STUDIES IN DENERVATION

E.—OBSERVATIONS CONCERNING ADRENALINE

BY

J. DOUPE *

(From the E.M.S. Hospital, Winwick, nr. Warrington)

(RECEIVED 14TH OCTOBER, 1943)

It is the object of this paper to report the effects of injections of adrenaline on the circulation of denervated digits and observations indicating the release of natural adrenaline.

The methods and apparatus are described in paper A.

Effect of Injections of Adrenaline

In paper B reference has been made to the demonstration of Fatherree *et al.* (1940) that denervation of the digital vessels of humans renders them hypersensitive to the vasoconstricting action of adrenaline. Atlas (1938) had previously shown the same phenomenon using neosynephrine and both authors agreed in attributing the action to the effects of degeneration of the sympathetic fibres. These effects were first fully described by Elliott (1905) and since have been amply confirmed though little new has been added to his observations. Freeman *et al.* (1934) demonstrated in the human

the hypersensitivity to adrenaline produced by sympathetic ganglionectomy while the success of the operations of preganglionic sympathectomy devised by Telford (1935) and Smithwick (1936) further testifies to the fact that Elliott's results are applicable to the human.

In as much as the present findings form no exception to those referred to above it is only necessary to refer to the figures illustrating these results. Fig. 1 is an enlargement of Fig. 5, paper B, showing that in response to intravenous injections of adrenaline the denervated digit (R.F.2) had a greater fall in temperature than did the preganglionectomized digit (R.F.5), while there was no certain effect on the normal digit (L.F.2). This figure well depicts the prolonged response in the vessels whose sympathetic fibres have degenerated as described by Elliott. It was on the basis of this type of response in R.F.5 and its absence in R.F.2 in subject S.S. (see Fig. 6, paper B) that it was concluded

FIG. 1.—Temperature chart of subject S.W. An extract from paper B, Fig. 5. Abscissæ are time in minutes. Ordinates are temperature in degrees centigrade. The broken line represents a normal digit, the dotted line a preganglionectomized digit and continuous line a denervated digit. The rate and duration of the adrenaline infusion is indicated by the hatched blocks.

* Working on behalf of the Medical Research Council.

FIG. 2.—Plethysmographic record ($\times \frac{2}{3}$) of subject L.S. In this and the succeeding figures the following conventions are used. Upper line is a signal operated by hand to indicate the time of the stimulus. The nature of the stimulus has been inserted. Time in 1-sec. and 10-sec. intervals. Respiratory downstroke indicates inspiration. In the volume tracings the upper tracing is the normal contralateral digit in which an upstroke indicates an increase in volume, while the lower tracing is the denervated digit in which a downstroke represents an increase in volume.

that a stellate ganglionectomy could produce both degenerative and non-degenerative section of the sympathetic fibres to the hand. Other illustrations of the effect of adrenaline on the temperature of digits affected by peripheral nerve lesions are shown in paper B, Figs. 2, 4, 5, and 7. A comparison of Fig. 2, subject L.S. of that paper with the plethysmographic record shown here in Fig. 2 indicates that in this subject the hypersensitivity of the vessels of the denervated toe is demonstrable by both thermometric and plethysmographic methods. Figs. 8 and 9 provide additional examples of this plethysmographic effect.

Despite the above, certain discrepancies have been

noted between the plethysmographic and thermometric methods. Thus, a comparison of Fig. 1 and Fig. 3 shows that while there was a definite difference in the thermometric responses of R.F.2 and R.F.5 there is little evidence of such a difference in the volume tracing. Similarly the temperature records in Fig. 4 show greater responses in the toes affected by lesions of the posterior tibial nerve than in the normal toes, while the plethysmographic records from these subjects, one of which is shown in Fig. 5, give no indication of this difference. These discrepancies appear to be explained by two findings of Elliott (1905). He found that cold potentiates the action of adrenaline and Ascroft

FIG. 3.—Plethysmographic record ($\times \frac{1}{2}$) of subject S.W. Conventions as in Fig. 2, with the addition of a central tracing of a preganglionectomized digit in which a downstroke represents an increase in volume.

