Jug douching effects considerable economies in cotton-wool, antiseptics, and the preparation of sterile water; it is simpler to carry out and more comfortable to the patients.

We wish to record our thanks to Mr. N. W. Please for constant advice in planning and carrying out this trial; to Professor Wilson Smith and Dr. Joan Stokes for invaluable help with the bacteriological aspects of the study; to Sister Curtis, who supervised the Phase I trial; to Mr. J. D. S. Flew for permission to include his patients in the trial; and to Professor W. C. W. Nixon, who suggested this study, for his guidance and encouragement.

SHOCK IN PHAEOCHROMOCYTOMA TREATED WITH NORADRENALINE

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The administration of noradrenaline to a patient suffering from phaeochromocytoma seems rather absurd outside surgical practice. Yet this treatment is the logical measure in those rare cases where "spontaneous" hypertensive crises are succeeded by severe shock.

As this treatment has not hitherto been tried the following case is of interest.

Case History

A 77-year-old widow was referred to the Hospital of "The Old People's Town" on April 15, 1953. Until this date blood-pressure values above 170/90 had never been registered.

She was rather adipose and showed signs of cerebral arteriosclerosis, enlargement of the heart to the left, and slight pulmonary hypostases. The blood pressure was 160/110 mm. Hg. Electrocardiographic findings were normal. Roborant treatment had a gratifying effect, and she was mostly up and about until April 25, 1955, when bilateral pneumonia, later complicated by deep phlebitis in the left leg, necessitated bed rest.

At 5 p.m. on May 22 she suddenly felt unwell, was pale and perspiring, dyspnoeic, and anxious, and complained of thoracic pains; her temperature rose to 100.4° F. (38° C.), and pulse rate to 100; the blood pressure was 130/85. On account of auscultatory findings a pulmonary embolus was diagnosed and anticoagulants were given.

At 6.30 p.m. the symptoms became acute, and severe precordial pains together with excitement and shivers set in. Her pulse rate was 120; blood pressure 180/100 (see Chart). The heart sounds were inaudible. Oxygen, procaine penicillin, and intravenous and oral digitalis were administered, but the condition steadily worsened, and at 9.30 p.m. a severe circulatory collapse was manifest: She was cold and perspiring, pale and remote; the palpated blood pressure was 60. As the blood pressure could not be measured by auscultation, only the palpated blood pressure is recorded.

Infusion with L-noradrenaline, 4 mg. in 1 litre of 5% glucose, was instituted, the drip rate being about 30 a minute (about 2 ml. a minute). The patient responded only slowly; but an increase in the noradrenaline concentration (see Chart) fixed the blood pressure at 120, and the noradrenaline concentration could be reduced the following day.

At 5 a.m. on May 25 she was suddenly taken ill with heavy shivers, polypnoea, and a hurried, unequal, but regular pulse at a rate of about 150. The blood pressure was 160 mm. Hg, rising steeply within a few seconds to 200. The noradrenaline infusion was stopped immediately, but the blood pressure did not fall until 30 minutes later, when the alarming symptoms disappeared. At 5.47 a.m. the blood pressure was 90 and the patient showed symptoms of imminent shock; the noradrenaline infusion was resumed, but with no avail until the noradrenaline concentration had been increased.

At 3.40 a.m. on May 26 another spontaneous steep rise in blood pressure occurred accompanied by the same symptoms as before, and the drip had to be stopped for 20 minutes.

This was the first occasion on which the diagnosis of a phaeochromocytoma was suggested, and surmise turned into belief when two typical paroxysms occurred within the next few days. On May 30—nine hours after the last of these attacks—the noradrenaline could be discontinued.

Within the ensuing five days six crises occurred: when most severe they were characterized by shivers so violent that the bed shook; the pulse rate, temperature, and blood pressure rose steeply. There was a pronounced general restlessness, and the patient became voluble, mentally confused, and at periods unconscious. At the onset of the paroxysms she became cold, pale, and cyanotic, but when the attack subsided her complexion became reddish and flushed, and perspiration was profuse. The crises lasted from 30 minutes up to two and a half hours, and were followed by extreme prostration.

During a paroxysm on June 1 a phentolamine ("rogitine") test was carried out. Within a few minutes 5 mg. of intravenous phentolamine caused a fall in blood pressure from 205 to 120 followed by a steep rise up to 185, after which the attack finally subsided.

A sample of venous blood taken during a paroxysm on June 3—that is, four days after noradrenaline had been discontinued—contained 19 μg. of noradrenaline + adrenaline per litre. (Our thanks are due to Dr. Alf Lund, who made the analysis.) The technique applied (Lund, 1950) gives normal values less than 2 μg. per litre (Lund, 1952, 1956).

