Section of Psychiatry

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The Action of Adrenaline in Anxiety

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THE part played by adrenaline in the major emotions of anger and fear has been generally recognized since the classical work of Cannon, who obtained evidence of a liberation of adrenaline from the adrenals and showed that the main somatic accompaniments of anger and fear could be attributed to the action of adrenaline.

There are few to-day who take the extreme view of James and Lange in regarding the emotions as little more than our perception of these bodily changes, yet the somatic effects are an important component of emotion. In anxiety it is certainly the somatic symptoms of which the patients chiefly complain and this is important from a therapeutic point of view, since it is frequently possible to relieve the condition to a considerable extent merely by removing the physical symptoms (Misch, 1935).

Anxiety cases often show symptoms such as diarrhœa or sweating which are produced by a cholinergic mechanism, but generally the main symptoms are referable to the action of adrenaline. The relationship between the effects of adrenaline and the anxiety state is further emphasized by the emotive action of adrenaline.

Patients frequently show emotional symptoms after a small dose of adrenaline. Generally it causes only a vague feeling of apprehension or anxiety, but often it produces a marked emotional upset: the patient may burst into tears and experience a profound emotional disturbance. The emotional response to adrenaline is absent in chronic schizophrenics (Dynes and Tod, 1940). Maranon (1924) found that it is generally slight in the most normal individuals and his work suggests that the response is particularly exaggerated in anxiety neurotics.

The observed sensitivity to adrenaline may depend on (*a*) the rate of destruction of adrenaline in the body, (*b*) the physiological conditions, involving such factors as pH, thyroprotein level and calcium level in the tissues, and (*c*) the mental condition of the patient.

Before we can get very far with this problem it is necessary to know more about the basic physiological and biochemical factors which control the action of adrenaline and particularly how it is inactivated in the body. We know that the activity of acetyl choline, which is liberated in the parasympathetic division, is controlled by the enzyme choline esterase which destroys it. It may then be asked if there is a corresponding enzyme which inactivates adrenaline liberated in the post-ganglionic sympathetic division.

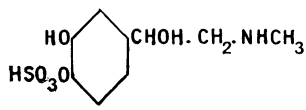
Until recently, nothing was known of the way in which adrenaline is inactivated in the body and this has held up research on the sympathetic nervous system to a considerable extent, since in nearly all experiments in which the effects of adrenaline are measured the rate of inactivation of adrenaline comes in as an unknown and possibly variable factor.

The effects of a subcutaneous adrenaline injection may last for an hour or more owing to the local vasoconstriction and slow rate of absorption, but adrenaline is rapidly removed from the circulation since the effects of an intravenous injection are brief and last for only a few minutes.

It has frequently been assumed that adrenaline is oxidized in the body and it has been suggested that the oxidation might be effected by the amine oxidase, an enzyme which is mainly responsible for the detoxication of amines in the body (Richter, 1938). This view was supported by Gaddum (1939) who put forward a theory of the action of ephedrine which is based on it; but recent work has shown that the rate of inactivation of

adrenaline in the body is too great to be accounted for by the amine oxidase (Richter and Tingey, 1939) so that we must look for some other enzyme.

The problem of how adrenaline is inactivated in the body has now been studied in a new way by taking large doses of adrenaline by mouth and searching for reaction products of adrenaline in the urine. It was found that after taking adrenaline a substance appears in the urine which has the properties of an adrenaline ester (Richter, 1940). The amount of this adrenaline ester found in the urine is necessarily small, since only small doses of adrenaline can be given, and it has not yet been isolated in the pure state, but the chemical work has advanced sufficiently to show that it is probably the sulphate ester or "ethereal sulphate" in which adrenaline has been conjugated with sulphate on one of the phenolic hydroxyl groups. About 70% of the amount of adrenaline administered was found in this form in the urine.



This suggests that the chief method by which adrenaline is inactivated under physiological conditions is by conjugation and the inactivating enzyme is the "sulphosynthase" or system responsible for the synthesis of sulphate esters. There is further evidence which supports this view. It might be expected that adrenaline, which is a phenol, would also be inactivated in the same way as other phenols, which are known to be mainly detoxicated by conjugation. Animal experiments have shown that the liver is particularly effective in inactivating adrenaline since the effects of adrenaline are prolonged and intensified by hepatectomy; the liver is also the chief site in which the detoxication of phenols by conjugation occurs.

