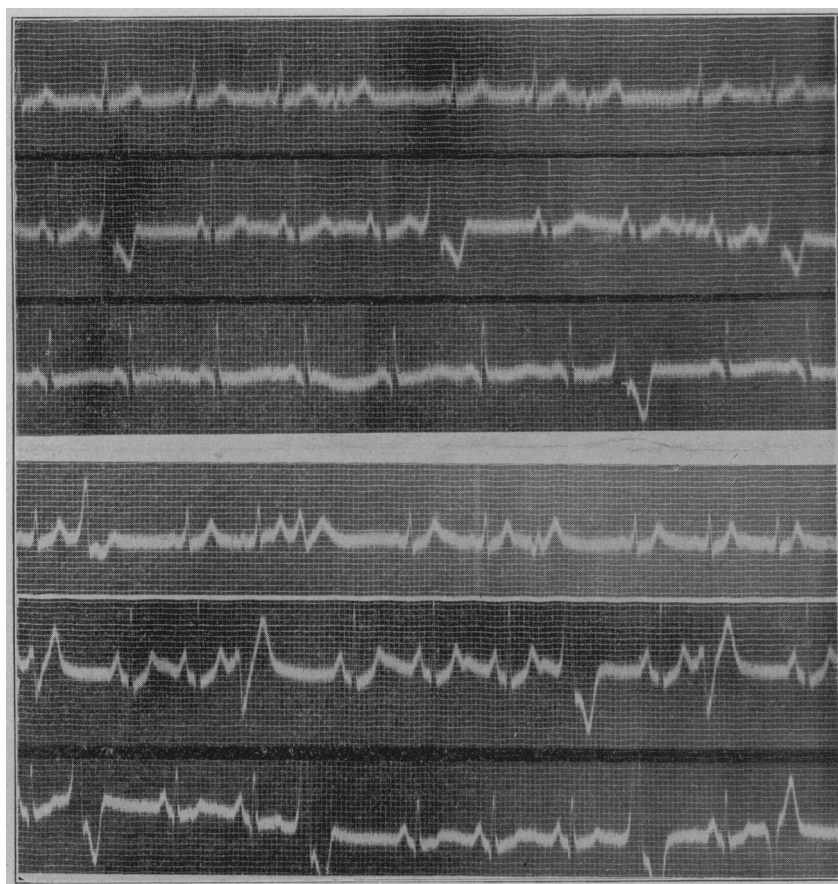


Fig. 6.—Increased number of extrasystoles caused by tyramin. Record above taken before and record below taken after the injection of 0.06 gm. (Case 15, Table 2.)

tremulous sensations which are demonstrable objectively as a tremor of the extended hands. This tremor seems to be somewhat coarser and less regular than is the typical tremor of exophthalmic goiter, and it frequently involves the arms as well as the hands and fingers. In

addition the susceptible person often feels anxious and nervous, and is conscious of palpitation and uneasy sensations about the precordium and epigastrium. Patients with exophthalmic goiter are particularly prone to exhibit distressing symptoms of this type after epinephrin injections, and several have said to the author that for the time being the usual symptoms of their disease became much worse. For this reason a considerable number of epinephrin injections were given to nervous persons with the hope that the degree of reaction might prove of some value in the diagnosis of incipient exophthalmic goiter. No

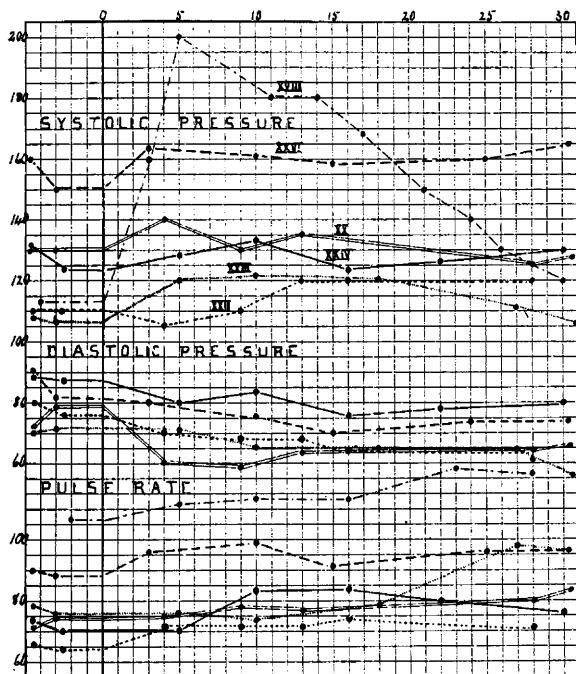


Fig. 7.—Chart showing the effect of subcutaneous injections of epinephrin on the systolic and diastolic blood pressure and on the pulse rate. The Roman numerals correspond to the cases in Table 3. The marked rise of blood pressure (Case 18) was in a patient with exophthalmic goiter. In this patient auricular extrasystoles also occurred; most numerous at sixteen minutes and less numerous at twenty-three and twenty-eight minutes after the injection.