Simultaneously with a paroxysm on June 4, a pronounced tachycardia occurred; the pulse was often too hurried to be counted, and the blood pressure fell from 170 to 70; every symptom of a severe shock was apparent. As "cedilanid" (lanatoside C) and quinidine had proved of no avail, and since the shock might have been due to the rapid heart action, 500 mg. of intravenous procaine amide was administered; the result was a fall in pulse rate and, unfortunately, also in blood pressure.

The shock was now so profound that the patient was considered to be beyond treatment; however, the noradrenaline infusion was resumed with increasing concentrations. A rise in blood pressure followed, but recurrent symptoms of incipient shock necessitated a further increase in the noradrenaline concentration and noradrenaline proved indispensable for 24 days.

During the second period of noradrenaline treatment no *typical* paroxysms occurred until June 28, when a hypertensive crisis demanded an interruption of the infusion. When the paroxysm subsided the blood pressure remained normal, and so noradrenaline was definitely abandoned.

From May 30 cortisone and/or corticotrophin were administered in order to improve the patient's general condition; also, nine blood transfusions were given. Severe hallucinations, even actual psychoses, which failed to respond to other therapy, had to be treated by chlorpromazine ("largactil").

From June 5 all peroral administration of drugs, vitamins, proteins, and nutriment (mostly saccharose, cream, and stout) was by stomach tube, which was retained for two and a half months.

At first the polyethylene catheter was repeatedly inserted into new arm veins because of phlebitis or clotting; when the veins were difficult to locate this was an acute problem. After the institution of intermittent heat treatment of the arm, and particularly after 1,500 units of heparin had been added to each litre of infusion fluid, the constant intravenous therapy presented no further problems.

After June 30 operation was under consideration, but had to be abandoned, since the patient sank rapidly and a left-sided pleural empyema occurred. The establishment of pleural drainage (performed by Mr. K. H. Köster) and irrigation of the empyema cavity resulted in typical hypertensive crises—the last to occur. When, on August 13, treatment of the empyema was finished, the patient recovered steadily and at the time of writing she was up and about. Her blood pressure ranged around 130/80, the pulse rate around 80, and there was no indication that she should be the carrier of a "veritable pharmacological bomb" (Aranow, 1952).

Relevant Laboratory Findings

Haemoglobin (100% = 14.8 g. per 100 ml.): 83%, 56%, 79%; colour index and differential count, normal. Non-resting blood-sugar, not above 156 mg. per 100 ml. Urinalysis; generally, + protein; repeatedly, − blood; − sugar. Blood urea, 48, 167, 88, 255, 35 mg. per 100 ml. Electrocardiogram: normal findings until after the paroxysm on May 22; later slightly depressed ST I, rather pronounced Q III, slightly elevated ST III, and negative slightly coronary T III. These changes had disappeared on May 31. Besides some digitalis effect, a left-axis deviation had developed and persisted. Unfortunately, no electrocardiograms were taken during the periods of fluctuating heart rate.

Ophthalmological findings:—June 24: narrow arteries, irregularly calibrated. July 4: thin arteries with uniform calibres; no venous stasis. Normal branch angles.

Radiography of thorax (supine position) (July 9): moderate enlargement of the heart and the great vessels; a shadow obscured the left lung, probably due to pleural exudate. Intravenous pyelography with tomography of the kidneys (July 9): pyelogram blurred by intestinal gases. Pelves and calices, presumably normal findings. No abnormal soft-tissue shadows at the site of the adrenals.

Intravenous pyelography with tomography (May, 1957) showed nothing abnormal except a rather low position of the right kidney.

December, 1955: All laboratory findings normal, including the basal metabolic rate, and adrenaline + noradrenaline in the urine.

Comment

A 77-year-old woman developed symptoms which were diagnosed as a pulmonary embolus and were followed by a severe vascular collapse. During the subsequent noradrenaline treatment repeated hypertensive paroxysms occurred, suggesting the diagnosis of phaeochromocytoma. This diagnosis was confirmed by the demonstration of increased content of adrenaline-noradrenaline in venous blood sampled during a paroxysm four days after noradrenaline was abandoned.

