the case of a tumour, in which the radium is embedded, it would mean a minor surgical operation each time the emanation tubes were changed.

Another point of importance is to give the whole maximum dose at first, and not to break it up into smaller ones which are repeated. The latter course may in certain cases turn out a fatal error, and this chiefly because the malignant cells, which were stunned but not killed by the first application, will, when they recover, tend to breed cells which are more immune to radiation, until the same process continuing after several exposures, only those cells will survive which are refractory to the rays. There is a tendency by natural

selection to breed cells which are immune, and further exposures will now only do harm. The knock-out blow should be given by a sufficiently long exposure to a sufficient amount of radium while the cancer cells are not suspecting an attack; they must be taken by surprise, so that they will be unable to organize a resistance and be incapable of putting up a serious defence.

Were more attention paid to these points there would, I venture to think, be fewer failures following radium treatment.

REFERENCE.

¹ *Annals of Surgery*, vol. 67, p. 442.

THE FUNCTION OF THE ADRENAL GLANDS AND ITS RELATION TO CONCENTRATION OF HYDROGEN IONS.*

BY

ROBERT McCARRISON, M.D., F.R.C.P.,

LIEUTENANT-COLONEL, INDIAN MEDICAL SERVICE; IN CHARGE OF THE DEFICIENCY DISEASES INQUIRY, INDIAN RESEARCH FUND ASSOCIATION.

(From the Pasteur Institute of Southern India, Coonoor.)

THE object of this research was to inquire further into the causation of the adrenal hypertrophy occurring in inanition and in avitaminosis.¹ This hypertrophy is accompanied by an increased epinephrin content of the glands,¹ and is due, in the avitaminosis of birds, to the absence of vitamins A and B from the food. It is associated also, as shown by Cramer,² with an almost complete disappearance of lipoids from the adrenal cortex. The enlargement rapidly reverts to a more normal state when the missing vitamins are supplied. The question as to why hypertrophy of the adrenal glands should occur under conditions that give rise to greater or lesser degrees of atrophy of all other organs (the pituitary body in males excepted)¹ is of fundamental importance both in relation to the disorders of nutrition in which it is found and to the function of the adrenal bodies themselves. The facts suggest some purpose underlying their enlargement; some purpose, also, in their increased content of epinephrin. It was thought that it might be related to the increased concentration of hydrogen ions that occurs in avitaminosis. Recently Kato,³ Takahira,⁴ and others have drawn attention to the increased hydrogen ion concentration of nerves, spinal cord, heart, and blood vessels in polynuritis avium. I have confirmed this observation in so far as it relates to the heart, and found also an increase of PH concentration in pectoral muscle. In a few cases of polynuritis columbarum accompanied with effusion into the pericardial sac or with oedema of the tissues, the dropsical fluid has been well on the acid side of neutrality—pericardial effusion, for example, having a PH of approximately 6.5.

Experiments were accordingly undertaken to ascertain the effect of changes in concentration of hydrogen ions on the action of commercial adrenaline hydrochloride and of the active principle of the adrenal medulla—epinephrin—in various media.

Enucleated eyes of the toad (*Bufo melanostictus*) were employed for the purpose; in all 1,300 were used. Each test on one eye was controlled by the other eye of the same animal. It has been stated that while adrenaline causes mydriasis of the enucleated frog's eye, it does not do so in the enucleated toad's eye. So far as *Bufo melanostictus* is concerned this is not the case. It has long been known that, by its action in stimulating the dilator mechanism of the iris, adrenaline causes mydriasis; but, so far as I can find, no

reference is made in the literature to its further and, as I believe, more important action of sensitizing the enucleated eye in such a way that the iris responds more readily to the normal stimulus of light through its maximum range of action. This sensitivity of the toad's iris to the stimulus of light, when under the influence of adrenaline hydrochloride or of epinephrin, was utilized as a means of determining the effect upon the action of these substances of changes in concentration of hydrogen ions in various media. PH indicator tablets ("A. and H.") were used throughout; the PH values are therefore approximate.

The observations made in the course of the inquiry are enumerated below; the reader is referred to the full paper for details regarding them.

1. There is in the eye of *Bufo melanostictus* a peripheral mechanism which can act independently of the nerve centres. It is responsive to the stimulus of light within a limited range—25 per cent. dilatation in the dark to slit-like contraction on exposure to light—provided the eye be preserved in media of suitable composition and suitable PH concentration. In such it retains a gradually waning sensitivity for a comparatively short period—approximately two hours.