(1937) noted this with particular reference to denervated tissues. Some evidence of this is seen in Fig. 4, because after warming the room the difference in responses of the normal and affected toes became somewhat less marked. In the plethysmographic technique used here the environmental temperature of the digits must approach

is destroyed, an increased irritability to chemical agents develops in the isolated structure or structures, the effect being maximal in the part directly denervated." This concept may be criticized on the grounds that it ignores a qualitative difference in the reactions of tissues which are subjected to degenerative and non-degenerative nerve section.

FIG. 4.—Temperature charts of subjects A.M. and J.P. Lines representing the different digits are identified on the charts. The lower line of blocks if filled indicate arms in water at 18° C.; if empty in water at 44° C. Blocks with oblique hatching show rate of intravenous injection of adrenaline.

blood temperature so that this potentiating factor would be absent.

Elliott also noted that in denervated tissues, not only was the threshold to adrenaline lowered, but that the response was unusually prolonged. Evidence of this was found in almost every thermometric record as shown by a continuation of the fall in digital temperature throughout the period of injection. It seems probable, therefore, that the brief injections used in the plethysmographic experiments would be less likely to display the full extent of the abnormal response to adrenaline than would the longer injections used in the thermometric records.

It will be seen in Fig. 1 that the primary difference between the digit (R.F.2) to which the nerves have degenerated and the digit (R.F.5) to which the nerves are intact but have been sectioned proximal to the ganglion, is not a matter of threshold but a matter of type of response. The denervated digit appears to show very little accommodation to adrenaline in comparison to the preganglionectomized digit. That this is not due to an inability of the vessels of the denervated digit to react rapidly is shown by the response in Fig. 3. While the term "accommodation" does not seem quite appropriate in this usage it is employed for want of a more adequate expression and to draw attention

FIG. 5.—Plethysmographic records ($\times 1/4$) of subject J.P. Conventions as in Fig. 2.

The present observations, which are reassuringly consistent with those of Elliott, permit a suggestion to be made with reference to the theory of denervation sensitivity. Cannon (1939) has generalized previous observations in a law of denervation which states "when in a series of efferent neurons a unit

to the similar lack of "accommodation" in denervated skeletal muscle described in paper I. An attempt to obtain further support for this observation by comparing the responses of denervated digits with normal digits has been unsatisfactory, as indicated in Fig. 6. This figure

FIG. 6.—Temperature chart of subject B.K. Patient sat with legs in hot water for 30 min. before start of chart. Conventions as in Fig. 1.

shows that there was no difficulty in demonstrating the response of denervated vessels, but it is impossible to be sure that part of the reaction in the normal digit was not mediated by nervous influences. Fig. 7, which is an enlargement of a section of Fig. 4, offers a similar difficulty in interpretation. Because of this, these observations have not been extended.

It is tentatively concluded that an essential difference exists between the sensitivity developed after degenerative and after non-degenerative section of sympathetic nerves, the former producing a loss of "accommodation" not produced by the latter, though both have a lowered threshold to adrenaline.

The Secretion of Adrenaline

In studying the effects of denervation on the circulation of the digits it was necessary to ascertain

the circumstances and extent of the secretion of adrenaline in man.

In paper B it was shown that a circulating vasoconstricting substance was present at times, and this was assumed to be adrenaline. No evidence is advanced here to prove this supposition, and it may be noted that Wilkins and Eichna (1941) appear to be the only workers to have offered evidence on this point. Using sympathectomized limbs they found that emotional stimuli caused a vasodilatation in muscle, while this was absent after bilateral splanchnicectomy. For confirmation the observations made in cases of pheochromocytoma might be cited. In a case reported by Engel *et al.* (1942) emotion produced all the signs associated with a large injection of adrenaline, while these were absent after removal of the tumour. Thus there is

FIG. 7.—Temperature chart of subject J.P. An extract from Fig. 4.

in man good evidence that the hormone is adrenaline and this is particularly acceptable because it has been so frequently proven in animals. Moreover, evidence of an adrenaline-like substance has been found in man in such conditions as hypoglycæmia (Freeman *et al.*, 1934), emotion (Wilkins *et al.*, 1941), and struggling (Grant, 1935), while similar conditions have been shown to liberate adrenaline in animals. It is concluded, therefore, that in attributing the effects to be described to the action of adrenaline there is little possibility of error.