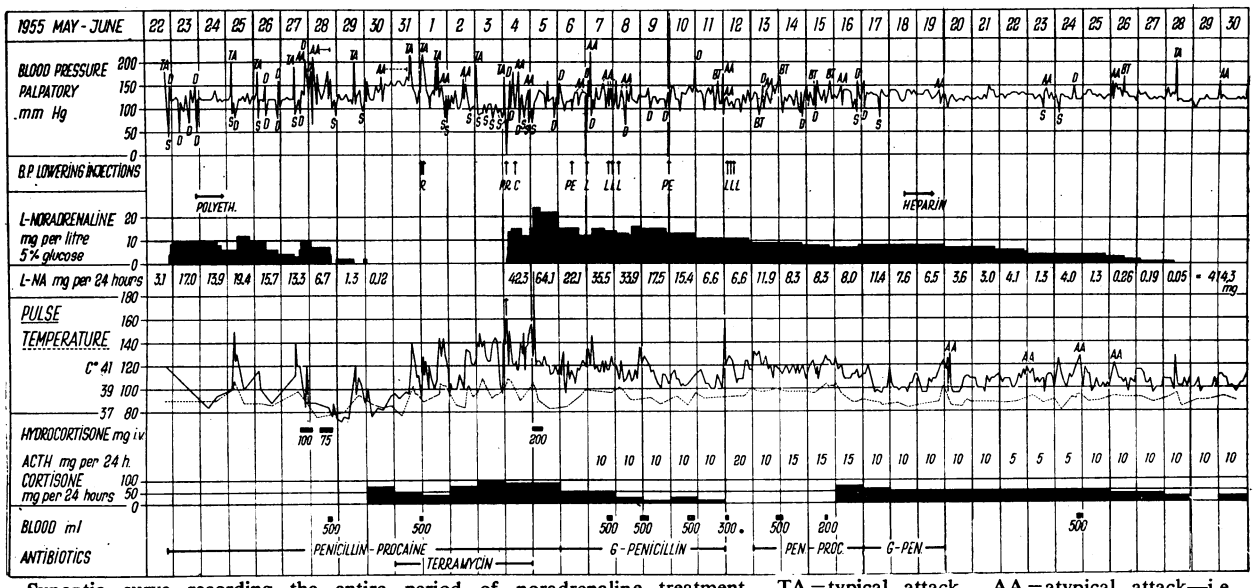
Hypertensive crises occurred almost daily, and one of these was followed by another severe shock requiring the noradrenaline treatment to be resumed for 24 days.

An exploratory operation could not be performed because of the patient's poor condition, which had further deteriorated on account of a pleural empyema. After her recovery from the latter she improved gradually and no hypertensive paroxysms have occurred since.

Discussion

Symptoms in paroxysmal forms of phaeochromocytoma are often so characteristic that the clinical diagnosis can be made without any hesitancy. The final proof can be obtained by operation, or by demonstration of increased noradrenaline-adrenaline contents in the urine or in the blood.

In the present case a pulmonary embolus occurred at 5 p.m. on May 22, followed by an attack which, though not



Synoptic curve recording the entire period of noradrenaline treatment. TA=typical attack. AA=atypical attack—i.e., paroxysms lacking one or more of the classical symptoms. S=spontaneous shock. D(=drop)=blood-pressure fluctuations released by unwanted variations in the noradrenaline supply caused by clotting in the catheter, venous spasms, leakage, difficulties of regulation during spontaneous blood-pressure fluctuations. BT=bronchial toiletage causing either a fall or a rise in blood pressure.

Discontinuation of the drip for less than one hour (involuntarily or during paroxysms) has been impossible to record in the noradrenaline diagram.

The following drugs which may have induced hypotension are recorded below the blood-pressure curve: C=cedilanid; L=largactil; PE=pethidine; PR=procaine amide; R=rogitine; Polyeth=polyethylene catheter in vein.

For long periods the blood pressure was measured once a minute; in less critical periods once every 5 to 10 minutes. The curve is based on a selection of the most characteristic readings.

The noradrenaline dosage is given as (1) noradrenaline concentration in mg. per litre of 5% glucose; (2) total 24-hour dose in mg. (the estimated error is on the last figure). A more relevant curve would show the one-hourly noradrenaline dose (or rather the one-minute dose), but the range of such a curve would be 5,761 to 4 μg. per hour.

The sparse measurements of the temperature are all given in the curve. The pulse curve is based on chosen characteristic values.

realized until several days later, showed several clinically characteristic features of a phaeochromocytoma paroxysm, including shivers, restlessness, and rising blood pressure (cf. beginning of Chart). The subsequent shock very nearly became fatal, but noradrenaline treatment was started, and the clinical condition improved.

The hypertensive crises within the next few days suggested the diagnosis of phaeochromocytoma. An overdosage of noradrenaline could not be the explanation of the sudden and violent increase in blood pressure, as the hypertension lasted for about 60 minutes after closure of the drip; between the crises, withdrawal of noradrenaline was invariably followed by immediate shock. Furthermore, the paroxysms continued in rapid succession when the noradrenaline was stopped on May 30.

