THE NATURE OF ADRENERGIC NERVE MEDIATORS

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I. INTRODUCTION

Our knowledge of the nature of adrenergic (77) nerve mediators, sympathins (64), is founded upon the pioneer research of Loewi (177) and Cannon (68) and their associates.

A number of excellent reviews dealing with this subject are available and should be consulted for detailed information (12, 16, 32, 49, 59, 68, 78, 114, 115, 138, 177, 195, 198, 212). By the recent demonstration of noradrenaline as the chief sympathomimetic agent serving to transmit adrenergic impulses during normal conditions, certain new aspects have been added. An account of the history and development of this concept will be found in more recent reviews (95, 232).

Methodological details which take these results into account have been published recently in two reviews (96, 116).

The term *adrenaline* has been used in the following as a synonym for *adrenine* or *epinephrine* in agreement with the opinion of Cannon. In a paper with Lissák (65) he wrote: ". . . Meanwhile, in foreign languages, and commonly in English writing, the term "adrenaline" has become customary. In accordance with this growing practice that word has been adopted here." Adrenaline also goes well with the generally accepted term "adrenergic." The term *noradrenaline* has been used in the present review as synonymous with *norepinephrine* or *arterenol.* (N.O.R. = N ohne Radikal.)

The occurrence in, and liberation of, noradrenaline and adrenaline from the suprarenal medulla and the chromaffine tissue has been reviewed elsewhere (95, 142) and will be referred to only occasionally in the present review.

II. HISTORICAL

After the first successful demonstration of a chemical transmission of sympathetic nerve effects (70, 176), it was generally believed that the active agent was adrenaline. The discrepancies noted between the effects of sympathetic nerve stimulation and the action of adrenaline (67) then led to the theory of the two sympathins, these agents being supposedly formed by the interaction of a mediator (adrenaline) and certain cell constituents (66, 68). However, doubts as to the validity of this theory were expressed by several investigators (11, 135, 136, 193, 227), and the possibility was pointed out that noradrenaline (arterenol) might be identical with sympathin E and adrenaline with sympathin I. This would also be in accord with the older observations of Barger and Dale (26). However, the findings that postganglionic stimulation of the nerves of the rabbit's ear released what appeared to be adrenaline (118, 120) and that certain organs and their adrenergic nerves seemed to contain adrenaline (65, 174) spoke in favour of adrenaline as a mediator, an opinion which was generally held until 1945.

A closer biological analysis of extracts of sympathetic nerves and of organs innervated by such nerves revealed, however, that the sympathomimetic agent present in such extracts had the characteristic properties of noradrenaline and not adrenaline (86–88).

The previous results of Cannon and Rosenblueth and others (9, 10, 135, 136, 193, 227) could easily be brought in harmony with this finding. Carefully analysed, direct experiments by Gaddum and Goodwin (117) gave further strong support to the concept of noradrenaline as the chief adrenergic mediator. As will be seen in the following, although noradrenaline is the dominant adrenergic chemical transmitter substance, it is not the only one and as pointed out by Bacq (15), is supported by adrenaline and possibly also by other catechol amines. The recognition, for example, that the structural requirements for myocardial stimulation differ from those favorable for sympathetic excitatory or inhibitory action (170) is, in a way, suggestive of other active substances in this group, and so is the finding that so-called adrenolytic substances do not annul the tachycardia provoked by sympathetic nerve stimulation of the heart (200).

III. NATURE OF SYMPATHOMIMETIC SUBSTANCES IN ADRENERGIC NERVES AND IN ORGANS WITH ADRENERGIC NERVE SUPPLY

The demonstration of active substances in the blood leaving an organ or in the bathing fluid of an isolated organ during or after nerve stimulation does not prove, strictly speaking, that these substances are derived from the nerves and serve as chemical mediators. The same criticism may be applied to the evidence based on the occurrence of active agents in extracts of organs. The possibility should be borne in mind that the chemical mediator may appear as an inactive precursor.

From this point of view the demonstration of noradrenaline (87, 89) in adrenergic nerves was particularly clarifying since it not only gave a natural explanation of previous experimental findings as to the effect of stimulation of such nerves but also directly indicated that this substacne was actually the chemical mediator. Inferences as to the adrenergic mediators drawn from the relative activity of certain possible candidates for such transmitters may be misleading (2).

Since a mixture of active substances is generally found in extracts of nerves or organs, and is likely to interfere with the demonstration of specific adrenergic mediators, *e.g.*, acetylcholine and particularly histamine (90, 91), the extracts have to be purified by different methods. These methods have consisted in removal of disturbing agents, for example, by adsorption on fuller's earth (87, 107), or in specific adsorption of the active substances with the aid of alumina or aluminium oxide (90, 182, 206, 223). Anticholinic and antihistaminic compounds have been used to exclude the action of disturbing agents (219). Separation of the active catechol amines may be achieved by countercurrent distribution according to Craig (30), by partition chromatography either on filter paper (160, 161) or on columns (31, 140) or by biological methods (96, 116, 121). Colorimetric methods are generally inapplicable (7, 100), with the exception of Shaw's method (223) and the fluorescence method (45, 171, 182) which require only small amounts of material.

a) Adrenergic nerves

The first evidence of sympathomimetic activity associated with the sympathetic nerves themselves was produced in experiments by Gaddum and Khayyal (115). These authors found that stimulation of adrenergic fibres caused the liberation of a substance acting like adrenaline on the frog's heart. Cannon and Lissák and Lissák (65, 174) made extracts of various nerves containing adrenergic neurones and tested them after dialysis. They reached the conclusion that "the peculiar material which is extracted from sympathetic neurones is adrenaline itself." Part of the evidence was based on the reversal of the effect of the extracts on the cat's blood pressure after ergotoxine. This observation was misleading, however, probably owing to the presence of depressor material such as histamine in the nerve extracts (93, 169).

Subsequently it has been shown that the biological effects of extracts of nerves containing adrenergic fibres agree with those of noradrenaline (87, 89). The extracts were made with acid alcohol and purified with fuller's earth, which

removed most of the depressor material. The conclusion that the chief active agent was noradrenaline was based on the following evidence: a) the pressor effect was diminished or even abolished by sympatholytic substances but not reversed as is that of adrenaline; b) the weak relaxing effect on the non-pregnant cat's uterus; c) the weak pupil dilating action; d) the weak fluorescence in ultraviolet. In all these respects there was good agreement between the action of the nerve extracts and those of noradrenaline, when equi-pressor amounts on the cat's blood pressure were compared, but marked differences from those of adrenaline.

The naturally occurring noradrenaline was identified as the laevo-isomer by comparing the biological activity and the strength of the colorimetric iodine reaction of nerve extracts and *dl*-, and *l*-noradrenaline (89). By such tests good agreement was found only with the *l*-noradrenaline, available just at that time (233, 235).

Although chemical evidence that the predominant adrenergic substance is *l*-noradrenaline is still lacking there is little doubt of their identity on the evidence given above. Further support accrues from the fact that *l*-noradrenaline has been isolated from suprarenal extracts (30) and from commercial non-synthetic "adrenaline" (236), indicating that it does occur biologically.

Noradrenaline has been demonstrated in sympathetic chain and ganglia, postganglionic fibres to various organs, including grey rami, splanchnic nerves and sensory nerves to the skin. It has been found as the predominant adrenergic nerve substance in such nerves from all vertebrate animals examined. Particularly high amounts have been found in the splenic nerves from various animals, which consist largely of unmyelinated postganglionic adrenergic fibres. After removal of the sheath the noradrenaline content of the cow's splenic nerves was found to reach figures as high as 20 μg. per gram (89).

In some cases methods have been used which do not identify the "adrenaline-like" material obtained in extracts of nerves (180, 208).