2. This mechanism can be so sensitized by adrenaline hydrochloride or

by epinephrin that, under appropriate conditions, the iris will respond with enhanced sensitiveness to the stimulus of light through its maximum range of action. It retains its enhanced sensitivity for prolonged periods—three to eight hours—and in exceptional cases for even longer periods. This effect of adrenaline and of epinephrin is spoken of as "the adrenaline-iris-light-sensitivity reaction."

FIG. 1.—Showing the effect on the action of adrenaline hydrochloride on the iris of the enucleated eye of adding increasing quantities of N/10 HCl to Ringer's solution containing 0.02 c.c. of the commercial solution of adrenaline (1 in 1,000). As the PH of the medium falls from alkalinity towards neutrality the curve of maximum dilatation of the pupils (shown as a thick black line) gradually heightens, and the range of action of the irides increases (shown as vertical continued lines falling from the points of maximum dilatation to points of maximum contraction). The curve of maximum dilatation and the ranges of action of the irides of control eyes subjected to the influence of the same dose of adrenaline, but without the addition of increasing amounts of N/10 HCl, are shown in dotted lines. The approximate initial and final PH in the tubes to which HCl was added are shown at the top of the figure. Initial PH of control tubes was approximately 8. It will be noted that under the influence of the metabolic activities of the eye the PH falls towards neutrality during the course of the experiment (thirty minutes).

FIG. 2.—Showing the effect on the action of adrenaline hydrochloride of adding increasing quantities of N/10 HCl to normal saline solution containing 0.02 c.c. of the commercial solution of adrenaline (1 in 1,000). As the acidity increases the curve of maximum dilatation and the range of action of the irides drop precipitately until the critical point of acidity is reached at 0.03 c.c. N/10 HCl. The lesser degrees of acidity (0.01 and 0.02 N/10 HCl) enhance the action of adrenaline on the pupil of the enucleated eye; greater degrees (0.03 to 0.5 N/10 HCl) inhibit its action; greater degrees still enhance it again, while the irides tend to be fixed in the position of mydriasis. The Gulf of inhibition is wider in normal saline than in serum (compare Fig. 3). Approximate initial and final PH in acid tubes are shown at the top of the figure; initial PH of control tubes was approximately 7. It will be noted that under the influence of the metabolic activity of the eyes the PH in the acid tubes rises towards neutrality. Experimental eyes, uninterrupted lines; controls, without acid, dotted lines. Duration of observation, thirty minutes.

* Abstract of Twelfth Report to the Indian Research Fund Association on the Pathogenesis of Deficiency Disease. The full paper will appear in an early number of the *Indian Journal of Medical Research*.

It is markedly influenced by temperature conditions—heat inhibiting it, cold enhancing it.

3. The action of adrenaline hydrochloride and of epinephrin is dependent in some measure on the composition of the media in which the eye is contained: it is greatest in fresh serum and normal saline solution, least in Ringer's solution. Compare "controls" in Figs. 1, 2, 3, 5, and 6.

4. The action of adrenaline hydrochloride and of epinephrin is intimately correlated with the concentration of hydrogen ions in the medium containing the eye:

(a) Slight increases in acidity enhance the action of small doses of adrenaline hydrochloride or of epinephrin; greater increases of acidity retard it; greater increases still tend to fix the pupil in the mydriatic position. (Figs. 2 and 3.)

(b) As the medium approaches neutrality from alkalinity the range of action of the irides, under the influence of adrenaline hydrochloride or of epinephrin, increases until at the neutral point they respond to the stimulus of light through a wide range of action. (Fig. 1.)

(c) As the medium departs from neutrality towards acidity the range of action of the irides, under the influence of adrenaline hydrochloride or of epinephrin, diminishes until a point is reached—"the critical point of acidity"—at which their action is completely inhibited. (Figs. 2, 3, and 5.)

(d) This point is attained when 0.03 to 0.04 c.cm. N/10 HCl is added to 10 c.cm. of serum containing 0.02 c.cm. commercial adrenaline solution (1 in 1,000)* or 25 mg. of emulsion of guinea-pig's adrenals (equivalent to approximately 0.013 mg. of epinephrin). (Figs. 3 and 5.)

(e) Epinephrin, in appropriate dosage in normal saline and Ringer's solution, exerts its optimum effect within a range of pH of approximately 7.4 to 6.8; above or below these limits its action is inhibited.

5. By increasing the concentration of adrenaline hydrochloride or of epinephrin in proportion to the increase in acidity the gulf of inhibition can be bridged. (Figs. 3 and 4.) In order, for example, that the same effect may be produced by adrenaline hydrochloride in 10 c.cm. of sheep's serum, containing 0.04 c.cm. N/10 HCl, as is produced in 10 c.cm. neutral serum three times the amount of adrenaline is required. (Fig. 4.)