definite relation was found, however, between susceptibility to epinephrin and the milder degrees of hyperthyroidism as judged clinically. In making these tests a number of records were made of the circulatory changes produced by subcutaneous injections of epinephrin. These will be reviewed briefly in order to contrast them with the circulatory changes induced by tyramin.

It is well known that the marked rise of blood pressure which occurs after the intravenous injection of a large dose of epinephrin is rarely observed when the drug is administered subcutaneously. The gradual absorption from the subcutaneous tissues, together with its destruction or disappearance in the tissues, prevents any marked rise in the concentration of epinephrin in the blood. Even though there is little or no rise in the blood pressure, nevertheless subcutaneous injections of epinephrin often produce definite physiologic effects in man. In addition to the tremor, nervousness and palpitation, we may mention the occasional production of glycosuria and the remarkable relief from asthmatic paroxysms that is often afforded by this drug. It is now known that in laboratory animals intravenous injections of small doses of epinephrin usually cause a fall of blood pressure and a dilatation of certain vascular areas, particularly those supplying the muscles in the extremities.¹² Analogous effects might be anticipated, when, owing to its subcutaneous administration to man, the absorption is slow.

Like others, we found that the changes in blood pressure after subcutaneous injections of epinephrin into patients varied considerably (Fig. 7 and Table 3). Occasionally there was a very marked rise in the systolic blood pressure similar to that produced by intravenous injections of the drug; but as a rule the systolic pressure rose only moderately or at times not at all. The diastolic pressure rarely rose.

In most cases it was either uninfluenced to any definite degree or it showed a distinct fall. Watson,¹³ who was much impressed with this fall, suggested that inasmuch as "adrenalin had been proved so clearly to cause contraction of the peripheral vessels" the fall of diastolic pressure was attributable to a temporary aortic regurgitation. In the light of our present knowledge of the vasodilator action of epinephrin, however, it appears more reasonable to attribute the fall of diastolic pressure to vascular relaxation.

In our experience the most constant effect of this drug on the blood pressure was an increase in the difference between the systolic and diastolic pressures; that is, in the pulse pressure. There was also in almost every instance a very definite increase in the loudness of the

12. Cannon, W. B., and Lyman, H.: The Depressor Effect of Adrenalin on Arterial Pressure, *Am. Jour. Physiol.*, 1913, **31**, 376. Hartman, F. A.: The Differential Effect of Adrenalin on Splanchnic and Peripheral Arteries, *Am. Jour. Physiol.*, 1915, **41**, 513. Hoskins, R. G., Gunning, R. E. L., and Berry, E. L.: The Effect of Adrenin on the Distribution of the Blood, *Am. Jour. Physiol.*, 1916, **42**, 513; 1917, **43**, 399. Hartman, F. A., and McPhedran, L.: Further Observations on the Differential Action of Adrenalin, *Am. Jour. Physiol.*, 1917, **43**, 311.

13. Watson, A.: Some Observations on the Effect of Hypodermic Injections of Adrenalin on the Blood Pressure, *Practitioner*, London, 1914, **92**, 94.

vascular sounds which are heard below the pressure cuff during the auscultatory determinations of blood pressure.

The pulse rate after subcutaneous injections of epinephrin was usually somewhat increased (Fig. 7, Table 3). The volume pulse in the arm became larger (Table 3), and its form, while often unaltered, tended to become more collapsing (Table 3, Fig. 8). This change suggested a vascular relaxation in the arm. Unfortunately, no records