Table I gives the content of noradrenaline found in various nerves (95). The figures have been compiled from various sources (19, 95, 150, 174).

Information is still lacking as to whether noradrenaline acts as an adrenergic nerve mediator in fish, amphibia and invertebrates.

Closer analysis has revealed that extracts of adrenergic nerves contain, besides noradrenaline, small amounts of adrenaline (94). This evidence is based on the use of methods for differential estimation of noradrenaline and adrenaline (61, 96, 116, 121). For this purpose the action of the extract is tested biologically on two preparations having a sufficiently wide difference in activity ratio between the two catechol amines, such as the blood pressure of the cat and the isolated hen's rectal caecum or the rat's uterus. Other preparations which have been used include the rat's colon, the innervated and denervated cat's spleen, the rabbit's ear (122), the rabbit's or cat's intestine *in situ* (50, 155), and the cat's uterus *in situ* (155). In raising the cat's blood pressure the action of noradrenaline is 1–5 times that of adrenaline, whereas its effect on the rat's uterus may be as little

as $\frac{1}{300}$ that of adrenaline. Other test preparations are intermediate. If the activity of the extract on an appropriate pair of preparations is evaluated in terms of noradrenaline and the activity ratio of adrenaline to noradrenaline is estimated on each preparation, the amounts of noradrenaline and adrenaline can be calculated according to a simple formula (56, 94).

TABLE I

Amount of l-Noradrenaline in μg. per Gram of Nerve

NERVE	ANIMAL SPECIES						
	Cattle	Horse	Sheep	Dog	Cat	Rabbit	Man
Brain	0.04–0.2		0.08			0.2	
Spinal cord	0.12						
Vagus	0.1			4	0	0	
Cervical sympathetic	0.6			1	0		
Sympathetic trunk	2.5–4.9	1	3.8	10, 12	12		2–3
Splanchnic	4						
Splenic	8.5–18.5	1.75	8	10–15			
Mesenteric	1.5–3		3.5	20, 18	20	1	
Phrenic	0.15–0.25			0	0	0	
Sciatic			0.14	2.4	4	3.2	
Saphenous	0.2–1						
Superior cervical ganglion	1				16	14	

A = μg noradrenaline equivalents per gram tissue, on hen's rectal caecum.
a = μg noradrenaline equivalents per gram tissue, on cat's blood pressure.
Q = activity ratio adrenaline/noradrenaline, on hen's rectal caecum (>1).
q = activity ratio adrenaline/noradrenaline, on cat's blood pressure (<1).

Adrenaline μg./gram $= x = \frac{A-a}{Q-q}$

Noradrenaline μg./gram $= y = A - xQ$

Relative amount of adrenaline $= \frac{x}{x+y}$ (degree of methylation)

By use of such biological methods small amounts of adrenaline have been found in nerve extract preparations. Table II gives some examples (98).

Quantitative separation of adrenaline and noradrenaline in nervous tissue extracts by partition chromatography (31, 140) do not seem to have been made. Paper chromatography of splenic nerve extracts have not indicated the presence of catechol amines other than noradrenaline and adrenaline (98).

b) Organs

A number of earlier investigations have been concerned with the demonstration in organ extracts of substances having the properties of sympathomimetic amines, biologically (65, 84, 178, 179, 217, 243) or chemically (10, 178, 179, 204–

208, 223). In many of these, evidence for adrenaline-like actions has been brought forth.

By the use of more precise preparative and analytical methods differences between the active organ substances and adrenaline were detected and agreement was found with noradrenaline, as in the case of nerve extracts (86, 88). In confirmation of this, subsequent authors found that the activity in most organ extracts was in all probability chiefly due to noradrenaline (14, 19, 95, 109, 127, 209, 219, 238).

One organ, the placenta, lacks nerves and also sympathomimetic activity (87, 219). Denervation of an organ deprives the extracts of activity (65, 98, 110, 130) and regeneration of degenerated nerves restores it (130). It is therefore likely that the extract activity is due to the nerve mediators present in the nervous tissue. As only adrenergic nerves have been found to contain sympathomimetic substances the available evidence points to the adrenergic nerves as bearers of the corresponding activity of organs.

Estimations of the content of catechol amines in extracts of various organs with the arsenomolybdate colorimetric method of Shaw have indicated that,

TABLE II

	l-ADRENALINE	*l*-NORADRENALINE	% ADRENALINE
	μg./gram	*μg./gram*	
Splenic nerves, cow	0.09–0.28	7.5–9.4	1.1–3.5
" " sheep	0.1–0.56	5.0–7.7	2–7
Sympathetic chain, man	0.13–0.33	2.4–3.4	5–9
" " sheep	0.06–0.08	1.0–3.8	2–8
Mesenteric nerves, sheep	0.1–0.21	1.2–3.4	6–8

whereas in some organs practically all of the colour giving material may be adrenaline, other organs contain catechol amines of other kinds (206, 223), judging from the degree of colour increase on adding alkali. A low denominator of the specific ratio (s.d.r.) of colour increase, indicating substances other than adrenaline and possibly identical with noradrenaline, was found with spleen, brain, liver, kidney and heart (rat) (206). In rabbit's heart a higher s.d.r. was found and a still higher one in frog's heart (223). The results obtained with frog's heart are in good accord with the biological estimations (87) and the demonstration of adrenaline by the fluorimetric method (178, 179).

From biological and chemical estimations it appears that the absolute as well as the relative contents of noradrenaline and adrenaline show wide differences in various organs. Differences in the absolute amount of catechol amines may be explained in a natural way, assuming that they are due to variations in the number of adrenergic fibres reaching the organ. Thus the number of such fibres innervating the spleen far exceeds the number in the corresponding nerve supply to the liver, the heart, and the kidney per unit weight of organ. A similar difference holds for the amounts of noradrenaline found in these organs in all animals

thus far examined (95). Estimations of the amount of adrenaline as well as noradrenaline in various organs have been made by biological analyses on two test preparations as outlined above, and some of the results are presented in Table III (98, 130).

The predominance of noradrenaline is clearly brought out by the table. The relative adrenaline content is low in spleen and liver and highest in the heart and submaxillary gland. No relation has been found between the total catechol amine content and the adrenaline percentage. The low percentage of adrenaline in the liver is noteworthy in view of the effect of stimulation of hepatic nerves (68, 70, 117, 135), the sympathin of which has been described as "purely excitatory."

No direct evidence is so far available regarding the relative amounts of adrenaline in the nerves innervating striated muscle or in this tissue itself. The larger increase in heat production in the innervated muscle than in the sympathetically denervated muscle after heat puncture (27) would speak in favour of a relatively

TABLE III

ORGAN (SHEEP)	NORADRENALINE	ADRENALINE	ADRENALINE, %
	μg./gram	*μg./gram*	
Spleen	3.0–3.3	0–0.11	0–3.4
Parotid gland	0.5–2.2	0.03–0.19	5–14
Submaxillary gland	0.4–1.1	0.10–0.21	12–21
Heart	0.6–1.1	0.1–0.2	10–20
Kidney	0.4–0.6	0.05–0.07	11
Liver	0.15–0.20	0.007–0.011	4–7
Lung	0.08–0.1	0.002–0.01	2.5–10

high percentage of adrenaline, which has a much stronger effect on metabolic processes in general than noradrenaline.

The demonstration and estimation of the typical mediator substances in organ extracts have another interesting consequence; it allows certain conclusions as to the adrenergic nerve supply to an organ. In the brain, for example, the catechol amine content is very low (150) and may only correspond to the vascular supply which includes vasoconstrictor nerves (48).