These results are reported to demonstrate (1) the type of stimulus which evokes the release of adrenaline, (2) a dissociation between the nervous and hormonal actions of the sympathetico-adrenal system, (3) the amount and duration of adrenaline secretion.

(1) *Type of Stimulus.*—Subjects were examined by the plethysmographic method and given various

stimuli which have been shown (Bolton *et al.*, 1936, Stürup *et al.*, 1935) to cause neurogenic vasoconstrictions. Before the start of the experiment the subjects were told to sit quietly with their eyes closed and instructed to take a deep breath at command and then to resume normal breathing, to do sums in mental arithmetic and to give the answer when requested. At intervals throughout the experiment the subjects were given 4–5 quick stabs with a pin and at times a loud sharp noise was made. The results of such stimuli are shown in Figs. 2, 3, 4, 8, and 9. It has been consistently found that no definite vasoconstriction in response to a deep breath, pin prick or loud noise occurred in digits denervated by ulnar, median or sciatic nerve lesions. This confirms the observations of Bolton *et al.* (1936). However, in response to a sum a vasoconstriction not infrequently was found to occur 10–20 secs. after the vasoconstriction in the normal

FIG. 8.—Plethysmographic record ($\times \frac{1}{3}$) of subject L.R. Conventions as in Fig. 2, with the addition of a tracing of the pulsations of the left calf recorded from a cuff at a pressure of 115 mm. Hg. An increase in size of pulse wave indicates an increase in systolic blood pressure.

FIG. 9.—Plethysmographic record ($\times \frac{1}{4}$) of subject A.H. Conventions as in Fig. 2.

digits. This at times was associated with a further vasoconstriction in the normal digit (Fig. 5). To exclude the possibility that these diminutions in digital volume were due to a fall in blood pressure coincident records were obtained of the pulsations of a blood pressure cuff inflated to just below systolic pressure. In Fig. 8 it is seen that no fall in blood pressure occurred to account for the fall in finger volume. These observations indicate that a mental stimulus is especially apt to cause the secretion of adrenaline. However, it was shown in paper B that intense pain and the excitement of venipuncture could produce a vasoconstriction in denervated digits attributable to adrenaline and in paper C a marked vasoconstriction was produced in subject J.M. by immersion of the feet in very hot water.

It is concluded from these experiments that stimuli considered to be of emotional significance to the individual cause a release of adrenaline. This is in accordance with the results of the authors cited above.

The relationship of adrenaline to the thermoregulation is more difficult to determine. Cannon *et al.* (1926) have concluded from the increase of metabolic rate that occurs before the onset of obvious shivering when a subject is cooled that adrenaline is liberated to play one of its rôles as a homeostatic agent. That this method of detecting adrenaline is unsatisfactory follows from the work of Burton and Bronk (1937) who showed that increased muscular activity long precedes the onset of any gross shivering movements. The use of digital vessels sensitized to adrenaline by the section of their sympathetic fibres is a method without objection provided that the whole of the vascular tree of the limb has been decentralized. In this category fall three subjects, S.W., S.S., and S.B., in whom adrenaline sensitization was demonstrated. Pertinent experiments on subject S.W. are shown in Exps. 9 and 10, Fig. 5, in paper B. In Exp. 9, vasoconstriction occurred in response to immersion of the feet in cold and was relieved by subsequent immersion in hot water. This vasoconstriction might be associated with thermoregulation or with the sensory and emotional response to the cold stimulus similar to that which occurs from pain. That the latter explanation is correct is suggested by the fact that there was no

evidence of such a response in Exp. 10, and in both experiments there was no evidence of inhibition of adrenaline secretion when the body was initially warmed. In subject S.S., Fig. 6, of paper B, there was both vasodilatation on immersion of the feet in hot water and vasoconstriction when the body was cooled. This would be indicative of a release of adrenaline being intimately associated with thermoregulation, but subject S.B., Fig. 4, Exp. 31, paper B, showed only the slightest signs of a similar type of response. Duthie and Mackay (1940) have described this type of response in sympathectomized limbs, but they ascribed it to the persistence of vasodilator fibres. It is obvious that this explanation is insufficient in view of the fact that such changes occur after section of all the nerve fibres.