TABLE 3.—EFFECT OF SUBCUTANEOUS INJECTION OF EPINEPHRIN

Case	Hos- pital Number		Dose, 1:1,000 Solu- tion, Minims	Tremor	Blood Pressure			Pulse Rate	Volume Pulse	Sustained Quality
					Sys- tolic	Dias- tolic	Pulse			
18	56167	Before After	15	+ +++	113 200	112 124		
19	54169	Before After	7	0 +++	125 155	.. 80	.. 75	84 104	0.32 0.86	Lessened
20	54276	Before After	10	0 +	130 135	75 64	55 71	72 84	1.2 1.85	Lessened
21	53938	Before After	10	0.9 1.5	Lessened
22	54718	Before After	8	0 +	110 120	78 64	32 56	65 74	0.75 1.3	Lessened
23	54241	Before After	10	+ +++	106 {122 105}	71 65 50	35 57 55	76 {74 96}	0.85 1.2	No change
24	54035	Before After	10	0 +	128 {134 124}	88 84 76	40 50 48	72 84	0.6 0.9	Lessened
25	54263	Before After	10	+ ++	109 {108 104}	68 70 64	41 38 40	64 70	0.7 1.0	No change
26	54280	Before After	10	+ ++	155 {164 153}	86 84 70	69 80 88	89 96	0.8 1.0	Lessened
27	54745	Before After	6	+ ++	119 122	81 74	38 48	66 76	0.6 0.7	No change
28	17526	Before After	7	+ +	128 122	88 84	40 38	82 82	1.1 1.2	No change

were made of the rate of blood flow through the arm before and after epinephrin injections.

A few electrocardiograms were taken before and after the injections. In some there was a distinct increase in T similar to that produced by tyramin; in others this change was slight or did not occur. This increase of T was most marked in a patient who also showed a striking rise of systolic pressure (Case 18), but its relation to the blood pressure changes was not further studied.

The circulatory alterations produced by tyramin, by epinephrin, by pituitary extract and by nitroglycerin are compared in Table 4. From this it will be seen¹ that tyramin resembles pituitary extract in that

both tend to raise the diastolic pressure and to cause a more sustained pulse, (2) that epinephrin resembles nitroglycerin in that both tend to lower the diastolic pressure and to cause a more collapsing pulse, while (3) tyramin and epinephrin resemble each other in that both cause a definite increase of pulse pressure, augmentation of T in the electrocardiogram and occasional extrasystoles.

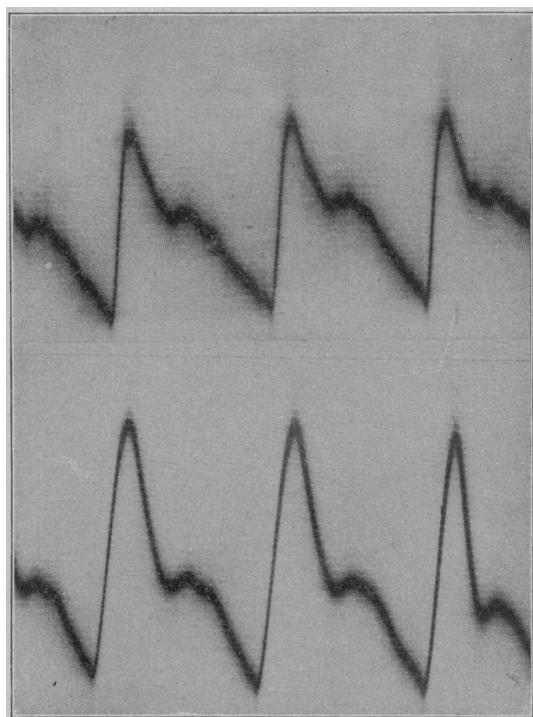


Fig. 8.—Volume pulse in the arm after the subcutaneous injection of 10 minims epinephrin solution (1 to 1,000). Upper before and lower twenty-four minutes after the injection. (Case 20 of Fig. 7 and Table 3.)

DISCUSSION

The most striking circulatory changes that we have observed in man after injections of tyramin may be summarized as follows:

- (a) an increase in the systolic blood pressure, the pulse pressure and the volume pulse in the arm;
- (b) a slowing of the heart rate, and
- (c) an increase in the size of T in the electrocardiogram with the occasional occurrence of extrasystoles.

The increase in pulse pressure appears to be due mainly to an increased output of blood with each ventricular systole. It is true that an increased pulse pressure might conceivably result from a constriction or a heightened tone of the blood vessels. In such a case,

however, one would expect to find a far greater rise in the diastolic pressure than was actually observed. Furthermore, we know that certain drugs which act primarily on the blood vessels produce characteristic changes in the volume pulse of the arm. Nitroglycerin, a typical vasodilator, causes the arm pulse to become larger and more collapsing,¹⁵ whereas pituitary extract, a typical vasoconstrictor, causes the collapsing pulse of febrile patients to become smaller and more