The significance of the presence of adrenaline in some of these extracts may be discussed from two points of view. Firstly, the adrenaline may be derived partly from chromaffine cells in the organ, and therefore not belong to the adrenergic nerve mediators in the strict sense of the word. Whether such chromaffine cells, like phaeochromocytomas (83, 125, 148), contain mostly noradrenaline or mostly adrenaline is unknown. However, the results obtained with extracts of the prostate gland, which contains chromaffine cell groups, suggest that adrenaline is present in this organ (75, 85, 223). Furthermore, in the superior cervical ganglion the chromaffine cells seem to contain adrenaline (55). Secondly, part of the adrenaline-like activity as determined biologically may be contributed by other catechol amines, such as hydroxytyramine. This catechol derivative which occurs

regularly in urine (101, 152) has also been found in extracts of heart (128) and suprarenals (129). Since it may be more active compared with noradrenaline on the isolated hen's rectum than on the blood pressure of the cat, it may simulate adrenaline when extracts are tested on these preparations. On the other hand the amounts of hydroxytyramine found in chromatographic analysis of heart extracts do not account for more than a small fraction of the adrenaline found by the biological method. Other catechol derivatives have so far not been demonstrated. Accordingly, there is good reason to believe that the adrenaline figures represent, at least approximately, the true amounts of adrenaline. Again, the proportion of adrenaline which is due to the presence of chromaffine cells in the organ is harder to evaluate. A contribution to this question has been made by Goodall (130) who found that, in the sheep's heart, the adrenaline content diminished at an even faster rate than that of noradrenaline upon sectioning of the sympathetic nerves. After regeneration the adrenaline content rose again. There is no evidence for a regeneration of preganglionic fibres contacting chromaffine cells left in the organ, so one must assume that the reappearance of catechol amines is due to the ingrowth of postganglionic fibres. It seems reasonably safe, therefore, to assume that the adrenaline found in organ extracts is derived from the adrenergic nerves in those cases where it disappears on denervation.

c) Release of sympathomimetic substances from isolated nerves

Several authors have reported that isolated nerves containing adrenergic fibres release adrenaline-like substances on electrical stimulation (8, 63, 99, 173). The significance of such results has been questioned (119) on the ground that the release may be due to damage to the nerve. Although the amounts released are very small and the results rather dependent on the experimental conditions (freshness of nerve, freshly cut surface, etc.), the evidence for such a release seems fairly satisfactory although the physiological significance of the release is doubtful. The results may be of interest for the elucidation of the mechanism of release at the nerve endings, which is not yet understood. Possible mechanisms seem to be increased permeability of the nervous tissue or, rather, a shift in the ion balance causing a release from a complex compound.

d) Tyramine and hydroxytyramine

Both tyramine and hydroxytyramine (3,4-dihydroxyphenylethylamine) might come into consideration as supplementary adrenergic nerve mediators, since they exert definite although comparatively weak sympathomimetic actions. A conclusive account of their possible roles in this connection cannot be given at present for lack of experimental evidence. Even if it should be demonstrated that these substances are liberated on adrenergic nerve stimulation, they would probably have a rather limited scope of action.

Whether tyramine occurs as a natural constituent of organs is still a matter of dispute. It is known, however, that it is formed during bacterial decomposition and possibly also in nonbacterial anaerobic autolysis of tissues by decarboxylation of tyrosine (108, 149). In invertebrates tyramine has been found in the sal-

ivary secretion of cephalopods (144) and has been considered as a chemical mediator for the cardiomoderator nerves (114). The peculiar observations that low concentrations of adrenaline increase the vascular actions of tyramine and that of nerve stimulation (57, 58, 62, 197) may have physiological importance, and have led to the theory that tyramine acts on the nerve endings and liberates sympathin. Gaddum and Goodwin (117) concluded from their experiments that liver sympathin obtained by hepatic nerve stimulation in the cat might be noradrenaline or perhaps tyramine. Although there is little doubt that noradrenaline is the chief constituent of liver sympathin, an admixture of tyramine cannot be excluded. Further experiments are needed to elucidate this problem, especially since it has been shown that ortho-tyramine and meta-tyramine, which both have effects very similar to those of tyramine, are formed by the action of the enzyme *l*-DOPA-decarboxylase (42) which does not act on tyrosine.

The case for hydroxytyramine as a possible adrenergic mediator is perhaps stronger, since, like noradrenaline and adrenaline, it is present in urine normally and also in organ extracts such as those from the heart and the suprarenals (101, 128, 129, 152). The circulatory effects of hydroxytyramine are weaker than those of adrenaline, the pressor effect in the cat being estimated as $\frac{1}{50}$ to $\frac{1}{100}$ that of *l*-noradrenaline (4, 98).

The formation of hydroxytyramine from DOPA has been demonstrated with renal tissue or suitable extracts (151), and also in the kidney itself under anaerobic conditions (37). Further investigations are needed to ascertain whether any actions of adrenergic nerve stimulation may be explained by the liberation of hydroxytyramine. Its possible role in the formation of noradrenaline and its formation by the decarboxylation of dihydroxyphenylalanine (see p. 266) make a closer analysis of this point desirable.

IV. RELEASE OF ADRENERGIC NERVE MEDIATORS IN VIVO

a) Electrical stimulation of nerves

The critical discussion by Barger and Dale (26) on the effects of adrenaline and of sympathetic stimulation gave the first intimation that the adrenergic nerve mediator differs from adrenaline in its action. The results of Cannon and his coworkers clearly showed that the active agents liberated into the blood stream after electrical stimulation of sympathetic nerves differed, to a greater or lesser extent, from adrenaline. Critical discussions of the theory of Cannon and Rosenblueth concerning the nature of what was believed to be the mediator and the final active products called sympathins I and E will be found elsewhere (11, 95, 117, 135, 136). The bulk of available evidence is in favour of the concept adopted by several investigators (11, 17, 92, 117, 135, 136) that the remote effects observed after stimulation of adrenergic nerves are due to noradrenaline or variable mixtures of noradrenaline and adrenaline. So far no points have been brought forward which are incompatible with such a view.

The evidence for noradrenaline being released by adrenergic nerve stimulation may be summarized as follows:

1. Stimulation of hepatic nerves produces effects on the blood pressure, on the cat's uterus, and on the iris which correspond to those of noradrenaline (117, 135).

2. The rise in blood pressure caused by hepatic nerve stimulation is weakened but not reversed by ergotoxine (66).

3. Adrenergic nerves contain noradrenaline (19, 87, 89).

4. Venous blood from an organ contains noradrenaline after stimulation of its sympathetic nerves (203).

The evidence for adrenaline is of a similar character (66, 94, 189, 203, 241). In some earlier experiments on splenic stimulation, the results would not allow discrimination between adrenaline and noradrenaline (20, 218). The demonstration of noradrenaline and adrenaline in adrenergic nerves seems to make assumptions of a special mediator and secondary active agents superfluous.

If one adopts the term *sympathin* to designate the active group of substances liberated on adrenergic nerve stimulation it becomes advantageous to characterize

TABLE IV

NERVES	EFFECTS OF STIMULATION		REFERENCES
	Noradrenaline-like	Adrenaline-like	
Hepatic (cat)	+++	−	68, 117, 136, 189
Splanchnic (cat)	+++	+	68
Abdominal sympathetic trunk (cat)	+++	(+)	
Duodenal (cat)	+++	+	
Sympathetic tail nerves (cat)	+++	(+)	
Sciatic	+++	(+)	12, 186, 187
Hypogastric	+++	(+)	
Splenic (cat)	+++	(+)	203, 189
Cardiopulmonary (cat)	+++	(+)	68

Parentheses indicate slight or inconstant action.

the various components. An attempt in this direction has been made by the introduction of the terms sympathin N and A for noradrenaline and adrenaline, respectively (92). Any additional component could then be marked by an appropriate suffix. Whether the term sympathin should be used to include the adrenal medullary secretion ("adrenal sympathin" [242]) is highly questionable.