It may be noted that the literature affords no unequivocal examples in the human of the release of adrenaline in response to body cooling. Freeman (1935) has shown that placing ice on a subject's body induces a vasoconstriction in sympathectomized limbs but this is probably due to the psychogenic aspects of the stimulus rather than to the need for thermoregulation. Moreover, Wilkins and Eichna (1941) could find no evidence of such a release in response to body cooling. It may also be of some importance that Howard and Barker (1937) in reviewing the circumstances which have been reported to induce the liberation of adrenaline from pheochromocytomata record no instance where the need for thermoregulation was a recognized cause. In animals Cannon *et al.* (1926) have found that adrenaline was released when cats were cooled by gastric lavage with cold water. It may be that other circumstances than heat loss were responsible for this release because Grant (1935) found that the sympathectomized vessels of rabbit's ears constricted in response to a great variety of stimuli but not to that of heat loss, and Hemingway and Hathaway (1941) have also presented evidence controverting the theory of Cannon.

This discussion may be summarized by saying that adrenaline liberation in the human is commonly caused by stimuli which appear to be of emotional significance while the necessity for heat conservation is a more variable and less constant cause of such liberation. It would seem, therefore,

that Cannon's original view of the association of the secretion of adrenaline with mental excitement is more correct at least for the human than his later modification of the emergency theory (1929) which invokes the participation of adrenaline in many of the ceaseless variations in bodily function required to maintain the "milieu interieur."

Dissociation between the Nervous and Hormonal Actions

Cannon has developed an holistic conception of the functioning of the sympathetic part of the autonomic nervous system. He states (Cannon, 1932) "The sympathetic (innervation) is like the loud and soft pedals, modulating all the notes together" and this opinion has won the approval of White and Smithwick (1942). It is hardly necessary to indicate that this conception cannot be meant to apply universally to the sympathetic nervous system because the activation of sweat glands occurs in the presence of inhibition of vasoconstrictor fibres. However, it might not unreasonably be held to imply that the release of adrenaline and neurogenic vasoconstriction were always intimately associated.

The observations reported here do not support such a contention. It has been pointed out above that the neurogenic vasoconstriction associated with a deep breath is not associated with the release of adrenaline nor is the neurogenic vasoconstriction in response to undue loss of heat necessarily associated with release of adrenaline. In this study no clear indication was found of the reverse effect, i.e. adrenaline release not associated with neurogenic vasoconstriction, but a particularly striking example of this has been furnished by Freeman *et al.* (1934). Their Fig. 3 shows that in response to hypoglycaemia adrenaline was liberated and was associated with vasodilatation in the normally innervated hand. That inhibition of vasoconstrictor fibres occurs in hypoglycaemia has also been indicated by Abramson *et al.* (1939).

It is clear, therefore, that within the sympathetico-adrenal system there are different patterns of behaviour elicited by stimuli of different types. Such physiological manifestations are also in accord with the central organization of the sympathetic system because separate spinal pathways have been demonstrated for pupillary, sweat, and vasomotor impulses (Duthie *et al.*, 1940, Stead *et al.*, 1942). The opinion may even be ventured that a distinct pathway also exists for impulses actuating the adrenal medulla.

The Amount and Time Course of Adrenaline Secretion

To assay the amount and duration of adrenaline secretion comparisons were made between the effects of mental stimuli and the effects of intravenous injections of adrenaline. In several instances the vascular effects of naturally occurring adrenaline have been fairly closely mimicked by intravenous injections and so permit the deduction that they were produced by concentrations of adrenaline similar both in amount and in time. Thus, in

paper B, Fig. 2, subject L.S., venipuncture induced a secretion of adrenaline not far removed from 6 μ g. per minute for five minutes. In Fig. 5 of this paper a sum is seen to have caused the same vascular effect as 0.5 μ g. adrenaline injected over the course of 1–2 seconds, while Fig. 9 shows that in subject A.H. the response to mental exercise was fairly stereotyped and caused a secretion of adrenaline, probably in the region of 0.1 μ g. within 1–2 seconds. In certain subjects such as S.S., paper B, Fig. 6, a continuous secretion of adrenaline has had to be presumed in order to account for a vasodilatation when the body was warmed. No satisfactory estimate of the rate of this secretion has been made but it is probably less than 1.0 μ g. per minute.