A phentolamine test was positive but, unfortunately, was without much diagnostic value, as an increased blood urea (95–130 mg. per 100 ml.), and the administration of certain drugs (barbiturates and pethidine) within the preceding 24 hours, are known occasionally to cause false-positive depressor reactions (Hightower, 1955).

A blood analysis revealed an increase in the content of pressor amines—19 μg. of noradrenaline + adrenaline per litre—and thus established the diagnosis of a phaeochromocytoma; further pharmacological tests were therefore considered superfluous and massage of the adrenal areas was too dangerous. The normal content of noradrenaline + adrenaline in venous blood is less than 2 μg. per litre (Lund, 1952, 1956).

By the same technique von Euler (1952) found moderately increased values in some patients with essential hypertension, and Manger *et al.* (1954) found, with a different and less specific fluorimetric method, increased values in a few patients with uraemia (blood urea in the present case was 130–167 mg. per 100 ml.); yet values as high as 19 μg. have never been encountered except in patients with phaeochromocytoma. Blood for analysis was sampled four days after abandonment of the noradrenaline, thus precluding the administered pressor hormone as contributing to the high blood concentration : elimination of noradrenaline is almost instantaneous.

The very high content of pressor hormones in the blood during a paroxysm seems inconsistent with diagnoses other than phaeochromocytoma, and the hypertensive attacks often conformed to classical descriptions of the typical crises in phaeochromocytoma : a steep rise in blood pressure, pulse rate, and temperature, violent shivers, and cold, pale, cyanotic skin. When the paroxysm subsided the blood pressure decreased rapidly, the patient became warm, flushed, and profusely perspiring; the pulse rate and temperature fell more slowly.

Noradrenaline treatment of our patient was instituted at a time when her condition was highly critical and the blood pressure rapidly falling. At that time a pulmonary embolus was assumed to be the cause of the shock. When a phaeochromocytoma was surmised, and later verified, we were first inclined to consider the treatment as "carrying coals to Newcastle." But the treatment proved indispensable, and the patient would have succumbed without it. The total amount of noradrenaline administered was 414.3 mg.

Conclusion and Summary

Only a few records are available of treatment of shock induced by "spontaneous" crises in phaeochromocytoma, as the occurrence is rare. Occasionally adrenaline injections have been used, but only with transient effect—for example, Evans (1937)—but noradrenaline was never given in such cases.

In the case of phaeochromocytoma here reported the diagnosis was confirmed through an analysis of the blood sampled during a hypertensive crisis. On two occasions these attacks were followed by severe shocks, which were successfully treated with 414.3 mg. of L-noradrenaline during 7 and 24 days. Noradrenaline should always be tried in similar emergencies.

Our thanks are due to Dr. Torben Geill, chief physician of The Old People's Town, for his readiness always to assist us in the solution of the therapeutic problems, and his kindness in placing the facilities of his department at our disposal. We are grateful to Mr. M. Andreassen, senior surgeon, the State Hospital, Department D, Copenhagen, for his assistance and advice during the period when an operation was considered. We are indebted to colleagues and technicians for their assistance during several months.

The chart was drawn by Mr. Preben Saggau.

Special thanks are due to the nurses who tended the patient throughout days and nights for several months. Without their never-failing vigilance this case history might have had quite a different ending. The nurses were: Miss Solveig Pors, Miss Irma Klein, Miss Marie Louise Fugl Svendsen, Miss Kirsten Vestergaard, and Mrs. Rigmor Grønlund.

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TUBERCULOSIS IN MAN, DOG, AND CAT

BY

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Tuberculosis in the last few years has almost everywhere been associated with a falling death and notification rate and a reduced morbidity, so that now its eradication is regarded as practical policy. With this amelioration of the situation it has become reasonable to study aspects of the disease which would have been regarded as unimportant a decade ago, and it was therefore thought worth while to find out if tuberculosis in dogs and cats was making any contribution to the general pool of infection.

References to the incidence of tuberculosis in dogs followed quickly on the recognition of *Mycobacterium tuberculosis* by Koch in 1882. Faulenborg and Plum (1935) quote Frohner, in Berlin, as noting an incidence of 0.04% in 62,500 clinical examinations between 1886 and 1895, and Eber, in Dresden, who observed an incidence of 2.75% in 400 necropsies in 1893. In the United Kingdom it was not until 1929 that Smythe recorded a rate of 0.3 to 0.4% in dogs examined clinically at the out-patient department of the Royal Veterinary College of London. Lovell and White (1940) found tuberculosis in 4.6% of 543 canine necropsies. In Glasgow in 1955 an analysis of 175 consecutive dogs, submitted for pathological examination at the University of Glasgow Veterinary Hospital over a four-months period, showed generalized tuberculosis in all organs in eight, a rate of 4.5%.