In those cases where a differential analysis of the remote effects of sympathetic nerve stimulation has been made possible by observations on more than one organ it has been possible to gain an idea of the nature of the adrenergic mediators in various regions. Table IV is an attempt to correlate the results in terms of noradrenaline and adrenaline.

Especially illuminating were the experiments in which liver sympathin was produced by stimulation of hepatic nerves (117, 135). In these cases a direct comparison of the results of stimulation with those of noradrenaline showed good agreement. Further evidence has been adduced by analysis of hepatic vein blood from cats after stimulation of the hepatic nerves. Noradrenaline was found to be pres-

ent in the surprisingly high mean concentration of 0.48 μg. per ml. and adrenaline was found only in small amounts (189). Taking this evidence together with the finding of noradrenaline as the dominant sympathomimetic agent in liver extracts (98), there is every reason to believe that this substance actually is responsible for the effects observed and thus serves as the chief adrenergic nerve mediator in the liver.

Since there is not complete similarity between the effect of either adrenaline or noradrenaline and that of stimulating certain adrenergic nerves, the explanation may be advanced that a mixture of the two substances is liberated. As already stated, most other organs, with the exception of the spleen, contain a greater proportion of adrenaline than the liver.

It seems, therefore, that the present evidence is strongly in favour of the assumption that in those organs which contain predominantly noradrenaline this substance also serves as the adrenergic nerve mediator, and that in organs containing a higher proportion of adrenaline, a mixture of noradrenaline and adrenaline is released. A detailed analysis, extended to several organs, concerning the kind of remote effects obtained by sympathetic nerve stimulation compared with the contents of noradrenaline and adrenaline in these nerves and the corresponding organs would, however, be desirable.

It should be possible to draw conclusions as to the nature of the adrenergic transmitter substances of a given organ simply by observing the effect on the organ of stimulation of its nerves, if the organ responds differently in kind to adrenaline and noradrenaline. The following examples of such organs have been reported. The rabbit's uterus in early pregnancy is inhibited by noradrenaline and stimulated by adrenaline (87). After partial postganglionic denervation of the nictitating membrane in the cat adrenaline and nerve stimulation had different effects (165). Adrenaline inhibits the isolated rectal caecum of the hen whereas noradrenaline in the same concentration (10^{-9}) is said to have a motor effect (132). Even in the nonpregnant cat it has been found that occasionally noradrenaline contracts and adrenaline relaxes the uterus freed from its nervous connections. During carotid artery occlusion uterine constriction has been observed, indicating noradrenaline rather than adrenaline as the mediator (133). The response of vessels in skeletal muscle might also be used (3). Nerve stimulation of the rat uterus was found always to simulate the noradrenaline response, whether the uterus was in a pregnant or non-pregnant state (186).

In some cases there is apparently little difference in action between noradrenaline and adrenaline. For example, the demarcation potential of mammalian skeletal muscle is affected similarly by noradrenaline and adrenaline (53), as well as by stimulation of the adrenergic fibres to this muscle, there being an increase up to 10 per cent.

Chronaximetric investigations have indicated certain changes in the content and liberation of nerve mediators from organs but do not seem to permit conclusions as to their nature (72). It is not known whether noradrenaline acts like adrenaline in increasing the salivary flow induced by acetylcholine or chorda stimulation (29).

A problem of particular interest is whether adrenaline is the adrenergic nerve mediator in organs in which this compound is more active than noradrenaline in producing the normal response to nerve stimulation. Such an organ is the intestine, although the difference between the responses to the two agents is not very large. The uterus and the iris show a more marked difference in response to noradrenaline and adrenaline. Adrenaline inhibits the non-pregnant uterus in much smaller doses than noradrenaline. It was therefore of interest that blood from the ovarian vein of a non-pregnant cat contained about 88 per cent of noradrenaline and only 12 per cent of adrenaline on stimulation of the hypogastric nerves (186). Similar results were obtained on the rabbit's uterus (187). On the other hand noradrenaline is a more powerful stimulator of the pregnant uterus than adrenaline (87, 239). One is therefore tempted to believe that the "choice" of the chemical mediator is largely determined by the effect on the organ in its most important functional state. Another question of interest is whether adrenaline serves as the chief adrenergic nerve mediator generally in some species, for example, the rabbit. Attention is called to the fact that the mesenteric nerves of the rabbit contain chiefly noradrenaline (95). The conclusion of West (242) that "in the rabbit adrenaline is more important than noradrenaline in the transmission of autonomic nerve impulses" is not justified and is at variance with the results of the same author (188).

b) Reflex liberation

Although it is reasonable to assume that the adrenergic nerve mediators liberated by electrical stimulation would be similar in kind to that produced by natural processes, such as reflex activity, the effects of the latter should be considered separately. A convenient way of producing strong reflex activity in the cardiovascular system is by eliciting the sinus or aortic pressor reflexes by lowering the pressure in the carotid sinus. Reflex activation of the sympathetic system has also been elicited, for instance, by stimulation of the central stump of the cut sciatic (52). When the effect is studied in the whole animal the participation of the adrenals should be taken into consideration. An increased secretion from these glands has been repeatedly shown as a result of carotid clamping, and the relatively high adrenaline content of the medullary secretion of many animals may lead to confusion.

Folkow and Uvnäs (112) produced vasoconstrictor discharge to the hind limbs of a cat having separate circulation in the cranial and caudal parts, by means of carotid occlusion, injection of acetylcholine, asphyxia, CO_2 or stimulation of the central stump of the brachial nerve. Injection of adrenaline or noradrenaline in the lower half of the animal, or stimulation of the sympathetic chain at L5 produced vasoconstriction in the hind limbs. After dibenamine in a dose of 20 mg./kg., adrenaline produced vasodilatation whereas the action of noradrenaline was abolished. On clamping the carotids under these conditions vasoconstriction of the hind limbs no longer occurred, nor did the vasomotor reflex discharge or noradrenaline produce dilatation. The effect of sympathetic stimulation was one of vasodilatation. These results show that the reflex vasoconstrictor action is

mediated by a substance differing from adrenaline and behaving like noradrenaline. CO_2 and asphyxia also produced similar effects. The possibility that electrical stimulation of the sympathetic chain produces vasodilatation after dibenamine or ergotamine by releasing adrenaline at the nerve endings seems to be ruled out by the observation that atropine annuls this effect (113). The vasodilatation therefore is interpreted as being due to stimulation of cholinergic vasodilator fibres running in the sympathetic nerves.

The results quoted above seen to show that reflexly elicited vasoconstriction is mediated by noradrenaline and not by adrenaline. However, extracts of hind limb vessels of the cat contain small quantities of adrenaline (98) and it is therefore possible that small amounts of adrenaline are liberated with the noradrenaline, although analysis of the vasomotor action so far has failed to reveal this. Experiments on the perfused leg of the dog (36) suggest a reflex vasodilator action not mediated through cholinergic nerves. (Also see 54, 76, 82, 100, 137, 145, 184, 190, 192, 204, 213, 214, 219, 229–231.)

Differences in action on the renal vessels have been observed after adrenaline and muscular exercise. Since adrenaline appears to constrict the efferent glomerular vessel and exercise causes a constriction of the afferent vessel it is concluded that adrenaline plays no significant role in the renal changes seen in exercise (23). It would obviously be of interest to compare the effects of adrenaline and noradrenaline in this respect.