Strong evidence of the function of choline esterase was afforded by the discovery of the anti-choline esterases, which prolong the effects of acetyl choline by competing with it for the enzyme and so preventing its destruction.

If adrenaline is inactivated by the "sulphosynthase" we might expect that other phenols would act in a manner analogous to the anti-choline esterases by competing for the enzyme and so prolonging the effects of adrenaline. This has been tested and Bacq (1936) found in some very striking experiments that polyphenols injected *in vivo* do, in fact, augment and prolong the effects of adrenaline. After injection of polyphenols the animals appeared hypersensitive to adrenaline or to the effects of stimulating the sympathetic nerves.

It would therefore appear probable that the system in the sympathetic division corresponding to choline esterase is the "sulphosynthase" and the polyphenols correspond in their action to the anti-choline esterases.

I have mentioned this work because a deficiency in the system inactivating adrenaline is a factor that might well play a part in certain types of anxiety and this is a possibility which cannot yet be excluded. These experiments, in showing that adrenaline is eliminated in a form that can be estimated in the urine, may also suggest other lines of investigation on the problem of anxiety.

Coming now to the physiological factors which affect the sensitivity to adrenaline, it is known that the intensity of the reaction to adrenaline runs parallel with the thyroprotein level and is increased in acidemia and after the administration of calcium. There are also many other factors such as the adrenal cortical hormone and sex hormones which have been stated to affect the sensitivity to adrenaline. In the present study I am particularly concerned with the emotional response to adrenaline, and Maranon, who investigated the point very thoroughly, established that the physical and emotional reactions to adrenaline are not directly related. It is true that an intense physical and emotional reaction frequently go together, but on the other hand there may be an intense physical reaction without any corresponding emotion. The emotion is not therefore directly determined by the physical response.

Before passing on to consider the mental factors there is one further biochemical process by which adrenaline might conceivably affect the emotional state.

Adrenaline causes an initial rise which is frequently followed by a secondary prolonged fall in the blood sugar, the fall being due to the diminished glycogen reserves and increased liberation of insulin. It is well known that a fall in the blood sugar is associated with nervous symptoms related to anxiety. This is shown for example in the anxiety which may be one of the first effects of an insulin injection. Many apparently normal individuals, and particularly "nervous" children, experience a mood of anxious depression in between meals and this is intensified by emotional excitement. The observation that this condition can frequently be relieved by administering glucose suggests that the fall in the blood sugar may be the main factor in determining the type of anxiety. That it is most commonly found in children may be attributed to their relatively high metabolic rate.

Until recently it was believed that adrenaline causes a breakdown of glycogen in the liver by activating the liver amylase, but it has now been shown that adrenaline acts on the phosphorylating system and increases the rate of phosphorylation of glycogen (Lee and Richter, 1940). The immediate hyperglycæmia causes a secondary liberation of insulin from the pancreas which may result in a marked hypoglycæmia. This effect of adrenaline on the glycogen reserves and blood sugar may possibly be a significant factor in the type of anxiety which responds to glucose and which is commonly found in "nervous" children; but this is still only a speculation and further research is needed to confirm it.

Returning now to the consideration of the direct emotional action of adrenaline, previous investigators have generally observed the effects after administering adrenaline by injection, but an injection which causes obvious physical effects may in itself be sufficient to cause anxiety in some subjects. I have found it an advantage to introduce the adrenaline electrically through the skin. The application of two small electrodes causes little discomfort or apprehension and the subject need not know that any drug is being put into him.

Maranon concluded that subjects may respond to adrenaline either by (*a*) a vague emotional sensation in which the somatic elements of emotion are perceived "en froid" or by (*b*) an outburst of true emotion in which the somatic and psychic elements are both present. This classification into two categories may be useful in drawing attention to the fact that the emotional response is different in different individuals, but in my experience these two types of response are not clearly defined but merge imperceptibly into each other.