TABLE 4.—COMPARISON OF THE USUAL EFFECTS ON MAN OF PITUITARY EXTRACT, TYRAMIN, EPINEPHRIN AND NITROGLYCERIN

	Pituitary Extract	Tyramin	Epinephrin	Nitroglycerin
Mode of administration	Intramuscularly	Subcutaneously	Subcutaneously	On tongue
Systolic pressure	No constant change ¹⁴	Marked increase	Usual increase; varies from little change to marked increase	Diminished
Diastolic pressure	Increased ¹⁴ (febrile pulse)	Slight increase or no change	Diminished or no change	Diminished
Pulse pressure	Diminished ¹⁴ (febrile pulse)	Marked increase	Moderate increase	
Pulse rate	Occasional slight slowing ¹⁴	Marked slowing	Some increase	Some increase ¹⁵
Volume pulse in arm	Diminished ¹⁴ (febrile pulse)	Increased	Increased	Increased ¹⁵
Sustained quality of arm pulse	More sustained ¹⁴ (febrile pulse)	More sustained or no change	Less sustained or no change	Less sustained ¹⁵
T wave in electrocardiogram	No change	Augmented	No change or augmented	No change ¹⁵
Tendency to produce ventricular extrasystoles	Apparently none	Present	Present ¹⁶	None

sustained.¹⁶ After tyramin the arm pulse becomes larger, but its form, if altered at all, is more sustained. Such a change is not typical of vascular constriction, and is more readily explained on the assumption that there is an increased systolic output from the heart.

Inasmuch as this increased output at each cardiac contraction is accompanied by a reduction in the heart rate, the question arises whether the total cardiac output in a unit of time is affected by tyramin. Our data do not furnish an accurate measure of the cardiac output. If this is roughly proportional to the product of heart rate \times pulse pressure, then it would appear that tyramin materially increases the total cardiac output, for under its influence the above product is often

14. Schmidt, H. B.: The Effect of Pituitary Injections on the Blood Pressure of Febrile Patients, *THE ARCHIVES INT. MED.*, 1917, **19**, 1059.

15. Hewlett, A. W.: Van Zwaluwenburg, J. G., and Agnew, J. H.: The Pulse Flow in the Brachial Artery, *THE ARCHIVES INT. MED.*, 1913, **12**, 7.

16. Hewlett, A. W.: The Pulse Flow in the Brachial Artery; the Influence of Certain Drugs, *THE ARCHIVES INT. MED.*, 1917, **20**, 1.

increased by 50 to 100 per cent. One must recognize, however, that various fallacies are possible in reasoning from these data. It is not our intention therefore to insist that tyramin, which has been demonstrated in animal experiments to possess a vasoconstrictor action, is without such an action when injected into man. We wish rather to point out that by the methods used an increased cardiac output seems probable, whereas vascular effects that were comparable to those produced by pituitary extract could not be demonstrated.

Subcutaneous injections of epinephrin also caused an increase in pulse pressure which was accompanied by a slight to moderate increase in the pulse rate. The product, heart rate \times pulse pressure was therefore increased, and this may again be taken, with some reserve, to indicate that the cardiac output was increased by subcutaneous injections of this drug. As compared with tyramin, however, the action of epinephrin, injected subcutaneously, was characterized by evidence of vascular relaxation. In the first place, the diastolic blood pressure usually fell. In the second place, the arm pulse usually became larger and it often became more collapsing, changes that are comparable to those produced by the administration of nitroglycerin. This view that subcutaneous injections of epinephrin usually relax the blood vessels, particularly in the arm, is in accord with recent animal experiments which have demonstrated that small doses of epinephrin may reduce the blood pressure and that the drug in appropriate doses dilates various vascular areas, particularly those supplying the voluntary muscles and the intestines.¹²

Tyramin not only alters the heart rate and the systolic output, but it modifies the ventricular contractions in other ways, as is shown by the augmentation of T in the electrocardiogram and by the occasional production of ventricular extrasystoles. The cause of these changes has not been determined. Among their possible causes are mechanical alterations in the circulation owing to the increased systolic output and the heightened blood pressure, nervous influences such as accelerator stimulation in addition to the vagus inhibition, and finally, a direct effect of the drug on the ventricular muscle. We have pointed out that similar changes in the electrocardiogram as well as occasional ventricular extrasystoles have been induced by epinephrin. According to Levy¹¹ the ventricular irregularities produced in animals by epinephrin cannot be explained solely by the alterations of blood pressure and Roth¹⁷ found no relation between the pressure changes and the ventricular extrasystoles induced in cardiac patients by epinephrin injections. By analogy, therefore, it would seem probable that the extrasystoles induced by tyramin are due in part to other causes than the changes in blood pressure and cardiac output.

17. Roth, O.: Ueber die Reaktion des Menschlichen Herzens auf Adrenalin, Deutsch. med. Wchnschr. 1914, **40**, 905.