On the isolated rabbit's ileum stimulation of the mesenteric nerves regularly causes inhibition (6); noradrenaline also causes inhibition (98), but adrenaline often produces inhibition which is followed by stimulation (71).

Here also should be mentioned the release of what has been considered to be adrenaline from the perfused heart by means of acetylcholine, presumably by an action on sympathetic ganglia in the heart (147, 185, 194). The experimental data do not exclude noradrenaline as the chief active substance in the perfusate, although some evidence makes it probable that adrenaline is present in the mixture.

As stated above, the effects of carotid reflexes resemble those of noradrenaline although it should be borne in mind that part of the effect is due to adrenal medullary secretion (50, 131, 155). In such experiments it also has been noted that in the beginning of an experiment noradrenaline predominated but that the proportion of adrenaline gradually increased (51). After asphyxia and hemorrhage the sympathin released from the dog's spleen was found to be increased (225). From the information as to the increased output chiefly of noradrenaline during muscular exercise one can assume that this sympathin originates chiefly from the adrenergic neurones and not from the suprarenals (103). More experiments will be needed to ascertain the kind of adrenergic nerve mediator in various forms of stress (222).

V. FUNCTIONAL SIGNIFICANCE OF NORADRENALINE AND ADRENALINE AS ADRENERGIC NERVE MEDIATORS

If the organism avails itself of two adrenergic nerve mediators or possibly more it would seem likely *a priori* that they differ not only in minor forms of action but

in a more fundamental way. Thus the scope of adrenergic activity would be enlarged.

Examples of such differentiation of action of chemically near related compounds are at hand both in the internal secretion of the ovary (oestrone and progesterone) and in the suprarenal cortex, where alterations in the hormone molecule impart striking differences in action. The unitarianism of the "adrenaline era" has given place to a dualism in regard to adrenergic nerve mediators, and it is not improbable that further research will reveal a still more complete situation.

Although it was noted as far back as 1906 (35) and repeatedly confirmed that noradrenaline was considerably less toxic than adrenaline (156, 233), only in the last few years have investigations brought to light a number of important differences in the actions of adrenaline and noradrenaline. It would seem fruitful to try to arrange these differences in a system, although it is certain to suffer from incompleteness at this early date and no doubt will require future modifications.

The rather weaker activity of noradrenaline in comparison with adrenaline on a number of smooth muscle organs was noted early (26) and often confirmed. Closer scrutiny of this fact seems to indicate, however, that this difference is firstly of a quantitative kind, and, secondly, that it is restricted to relatively few organs. It is particularly obvious in the non-pregnant uterus of various animals, but it should be remembered that the uterus occupies quite a special position in being an organ with larger variations in function than perhaps any other organ. The significance of this large difference in effect of the two mediators is still obscure, as is true also for the fowl's rectal caecum. Again in their effects on the digestive tract as a whole, noradrenaline and adrenaline do not differ very greatly. On other smooth muscle organs such as the bronchial muscles, the iris and the bladder, adrenaline is likewise more active than noradrenaline although the difference is moderate.

Two groups of reactions seem to merit particular attention, namely, the circulatory effects and the metabolic effects. Of the two agents noradrenaline is the more powerful vasoconstrictor and since it does not raise the minute volume of the heart while raising the mean blood pressure it must exert a general vasoconstrictor action, as first demonstrated in a careful and extensive study by Goldenberg and associates (126) and later confirmed by several authors (24, 162, 196). This is in contrast to adrenaline which, while increasing the minute volume of the heart (126), does not raise the mean pressure to any marked extent but sometimes even lowers it. This is compatible only with the conclusion that the net peripheral vascular effect of adrenaline is vasodilatation. The possibility remains, however, that in certain vascular areas noradrenaline may cause dilatation and adrenaline constriction. As might be expected, noradrenaline dilates the coronary vessels (60, 111) and, according to Smith and Coxe (226), *l*-noradrenaline has a dilating action on isolated coronary arteries of swine which is $2\frac{1}{2}$ times as strong as that of adrenaline. Also noradrenaline exerts a powerful inotropic action on mammalian heart muscle (123) and a marked positive chronotropic effect on the

isolated heart (159), which effects should not be confused with the reflex bradycardia produced in man (24). It remains to be seen whether the peculiar local effect of adrenergic transmitter substances in eliciting the sinus reflex is of physiological importance (145, 146).

These results give a valuable indication as to the functional significance of noradrenaline as a mediator of adrenergic nerve fibres to the heart and vessels. The adrenergic vasomotor nerves play a paramount role in the control of the blood pressure, and it seems logical that this activity should be elicited by a substance which does not cause vasodilatation as the sum of its actions but rather by one having a vasoconstrictor action. Likewise there is no obvious reason why the adjustment of blood pressure, when needed, should be accompanied by tachycardia and an increase in the minute volume of the heart, as would be expected if adrenaline served as the mediator.

No less conspicuous are the differences between the action of noradrenaline and adrenaline on various metabolic processes. Adrenaline in small doses raises the oxygen consumption of the organism whereas noradrenaline is much less active in this respect. Thus, doses of noradrenaline which would increase the mean blood pressure by 50 per cent would hardly influence the oxygen consumption in man, whereas adrenaline has a large effect (126). Similar results are reported in animals (234). The hyperglycaemic and glycogenolytic effects of noradrenaline are much less than those of adrenaline (183, 221), and the same is true for the effect on the ascorbic acid content of the suprarenals (199), on the eosinophils (158) and on the blood potassium level (79). Adrenaline is more active than noradrenaline in enhancing the effect of acetylcholine on a perfused sympathetic ganglion (167). Furthermore, the subjective effects of the two catechol amines show quite distinct features. In man adrenaline causes the well-known feeling of anxiety, but this is hardly noticeable after corresponding doses of noradrenaline. Noradrenaline is said to be rather more active as a diuretic than adrenaline (157) in rats. There is little doubt that future biochemical studies will reveal many more important differences, quantitative or qualitative, between the metabolic effects of noradrenaline and adrenaline.

There is reason to emphasize that the similarities as well as the differences in action between noradrenaline and adrenaline merit equal consideration, but that any one-sided view is likely to give an inadequate concept of the peculiar cooperation of these two agents. The fields of action of these two substances complement each other in an interesting way. The "usefulness" of noradrenaline was, in fact, emphasized several years ago as Stehle, Melville and Oldham (228) wrote "arterenol is a more potent substance than adrenaline . . . yet nature would seem to have made the second rate substance when a better one was more readily available".

Further information is required as to the occasions on which adrenaline may serve wholly or predominantly as mediator. Indications in this direction have not been lacking (19, 178, 179, 219, 242) but more complete evidence is necessary in order to form a definite opinion on each of these cases.

An attempt has been made in this section to provide an explanation of the fact that noradrenaline appears as the chief adrenergic nerve mediator, assuming that the most important "routine" functions of the adrenergic nerves are connected with the regulation of circulation. In performing the minor adjustments of homeostasis in which adrenergic fibres serve the circulatory system, there is probably no need for concomitant changes in either oxygen consumption or blood sugar, nor in the distribution of the eosinophils or the emotional pattern. All the metabolic effects, so characteristic of adrenaline, point to a supporting mechanism, the stimulation of which would produce results such as were attributed by Cannon to the adrenaline of the suprarenals in its role as an emergency substance. The reason for the occurrence of adrenaline as an adrenergic nerve mediator as well as for its presence in large quantities in the suprarenals, might therefore be sought in its possible local usefulness in certain conditions of stress.