6. The influence exerted on the action of epinephrin and of adrenaline by increased concentration of hydrogen ions is dependent on the quantity of epinephrin or of adrenaline hydrochloride present in the medium; while lesser degrees of acidity enhance the effect of the smallest dose of these substances that exerts any action whatever upon the eye, the

effect of larger doses may be retarded by the same degrees of acidity. (Figs. 5 and 6.) The maintenance of maximal functional activity by the iris of the enucleated toad's eye demands accurate adjustment between the quantity of epinephrin and the concentration of hydrogen ions.

7. The cortex of the adrenal glands, when associated in its action with adrenaline hydrochloride or with epinephrin, possesses the property of aiding the eye to bring the medium in which it is contained towards neutrality. This property may be lost by, or be greatly reduced in, the adrenal glands of birds suffering from polyneuritis columbarum. Its loss may possibly be correlated with the loss of cortical lipoids in this condition, and with the loss of lipoids from the blood in human beri-beri. Not only, therefore, is the adrenal medulla intimately related in its function to the concentration of hydrogen ions in the medium through which it acts, but the adrenal gland as a whole contributes its share to the regulation of the neutrality of the medium.

Figs. 5 and 6.—Showing (a) The effect of the lesser degrees of acidity—0.01 and 0.02 N/10 HCl in 10 c.cm. sheep's serum—in enhancing the action of approximately 0.013 mg. of epinephrin (from guinea-pig) on the irides of enucleated toad's eyes; (b) Effects on experimental eyes shown in uninterupted lines; on control eyes, without acid, in dotted lines. (c) The effect of the same degrees of acidity in retarding the action of a larger dose of epinephrin—approximately 0.017 mg. (Fig. 6). In Fig. 5 the critical point of acidity is shown at 0.03 c.cm. N/10 HCl. Duration of observation, thirty minutes.

8. The serum of birds suffering from polyneuritis columbarum enhances the action on the enucleated toad's eye of minute doses of adrenaline hydrochloride; this action, interpreted in the light of the above results, indicates increased acidity of their serums.

9. The pericardial effusion from birds suffering from polyneuritis columbarum (pH approximately 6.5) retards the action on the enucleated toad's eye of minute doses of epinephrin (healthy pigeon's adrenal emulsion); this action, interpreted in the light of the above results, indicates that such effusions have reached "the critical point of acidity" at which the action of epinephrin is inhibited.

Conclusions.

1. The active principle of the adrenal medulla maintains and enhances the sensitivity of, rather than stimulates, the myoneural junctions of the true sympathetic terminals of the enucleated toad's eye, so that their response to the stimulus of light is more sensitive and their sensitivity is longer retained.

2. If this sensitivity is to be sustained and optimum function of the iris is to be maintained in media on the acid side of neutrality, the concentration of epinephrin must be proportionate to the concentration of hydrogen ions in the medium.

3. The observations recorded in this paper provide evidence that: (a) The enlargement—with increased epinephrin content—of the adrenal glands in inanition and in avitaminosis may be correlated with the condition of acidosis associated with these states. Its occurrence, for the most part, during the terminal phases of avitaminosis, its association with marked respiratory disturbances,¹ with oxygen-want,¹ with falling body temperature,¹ and with interference with oxygenation, and its rapid disappearance on the provision of the missing vitamins, suggest that it is an emergency effort on the part of the adrenal glands. (b) The attempted exercise of an emergency function by the adrenal glands may be expected to occur in all conditions of alkalosis or of acidosis.

REFERENCES.

- 1 BRITISH MEDICAL JOURNAL, February 15th, 1919. *Studies in Deficiency Disease*, London, 1921.
- 2 *Proc. Phys. Soc.*, 1920 (May 15th). *Journ. Phys.*, liv. *Brit. Journ. Exper. Path.*, 1920 (August).
- 3 Kitasato: *Arch. Exper. Med.*, 1921, iv, No. 3, pp. 207-216.
- 4 *Keio Igaku (Keio Med. Journ.)*, 1921, Octo. I, No. 10.

* As adrenaline hydrochloride rapidly deteriorates in India on exposure to air this concentration of adrenaline will probably be found too high where fresher stocks of the drug are available. All my observations were made with stocks that had been in India for several years. It is to be emphasized that the effects of hydrogen ion concentration on the action of adrenaline or of epinephrin are demonstrable with such minimal amounts of these substances as exert any action whatever upon the enucleated eye.—R. McC.