

STUDIES ON THE FUNCTIONAL ACTIVITY OF THE
ADRENAL CORTEX IN SOME INFECTIOUS
DISEASES.

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Diaz-Rubio (1946) observed that systemic infections caused a condition of relative corticoid activity. Penner and Bernheim (1942) noted adrenal insufficiency in patients suffering from bacillary dysentery. Beneficial effects of the administration of corticoids in the treatment of acute infections, such as malaria (Bahtiyar, 1947), pneumonia (Perla *et al.*, 1940), meningococemia (Harrel, 1947), typhoid fever (Turner *et al.*, 1949) and diphtheria (Grenet *et al.*, 1943) have been reported. Langccker *et al.*, (1933) observed that resistance of animals to streptococcal and spotted-lever infections could be raised by the administration of adrenal-cortical extracts. Enlargement of the adrenal cortex with hyperemia, loss of sudanophilic granules and sometimes necrosis and haemorrhage were observed in cases of yellow fever (Magarinos-Torres *et al.*, 1928), spotted fever (Wajnapel, 1947), measles (Macciotta, 1931), scarlet fever (Bazgan *et al.*, 1932), generalized purulent peritonitis (Katsuragi, 1936), typhoid fever (Martinez *et al.*, 1948) and a variety of other infections in man (Pinchot *et al.*, 1949). Clinical studies regarding adreno-cortical activity in diseased conditions reported so far are not sufficient to evaluate the derangements of adrenals under these conditions. It was, therefore, thought desirable to study the adreno-cortical activity in patients suffering from various common infectious diseases with a view to use rationally adrenocortical extracts in the treatment of these diseases.

After the injection of ACTH, epinephrine and 11-oxysteroids there is a profound fall in the circulating eosinophils (Thorn *et al.*, 1947). This led to the development of a 4-hour eosinopenic response test to parenteral epinephrine to

evaluate the functional integrity of pituitary adrenal axis. A 50 per cent fall in the circulating eosinophils indicates normal adreno-cortical function.

The adrenal cortex is related to the metabolism of sodium and potassium in the body. After removal of adrenals there is a decreased sodium content and an increased potassium content of blood (Baumann and Kurland, 1927). Sodium chloride has a beneficial effect in adrenalectomized animals (Hartman *et al.*, 1927). Ascorbic acid is necessary for the synthesis of the adrenal cortical hormone (Long, 1947) and a diminution of the ascorbic-acid content of the blood might, therefore, lead to the deficient function of the adrenal cortex. In the present investigation, therefore, the eosinopenic response, 4 hours after the injection of 0.3 c.c. of a 1 in 1,000 solution of epinephrine hydrochloride, was studied and serum sodium and potassium and blood ascorbic acid were estimated in patients suffering from pneumonia, meningococcal meningitis, tubercular meningitis, typhoid fever and tetanus during the acute phase of those diseases in order to determine the adreno-cortical activity. The above investigations were also carried out in healthy adult subjects belonging to the same economic and social status as the patients selected for the study for comparison.

MATERIALS AND METHODS.

Four-hour epinephrine test.—Blood was collected from the arm vein and transferred into tubes containing known amounts of mixed oxalate and also in dry tubes for the separation of serum. 0.3 c.c. of a 1/1,000 epinephrine hydrochloride solution was injected subcutaneously early in the morning before any food was administered. Four hours after the injection, blood was again drawn from the opposite arm vein and collected in oxalated tubes. Eosinophils were counted in oxalated blood samples, collected before and after the administration of epinephrine, after staining them with phloxine-methylene blue stain by the method of Randolph (1944) and percentage reduction in the circulating eosinophils was calculated. The results are given in Table I:—

TABLE I.

Lowering of eosinophil count of blood (per cent) after subcutaneous injection of 0.3 c.c. epinephrine hydrochloride solution (1/1,000) in normal persons and in patients suffering from diseases.

Subjects.	Eosinopenic response, per cent.	t
Normal (28)	50.8 ± 0.8*	...
Meningococcal meningitis (25)	25.6 ± 2.8	10.0
Tetanus (25)	26.7 ± 2.2	14.2
Pneumonia (22)	35.4 ± 2.0	11.1
Typhoid fever (23)	30.7 ± 3.1	8.0
Tubercular meningitis (17)	31.6 ± 3.3	8.3

*Mean ± standard error.

Figures in parenthesis indicate the number of persons studied.

Estimation of serum sodium and potassium.—One c.c. of non-haemolysed serum was treated with 9 c.c. of a 10 per cent solution of trichloro-acetic acid. The mixture was shaken, filtered and an aliquot of the filtrate was diluted 100 times with glass-distilled water. The diluted filtrate was taken in a small beaker and atomized by compressed air in a Zeiss flame photometer and conducted to a pure-acetylene gas burner where the mixture was ignited. By the use of filters suitable for the estimation of sodium or potassium as the case may be, the emitted light was allowed to excite the photoelectric cell. The response of the photo-electric cell was measured in the instrument when the flame was steady. The percentages of sodium or potassium were determined from the calibration charts prepared by the use of standard solutions of sodium or potassium chloride in 10 per cent trichloro-acetic acid under identical conditions. The results are given in Table II:—

TABLE II.