VI. ADRENERGIC NERVE MEDIATORS IN BODY FLUIDS

a) Aqueous humour

Sympathomimetic activity has been repeatedly observed in aqueous humour of various animals (10, 95, 181) and it has been noted that it is increased after sitmulation of the cervical sympathetic nerves. It is therefore likely that the activity is derived from the adrenergic nerves of the innervated structures in contact with the aqueous humour. Attempts to analyze the action have shown that the relative amounts of noradrenaline and adrenaline differ in various preparations, but that the relative amount of adrenaline is comparatively high. Addition of strong alkali to concentrated extracts gives a red coloration (98). Although adrenaline is more powerful in causing dilatation of the pupil, noradrenaline also has this effect; hence it is not possible to draw any conclusions concerning the nature of the adrenergic nerve mediators from simple observations of the effects on the pupil.

b) Exudates

A few observations have been made on the sympathomimetic activity of peritoneal exudates in thyroidectomized sheep (98) and in scarification fluid (9). In both instances adrenergic substances could be demonstrated in small amounts.

c) Various secretions

Noradrenaline has been demonstrated in the seminal fluid of the bull (28). Whether the peculiar occurrence of large amounts of adrenaline in the parotid gland of *Bufo marinus* is due to adrenergic nerve activity is still unsettled (110). After sectioning the nerves to the parotid gland in *Bufo arenarum* the amount of adrenaline is often greatly diminished (110). However, this does not seem to be the case in all species of toad (73). The nature of the sympathomimetic agent

found in the salivary glands of certain species of *Octopus* (84) and its relation to adrenergic nerve mediators need further elucidation. It should be of interest to study the occurrence of sympathomimetic agents in tears and perspiration and to correlate their actions with those of stimulation of the corresponding adrenergic nerves.

d) Blood

There is a vast literature concerning the appearance of sympathomimetic agents in blood; however, in a large number of these studies the methods that have been employed cannot be regarded as adequate. The literature on this subject will not be reviewed here but the reader is referred to a series of papers of Lehmann (171) and others (4, 5, 46, 182, 240) from which further references may be obtained. Since there is every reason to assume that noradrenaline and adrenaline should be present in the blood, deriving from the suprarenal medulla or from the adrenergic nerve mediators (sympathin), as indeed is indicated by their presence in urine, their demonstration presumably depends upon the discovery of sufficiently sensitive methods.

In blood from human arm veins and in blood from the general circulation of animals being slaughtered, small amounts of sympathomimetic activity corresponding to 1–2 μg. of noradrenaline per 100 ml. of blood were found (107). The blood was extracted with acid alcohol and the extract tested on the cat's blood pressure after removal of depressor substances by means of fuller's earth. Since the action was typical of noradrenaline it is inferred that it derived chiefly from adrenergic nerves and not from the suprarenals which contain, in man and cattle, about 75 per cent of adrenaline and presumably secrete adrenaline in a similar proportion. The concentration of noradrenaline found in whole blood probably would exceed that in plasma since it is known that a certain proportion of the catechol amines is taken up by the red corpuscles (22). A noradrenaline-like substance has also been observed in cross-circulation experiments (202).

The appearance of adrenergic nerve mediators in venous blood coming from organs whose adrenergic nerves have been stimulated has partly been dealt with in section IV. Peart (203) succeeded in showing that stimulation of the splenic nerves considerably increased the noradrenaline content of splenic vein blood. On some occasions he also found a small proportion of adrenaline in such blood, an observation which is in accord with the findings that the splenic nerves and the spleen may contain a small amount of adrenaline in addition to noradrenaline. Similar experiments have subsequently been undertaken on other organs (187–189, 241). Table V shows some figures obtained from venous blood on stimulation of various organs.

e) Urine

Holtz and coworkers were the first to discover that urine normally contained sympathomimetic substances ("urosympathin") which were considered to consist of a mixture of noradrenaline, adrenaline and hydroxytyramine (152). In

subsequent papers members of Holtz's research group have expressed the opinion that the physiological effects observed are due chiefly or entirely to noradrenaline in man and some animals (154, 168). Recent investigations (101) have shown, however, that hydroxytyramine is the chief catechol amine in normal human urine. A large part of the catechol amines appear in free form (101).

The assumption that noradrenaline and adrenaline in urine derive chiefly from the adrenergic nerve mediators and not from the suprarenals is supported by the fact that the relative amounts of the two agents in urine is about the same as their relative amounts in adrenergic nerve tissue, noradrenaline appearing in 3–5 times as high concentration as adrenaline (102). The preponderance of noradrenaline accords with the findings in blood and in organs and nerves generally. Only a small fraction of the adrenergic nerve mediators present in the blood appears in urine, however, judging from experiments (106) in which noradrenaline was continuously infused in man at a fixed rate and the amounts excreted estimated. Thus out of 1 mg. *dl*-noradrenaline, infused during 1 hour, only 12 μg. *l*-noradrenaline in excess of the resting secretion was recovered in urine, or 2.4 per cent of the dose.

TABLE V

VENOUS BLOOD	NORADRENALINE	ADRENALINE	REFERENCE
	μg./ml.	μg./ml.	
Cat splenic	0.05–0.5	0–0.01	(203)
" "	0.13	traces occasionally	(189)
Rabbit uterine	0.046	traces occasionally	(187)
Cat hepatic	0.48	traces occasionally	(189)
Cat uterine	0.037	0.005	(188)

The significance of the comparatively large amounts of hydroxytyramine appearing in urine is as yet obscure. There are reasons for believing that this substance is formed by decarboxylation of DOPA since the decarboxylase of this amino acid occurs in a variety of organs. So far there are no indications either that hydroxytyramine is liberated on adrenergic nerve stimulation or that it serves as an adrenergic mediator, but admittedly there would be great difficulties in detecting this substance in the presence of noradrenaline and adrenaline by the methods available at present.

When discussing the significance of the appearance of adrenaline and noradrenaline in the urine, the secretion from the suprarenals and other chromaffine cell groups should be considered. It should be possible, however, to determine the extra-adrenal production by estimating the excretion in the urine after demedullation of the suprarenals, knowing the relationship between administered noradrenaline and adrenaline and the output of these substances in urine.

The increased output of noradrenaline in urine during heavy muscular work (103) is in all probability a sign of increased adrenergic nerve activity during this activity.

VII. EFFECT OF DEGENERATION AND REGENERATION OF THE ADRENERGIC NERVES ON THE OCCURRENCE OF THE MEDIATORS IN ORGANS

The following evidence lends strong support to the hypothesis that the sympathomimetic agents present in an extract of an organ are derived from the adrenergic nerves found in that organ: extracts of the nerve-free placenta are lacking in sympathomimetic activity (87, 219); likewise, this activity is almost entirely absent from organs in which degeneration of the adrenergic fibers has occurred as a result of section of the nerves (65, 98, 130). An interesting fact about the distribution of adrenaline and noradrenaline has been observed in extracts of organs after denervation. In the spleen of sheep the amounts per gram of fresh tissue are about 3 μg. of *l*-noradrenaline and 0.1–0.2 μg. of adrenaline, respectively; but after denervation the relative adrenaline content has been as high as 50 per cent of the small catechol amine residue (98). Similar observations have been made on the submaxillary gland of sheep, the adrenaline percentage showing an increase from about 10 or 20 to around 50 per cent. This may not mean a shift in the distribution of the mediators of the few remaining adrenergic nerves, but may equally well, or better, be explained by the presence of chromaffine cells in the organs. In fact the difference in the total adrenaline content of the submaxillary gland of the sheep in normal and denervated glands may be so small so as to cast serious doubt on the view that the adrenaline found in the normally innervated gland actually represents an adrenergic nerve mediator. The possibility must be considered, therefore, that adrenaline in an organ may partially represent the production of chromaffine cells which would not degenerate on denervation. On the other hand the decrease in the apparent adrenaline content of the heart after denervation approximately parallels the fall in noradrenaline (130). [For distribution of sympathetic fibres consult (47)].