The most normal subjects generally experience a feeling of apprehension which is well expressed by one subject who said: "I feel weak-kneed, as if I was just up for an exam!" This sensation is not a true emotion, but might be described as emotion with insight, for the subjects know that they have no real cause for emotion.

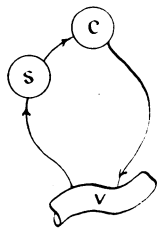
The simplest interpretation of the causation of true emotion by adrenaline is that the subject becomes conscious of the cœnæsthetic impulses arising as a result of the somatic disturbance and begins to think of previous emotional experiences in which he has felt a similar sensation and which, by repetition, may have become associated with this particular bodily sensation. The subject may, for example, think about his income tax, which has been causing him some anxiety. The consciousness becomes focused on subjects with a similar emotional content and the patient may begin to rationalize and find in these subjects sufficient reason for his feeling of apprehension.

If, as often occurs in anxiety neurotics, the mind contains some pattern that is highly charged with emotion (corresponding perhaps to the Freudian "complex"), the cœnæsthetic impulses produced by adrenaline may act as a form of suggestion and may give rise to an emotional discharge. This emotional discharge may in itself be sufficient to cause a further release of adrenaline through the action of the sympathetic nervous system; the original cœnæsthetic impulses are thereby increased and a vicious circle may result. The emotional response to adrenaline is most simply interpreted in terms of a "cœnæsthetic cycle" of this kind, in which there is a mutual interaction between a cortical pattern and a visceral organ so that each may increase the degree of excitation of the other (*see* illustration, p. 48).

The way in which the cœnæsthetic impulses arising from a visceral disturbance may cause the excitation of an emotionally charged cortical pattern (path VSC) is illustrated by the anxiety dreams, which may occur as a result of indigestion, a process which is

particularly marked in anxiety neurotics. The production of visceral changes by an emotional discharge (path CV) is well established.

The emotional response to adrenaline does not always take the form of anxiety, but depends on the type of emotional pattern which is associated in the subject with sensations produced by adrenaline. Maranon described a patient who expressed his sensations



Cœnæsthetic cycle.
V = viscera. S = sensory perception. C = cortical pattern.

after an adrenaline injection as being as if he was "expecting a great joy". This was illustrated similarly by a case I observed of a woman of 33 who was liable to attacks of anxious vomiting. She held an influential position as a civil servant and for many years she had felt sick and vomited before any important interview or before giving a lecture about which she felt anxious. She gave a clear emotional response to adrenaline, but it was not her usual anxious vomiting. Following an adrenaline injection she flew into a temper and became aggressive in her manner. Afterwards she tried at first to rationalize her behaviour, but finally said: "I just felt terribly angry—I can't think why!" One subject who was used to taking adrenaline as a remedy for asthma stated that adrenaline gave him "a feeling of confidence", which is the reverse of anxiety; this may be attributed to his associating the sensations produced by adrenaline with the relief of his asthmatic symptoms.

Lindemann and Finesinger (1938) have shown that the property of precipitating an anxiety attack is not specific for adrenaline, but attacks can sometimes be induced by mecolyl. It seems likely that a "cœnæsthetic cycle" is again responsible, but in this case there is an emotionally charged pattern associated with impulses coming from the parasympathetic division.

A cyclical mechanism of this type is well known to operate in normal sex behaviour. Here again an emotionally charged cortical pattern interacts with the impulses coming from a visceral organ and stimulation of either may increase the degree of excitation of the other. The cycle can in this case be started by direct stimulation of the organs, by suggestion or chemically by yohimbine and the aphrodisiacs, which act in a way which may be compared with the effect of adrenaline in inducing an attack of anxiety.

In certain types of anxiety state the various biochemical factors I have discussed may come in as a part of the picture, but the observed hypersensitivity of anxiety neurotics to adrenaline is most simply explained in terms of a cyclical mechanism which is conditioned by their having an emotionally charged cortical pattern which is excited by the impulses coming from a visceral or peripheral organ so that each tends to increase the degree of excitation of the other.

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