Sodium and potassium contents of serum of normal persons and of patients suffering from various diseases (mg. per 100 c.c. serum).

Subjects.	Serum sodium.	Serum potassium.	t	
			Sodium.	Potassium.
Normal (28)	326.7 ± 1.1	19.0 ± 0.1
Meningococcal meningitis (26) ...	295.9 ± 2.7	22.7 ± 1.1	11.0	2.8
Tetanus (26)	301.5 ± 2.4	21.5 ± 0.6	9.6	2.6
Pneumonia (22)	293.6 ± 3.3	20.6 ± 0.7	9.6	1.6†
Typhoid fever (23)	303.3 ± 1.9	20.0 ± 1.4	10.7	0.7†
Tubercular meningitis (17)	287.1 ± 3.3	20.5 ± 0.5	11.1	1.6†

† Except these values, other values of t are highly significant.
 Figures in parenthesis indicate the number of persons studied.

Estimation of ascorbic acid.—Immediately the blood was withdrawn from the vein it was laked and deproteinized with a molar solution of sulfosalicylic acid and ascorbic acid in the protein free filtrate was estimated by titration with a standardized solution of 2, 6-dichlorophenol indophenol taking all the precautions as reported by Banerjee and Belavady (1953). The results are given in Table III.

RESULTS.

There was 59.8 per cent lowering of the circulating eosinophils 4 hours after a subcutaneous injection of 0.3 c.c. of a 1/1,000 solution of epinephrine hydrochloride in normal persons. In patients suffering from the different infectious diseases the eosinopenic response varied between 25.6 and 35.4 per cent.

Serum sodium and potassium values in normal persons were, respectively, 326.7 and 19.0 mg. per 100 c.c. serum. In all the diseases studied significant

lowering of the serum sodium values was observed. Serum-potassium values increased significantly in patients suffering from meningococcal meningitis and tetanus but in patients suffering from other diseases the increase was not considerable.

Blood ascorbic acid level in normal persons was 0.87 mg. per 100 c.c. blood. This value considerably diminished in all the patients investigated,

TABLE III.

Blood ascorbic acid level in normal subjects and in patients suffering from various diseases, (mg. per 100 c.c. blood).

Subjects.	Blood ascorbic acid.	t
Normal (28)	0.87 ± 0.02	...
Meningococcal meningitis (26)	0.38 ± 0.02	17.5
Tetanus (26)	0.43 ± 0.03	13.3
Pneumonia (22)	0.39 ± 0.01	20.0
Typhoid fever (23)	0.68 ± 0.03	16.4
Tubercular meningitis (17)	0.50 ± 0.03	12.3

Figures in parenthesis indicate the number of persons studied.

DISCUSSION.

Injection of epinephrine stimulates the anterior lobe of the pituitary gland through the portal hypothalamico hypophyseal circulation whereby the gland secretes all the hormones including ACTH which in turn stimulates the adrenal cortex. One of the effects of adrenocortical hormone is the diminution in the number of circulating eosinophils. In all the patients suffering from various infectious diseases studied, the fall in the circulating eosinophils after epinephrine, was significantly low as compared with the response in normal subjects. The lowered eosinopenic response might be due to lowered secretion of ACTH with epinephrine due to hypo-activity of the anterior lobe of the pituitary gland or if its function was normal, to the decreased activity of the adrenal cortex whereby it was not responsive fully to the ACTH secreted by the pituitary gland. Whatever might be the mechanism, the resultant effect would be the diminished secretion of the adrenocortical hormone in the diseases investigated. The decreased serum-sodium and increased serum-potassium levels in these patients also indicate hypo-activity of the adrenal cortex. The diminished ascorbic-acid content of the blood of these patients, possibly due to increased katabolism of ascorbic acid, might, lead to the diminished ascorbic-acid content of the adrenal gland. As ascorbic acid is considered to be involved in the synthesis of adrenal cortical hormones by the adrenal gland the diminished ascorbic-acid content of the blood might be the cause of deficient secretion of the hormones of the adrenal cortex.

Injections of adreno-cortical extracts in patients suffering from acute infectious diseases may, therefore, be helpful in the treatment of these patients.

SUMMARY.

1. Eosinopenic response 4 hours after injection of epinephrine was studied in 28 normal subjects, in 25 patients suffering from meningococcal meningitis, in 25 cases of tetanus, in 17 cases of tubercular meningitis, in 23 cases of typhoid fever and in 22 cases of pneumonia. While in normal subjects the mean fall in the circulating eosinophils was 59.8 per cent, the average eosinopenic response in other diseases varied between 25.6 and 35.4 per cent.

2. Serum sodium and potassium and ascorbic acid contents of the whole blood were estimated in normal persons and in patients suffering from various infectious diseases mentioned above. There was a significant decrease in the serum-sodium value and blood ascorbic acid level and an increase in the serum potassium contents in all the patients investigated.

3. The above investigations indicated hypo-activity of the adrenal cortex in the diseased conditions studied.

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