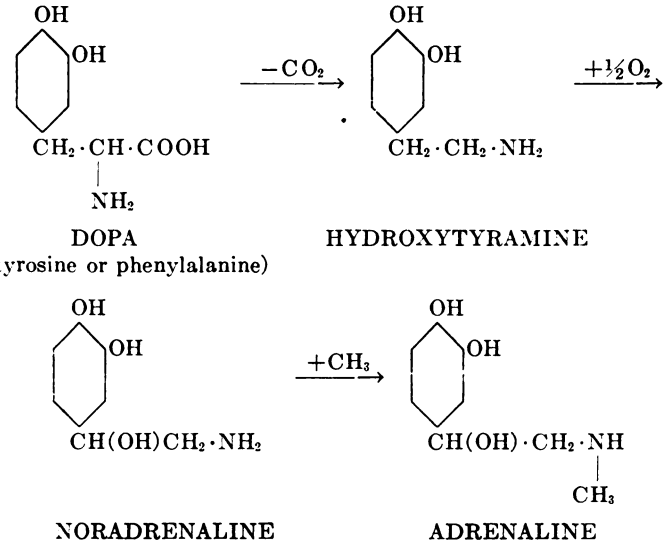
Of considerable importance are the experiments of Goodall, which have shown that after a certain lapse of time sympathomimetic substances reappear in previously denervated organs (130). After removing the sympathetics in the neck and the stellate ganglia in the sheep he found that the noradrenaline and adrenaline content of extracts of the heart fell nearly to zero. About 8 weeks after denervation, these extracts began to show an increase in their content of these substances and after 10–12 weeks the content was about normal. At this time the regeneration of adrenergic postganglionic fibres growing out from the sympathetic chain has proceeded enough to replenish the stores of adrenergic nerve mediators in the organ. No consistent alteration of the relative amounts of noradrenaline and adrenaline was noticed after regeneration.

VIII. FORMATION OF ADRENERGIC NERVE MEDIATORS

a) Chemical

Many theories have been proposed in the past for the formation of adrenaline *in vivo*. The most important contributions to what now seems to be the probable mode of formation have come from Holtz, Heise and Lüdtke (153) who discovered

DOPA-decarboxylase, and from Blaschko (38) who proposed a reaction series including noradrenaline. The biosynthesis may tentatively be assumed to take the following course:



This sequence of reactions is supported by a fair amount of evidence, although circumstantial in some points. If the first step is a decarboxylation of DOPA this substrate, as well as the enzyme, should be present in adrenergic neurons or nerve endings. Thus far DOPA has been demonstrated only in suprarenal extracts from thyroidectomized sheep (129). Hydroxytyramine is also found in such extracts as well as in heart extract (128) and in extracts of urine (101, 102). How the hydroxyl group is introduced into the side-chain of hydroxytyramine is unknown. N-methylation of noradrenaline to form adrenaline has been demonstrated in the suprarenal (56). The methyl group is supplied by methionine (163).

The possibility of adrenaline formation from various substances has been the subject of several studies (80) including some in which isotopes have been used (139), but none will be treated in detail here.

The possibility of the formation of noradrenaline by decarboxylation of the corresponding amino acid, dihydroxyphenylserine, has been considered, and small amounts of noradrenaline have been found on incubating the amino acid with enzyme extracts from guinea pig kidney (33, 41). Feeding rabbits with dihydroxyphenylserine seems to increase the urinary noradrenaline (220).

b) Local

Some information as to the site of formation of the adrenergic nerve mediators may be gained by a comparison of their amounts in the nerve and the corresponding organ. Such a comparison shows, for the splenic nerves and the spleen of the cow, that the content is some 5 times higher in the nerves than in the organ. If

the noradrenaline and adrenaline are confined to the nervous structures this would mean that the amounts per unit weight of nerve are many times higher in the peripheral parts (the nerve endings) than in the trunk. Attempts have been made to explain this by the assumption that the whole of the neurone contains the enzyme system necessary for the formation of the mediators but that the optimal conditions with regard to substrate supply, co-enzymes and ionic environment are found only in the nerve end regions (97).

The further possibility has been considered that the mediators should be formed in the central parts of the neurone and carried peripherally by the axoplasm flow (208, 232). This is rather unlikely for the reason that the axoplasm flow is very slow and the concentration in the nerve trunk low. Prolonged stimulation of sympathetic fibres does not diminish their content of mediator substances (180).

c) Storage

It has to be assumed that the concentration of adrenergic nerve mediators is relatively high in the terminal nerve structures (see p. 252). Assuming that the proportion of what may be counted as nerve endings in the spleen is 0.2 per cent of the weight of the organ in the cow, an estimate which is probably on the high side, the total amount of catechols being about 4 μg. per gram of organ, this would correspond to 2000 μg. per gram in the terminal structures. This calculation is admittedly somewhat arbitrary, but probably is of the right order of magnitude. Such a figure, however, would fall well within the range of the amounts found in the suprarenal medulla and shows that, basically, storage facilities of this order are conceivable. In fact, chromaffine cell tissue may contain as much as 10 mg. per gram and even more.

The relatively high concentration of mediators in the terminal structures indicates some special storage mechanism. This is not known, but attention should be drawn to the fact that phospholipids have the properties of combining with adrenaline and noradrenaline (25, 87, 164, 166, 201). The resulting product is soluble in ether or chlorofrom, solvents in which pure adrenaline or noradrenaline are practically insoluble. At a neutral or slightly alkaline reaction the proportion bound is considerable but diminishes rapidly at acid reaction (201). On the basis of such a linkage of the mediator substances to phospholipids a mechanism for their liberation has been tentatively suggested. Also it has been found that adrenaline may be stored in the red blood corpuscles (22).

d) Estimation of adrenergic nerve mediator production

If the normal urinary output of noradrenaline is 12 μg. per hour (102) the amount of noradrenaline leaking into the blood would be of the order of 40–80 μg. per hour if the same relation between administered and excreted noradrenaline holds as in the experiments quoted on p. 264 (106). The production of *l*-noradrenaline appearing in the blood in a resting state thus would be limited to 0.011–0.022 μg. per kg. per minute, assuming a body weight of 60 kg.

This figure is not incompatible with the findings of Goldenberg and associates (126) regarding the action of continuous infusion of small amounts of noradren-

aline in man, where 0.05 μg. *l*-noradrenaline per minute gave a barely perceptible pressure rise in normotensives.

e) Differential activation of noradrenaline and adrenaline producing fibres

The hypothesis has been advanced that two pharmacologically distinct types of cells exist in the sympathetic ganglia (224). According to this hypothesis one kind ('D'cells) produce sympathin I and the 'C' cells sympathin E, these terms designating adrenaline and noradrenaline, respectively. There is perhaps some support for this concept in the results of Brauner, Brücke and Kaindl (50) who noticed certain differences in the kind of response to sympathetic stimulation caused by occlusion of the carotids and by direct hypothalamic stimulation. In the latter case the mediator seemed to be predominantly adrenaline whereas in reflex liberation noradrenaline predominated. Their findings are of interest in suggesting that centrally-induced adrenergic nerve activity is connected with the liberation of adrenaline in a higher degree whereas the "routine" vascular reflexes make use of noradrenaline as the transmitter. Further study in this interesting field is highly desirable.

f) Oxidation products of adrenaline in relation to adrenergic nerve mediators

Alterations of the pharmacodynamic action of adrenaline at various stages of oxidation have suggested that the products formed may be the cause of the phenomena attributed to the postulated sympathins I and E (21, 143). There is, however, little experimental evidence to support the interesting hypothesis that such products as adrenoxin may serve as adrenergic nerve mediators, although it is possible that they occur and take part in the effects observed. It has also been suggested that adrenochrome (134), the red oxidation product of adrenaline, might serve as a precursor in the formation of adrenaline at the nerve endings (18), but it has never been demonstrated that the indole ring of this compound can be opened. (For further discussion of the metabolism of hydroxyphenol derivatives, consult 43, 44, 141, 172, 191, 215).