These observations indicate that the adrenal medulla is capable both of liberating gushes of adrenaline in a brief space of time and of maintaining a secretion for long periods. The stimuli used to elicit this secretion have been mild and it cannot be doubted that many of the annoyances of every day life would result in a considerably greater release of adrenaline. It is considered that this adds further force to the conclusions of paper B that circulating adrenaline may initiate a persistent vasoconstriction in denervated digits.

Summary

The action of adrenaline injected intravenously and liberated naturally has been studied in denervated and sympathectomized digits.

The vessels of denervated digits, because of the degeneration of their sympathetic fibres, showed a lowered threshold and a prolonged response to the action of adrenaline.

The vessels of preganglionectomized digits showed only a lowered threshold.

It was considered probable, therefore, that the phenomena of denervation sensitivity were essentially different in these two circumstances.

Adrenaline was found to be liberated in the body in response to stimuli which had a psychogenic component.

Conflicting results were obtained concerning the function of adrenaline in temperature regulation, and it was inferred that the need for heat conservation did not consistently evoke the secretion of adrenaline.

A peripheral neurogenic vasoconstriction was not necessarily accompanied by the release of adrenaline.

It was found that adrenaline could be liberated in the body in amounts comparable to the rapid intravenous injection of 2.0 μ g. and for longer periods at the rate of 6.0 μ g. per minute.

It was considered that under other circumstances much larger amounts might be liberated and would suffice to initiate a persistent vasoconstriction in a denervated digit.

REFERENCES

- Abramson, D. I., Schkloven, N., Margolis, M. N., and Mirsky, A. (1939). *Amer. J. Physiol.*, **128**, 124.
- Ascroft, P. B. (1937). *Brit. J. Surg.*, **24**, 787.
- Atlas, L. N. (1938). *Surgery*, **4**, 718.

- Bolton, B., Carmichael, E. A., and Stürup, G. (1936). *J. Physiol.*, **86**, 83.
- Burton, A. C., and Bronk, D. W. (1937). *Amer. J. Physiol.*, **119**, 284.
- Cannon, W. B. (1929). *Arch. Neurol. Psychiat.*, Chicago, **22**, 282.
- (1932). *The Wisdom of the Body*, p. 244. Kegan Paul, Trench, Trubner & Co., Ltd. London.
- (1939). *Amer. J. med. Soc.*, **198**, 737.
- Cannon, W. B., Querido, A., Britton, S. W., and Bright, E. M. (1926). *Amer. J. Physiol.*, **79**, 466.
- Duthie, J. J. R., and Mackay, R. M. I. (1940). *Brain*, **63**, 295.
- Elliott, T. R. (1905). *J. Physiol.*, **32**, 401.
- Engel, F. L., Meneher, W. H., and Engel, G. L. (1942). *Amer. J. med. Sc.*, **204**, 649.
- Fatherree, T. J., Adson, A. W., and Allen, E. V. (1940). *Surgery*, **7**, 75.
- Freeman, N. E. (1935). *Amer. J. Physiol.*, **113**, 384.
- Freeman, N. E., Smithwick, R. H., and White, J. C. (1934). *Ibid.*, **107**, 529.
- Grant, R. T. (1935). *Clin. Sci.*, **2**, 1.
- Hemingway, A., and Hathaway, S. R. (1941). *Amer. J. Physiol.*, **134**, 596.
- Howard, J. E., and Barker, W. H. (1937). *Bull. Johns Hopk. Hosp.*, **61**, 371.
- Smithwick, R. H. (1936). *Ann. Surg.*, **104**, 339.
- Stead, E. A., Ebert, R. V., Romano, J., and Warren, J. V. (1942). *Arch. Neurol. Psychiat.*, Chicago, **48**, 92.
- Stürup, G., Bolton, B., Williams, D. J., and Carmichael, E. A. (1935). *Brain*, **58**, 456.
- Telford, E. D. (1935). *Brit. J. Surg.*, **23**, 448.
- Wilkins, R. W., and Eichna, L. W. (1941). *Bull. Johns Hopk. Hosp.*, **68**, 425.
- White, J. C., and Smithwick, R. H. (1942). *The Autonomic Nervous System*, p. 67, 2nd ed. Henry Kimpton, London.