IX. INACTIVATION AND EXCRETION

A few facts about the inactivation and excretion of the adrenergic nerve mediators will be briefly mentioned here. Though easily oxidized by molecular oxygen at neutral or alkaline reaction in pure solutions, noradrenaline and adrenaline show a remarkable stability in organs or body fluids or extracts thereof. As preserving factors certain amino acids (1), ascorbic acid and other reducing substances come into account. The preservation in blood is very effective as shown by the fact that heparinized suprarenal vein blood was found to have the same activity after several days in the refrigerator at +5° C. as immediately after sampling (121). Also in urine the inactivation is slight even after 48 hours at room temperature (102). Adrenaline and noradrenaline resist heating in normal acid for a considerable length of time, although the biological activity of the laevoisomers is reduced 50 per cent by heating in N/10 solution for about 1 hour, owing to racemization (102).

The adrenergic nerve mediators are removed by enzymic inactivation and by elimination through the kidneys. Direct oxidation with oxygen seems to be of less importance. Amine oxidase is present in a variety of organs and tissues and inactivates both noradrenaline and adrenaline (39). An interesting fact has been observed by Blaschko and Burn (40) who found that noradrenaline is more readily broken down than adrenaline by amine oxidase from rabbit liver. The same is true for the enzyme present in the splenic nerves of cattle (237). Whether catechol oxidase also functions in inactivating the nerve mediators has not been demonstrated with certainty but such seems possible in view of the red coloration of solutions of adrenaline and noradrenaline on incubation with nervous tissue or spleen (237).

The inactivation of liberated adrenergic nerve transmitters seems to take place largely in the kidney (13). An interesting hypothesis with regard to the inactivation has been offered (60) on the basis of observations of wide variations in the relative activity of adrenaline and noradrenaline on the denervated nictitating membrane of the cat. The effects may be explained by assuming that some inactivating factor is removed by denervation which thus causes hypersensitivity (69; cf. 175).

Part of the adrenergic nerve mediators are inactivated by conjugation and excreted in the urine as ethereal sulfates (34, 210, 211) or as glucuronides (74, 81). Finally a certain proportion is excreted in the free form (102, 168).

The inactivation rate in the body could be determined if the amounts liberated into the blood and the blood concentration were known. The inflow rate might be approximately calculated from the urinary output, correlating known inflows, for example by infusion, with the output in urine which can be measured. The estimation of the blood concentration during infusion of noradrenaline or adrenaline requires sensitive methods.

X. ADRENERGIC NERVE MEDIATORS IN METABOLIC DISORDERS

It is likely that the enzymic formation of adrenergic nerve mediators are subject to alterations in quantity and in the relative amounts of their constituents during various abnormal conditions. Several observations seem to indicate that, for instance, during thyroid hyperactivity there is an increased formation of the adrenergic mediators. The experimental data obtained by direct estimation are very few as yet. It has been reported, however, that after thyroidectomy as well as following thyroxine administration in the sheep the catechol amines of the heart are increased 20 to 50% and that the relative amount of adrenaline is decreased (130). In cats and rats large changes may occur in the catechol amine content of the heart during various conditions (207).

Hypophysectomy does not seem to alter the catechol amine content in organs, but a shift towards a larger proportion of adrenaline has been noted (104). In vitamin B_1-deficiency the noradrenaline content of the heart of the rat is increased (130, 207). More refined methods will probably be required to ascertain whether the mediators liberated into the blood stream will show any modifications in amount and composition in endocrinological and metabolic disorders.

A striking alteration in the proportions of noradrenaline and adrenaline in urine has been noted as a result of ACTH and cortisone treatment of human patients (105). Soon after beginning the treatment the noradrenaline content of the urine decreased markedly, leaving the adrenaline almost unchanged. On some occasions only adrenaline was found in the urine. Whether this change is due to a difference in the composition of the mediators or is due to alterations in the inactivation process is not known.

XI. ADRENERGIC NERVE MEDIATORS IN INVERTEBRATES

This subject is extensively dealt with in an excellent review by Frédéricq (114). He points out that adrenergic fibres probably exist in the cardioaccelerator nerves of the *Gastropod Aplysia* and in *Cephalopods*. There is some evidence that the cardio-moderator nerves of *Cephalopods* are tyraminergic. Whether noradrenaline serves as a mediator in invertebrates is not clear, although it seems possible judging from experiments on *Annelids*, where extracts of muscle have shown some characteristics of noradrenaline (95). In extracts of the posterior salivary glands of *Octopods* an active sympathomimetic agent has been described which might be tyramine (144) or methyltyramine (84).

XII. ADRENERGIC NERVE MEDIATOR SUBSTANCES IN THERAPEUTIC USE

Adrenaline has found therapeutic use in the treatment of hypotension, in surgical shock and as a means of stimulating heart activity in circulatory collapse. After it had been established that noradrenaline is the chief physiological vasoconstrictor agent, interest turned in the direction of using this substance instead of adrenaline. Encouraging results have already been reported by Goldenberg and his associates (124) who were the first to put noradrenaline to clinical test. They found noradrenaline very useful, and superior to adrenaline, in restoring the low blood pressure after haemorrhage, in surgical shock and in other conditions. Similar good results, especially in connection with the administration of blood or blood substitutes, have also been reported by other authors (216). Noradrenaline should have many advantages over adrenaline as a blood pressure-restoring substance since it produces pure vasoconstriction without raising the minute volume of the heart, does not increase the oxygen need, does not cause tachycardia but bradycardia, has no untoward psychic effects and is but slightly toxic.

Especially on removal of phaeochromocytomas, whereupon the organism is suddenly deprived of a large inflow of noradrenaline, a continuous administration of this substance should be of great use, as indeed has proved to be the case.

XIII. SUMMARY

The chief points in the present concept of the adrenergic nerve mediators may be briefly summarized as follows:

1. Convincing evidence has been produced to show that *l*-noradrenaline is the chief adrenergic nerve mediator in mammals. In addition *l*-adrenaline occurs admixed in various small amounts with the noradrenaline. The hypothesis of purely

excitatory or purely inhibitory sympathins is no longer tenable. The liberation of other related substances such as hydroxytyramine, tyramine and oxidation products of dihydroxyphenyl derivatives in adrenergic nerve activity has not been proven in mammals.

2. The adrenergic nerve mediators *l*-noradrenaline and *l*-adrenaline can account for most actions observed on stimulation of adrenergic nerves.

3. Noradrenaline and adrenaline are formed in the adrenergic neurons and appear in small quantities in the nerve trunks and in larger amounts in the innervated organs, presumably occurring in the terminal nerve structures.

4. The adrenergic nerve mediators disappear from an organ after degeneration of the nerves but reappear on nerve regeneration.

5. There is some evidence in favour of the formation of noradrenaline by decarboxylation of dihydroxyphenylalanine and subsequent introduction of a hydroxyl group in the side chain of the hydroxytyramine so formed.

6. The adrenergic nerve mediators are rapidly inactivated in the tissues by enzymes (amine oxydase and catechol oxidase). A smaller part is excreted in free or conjugated form in the urine.

7. The physiological actions of noradrenaline and adrenaline differ in many important respects. The main function of noradrenaline seems to be the normal control of the circulation, while adrenaline produces various effects in conditions of stress and emergency.

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