This supports the view that anergy to tuberculin in sarcoidosis is due to an absence of lymphocytes in the circulation capable of reacting to tuberculin, and also suggests that the Kveim reaction is, unlike the classical delayed hypersensitivity reaction, probably not mediated by lymphocytes.

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D. C. COWLING, M.D., F.R.A.C.P.,
D. QUAGLINO, M.D., PH.D.,
Department of Medicine, University of
Cambridge.
P. K. M. BARRETT, M.B., M.R.C.P.,
Cambridge Chest Clinic.

Part Played by Calcium in Sympathetic Stimulation

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Evidence has been published recently that calcium is a key substance for the release of the catechol amines, adrenaline and noradrenaline, from the adrenal medulla. Splanchnic nerves transmit their impulses to the adrenal medulla by releasing acetylcholine. Douglas and Rubin (1961, 1963) perfused the adrenal gland with Locke's solution, stimulated the medulla by injecting acetylcholine into the artery leading to the gland, and measured the catechol amines liberated in the adrenal vein. They found that the amount liberated depended on the amount of calcium in Locke's solution. They showed that calcium was the only cation necessary for the release, since acetylcholine was effective when the perfusing fluid contained nothing more than sucrose, dextrose, and calcium. They suggested that acetylcholine either depolarized the membrane of the adrenal medullary cells or altered its permeability, so that calcium was able to enter the cells and to release catechol amines from the granules inside them. The amount of calcium entering depended on the external concentration of calcium, and therefore the amount of catechol amines released also depended on the external concentration of calcium.

SYMPATHETIC POST-GANGLIONIC FIBRES

Burn and Rand (1959) have put forward the hypothesis that the impulse passing down the sympathetic post-ganglionic fibre releases acetylcholine and that this in turn releases noradrenaline. The question thus arose how far calcium played a similar part in the release of noradrenaline from the sympathetic fibre to that which it played in the release of catechol amines from the adrenal medulla.

In order to make observations the preparation of the rabbit ileum described by Finkleman (1930) was used, in which a loop of ileum is suspended in an isolated organ bath and stimulation is applied to the periaxillary nerves in the adjacent mesentery. This stimulation causes inhibition of the pendular movements of the ileum.

A known number of supramaximal shocks were given to the periaxillary nerves, usually at a frequency of 10/sec., and the inhibition was observed in Locke's solution or Tyrode's solution containing the normal amount of calcium, approximately 2 mM. The calcium concentration was then increased in steps, twofold, fourfold, and eightfold. The inhibition was very much greater in twice normal calcium, again very much greater in

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four times normal calcium, and more prolonged in eight times normal calcium. On reducing the calcium to normal, stimulation produced an inhibition similar to that seen at first. Thus the effect of sympathetic stimulation was increased as the calcium concentration was raised.

EXPERIMENTAL RESULTS

Effect of Calcium on Response to Noradrenaline.—The increased inhibition could be explained in two ways. It could be due to an increase in the amount of noradrenaline released, or it could be due to an increase in the response to the same amount of noradrenaline. We were able to test this by comparing the inhibition caused by stimulation with the inhibition caused by adding noradrenaline to the bath. In raising the calcium from one-third normal to normal there was a great increase in the inhibition produced by stimulation in each of seven experiments, but there was an increase in the inhibition produced by noradrenaline in only one. On the other hand, in raising calcium from normal to twice normal there was some increase in the inhibition produced by noradrenaline in six out of seven experiments. This increase, however, did not appear to be as great as the increase in the response to stimulation. The results showed that the increase in the response to stimulation as the calcium concentration was increased was mainly due, particularly in the lower ranges, to an increase in the amount of noradrenaline released.

Raising Calcium During Continuous Stimulation.—Perhaps the most significant results were obtained by raising the calcium concentration during a period of continuous stimulation. An example of this is shown in the Chart, in which stimulation at a frequency of 10/sec. was applied in a solution containing

Contractions of isolated rabbit ileum in Tyrode's solution containing 0.6 mM. calcium. Periaxillary nerves in the mesentery stimulated at 10/sec. during the horizontal line. The contractions were inhibited to about 50%. At D.S. the drum was stopped for 5 min. At the arrow the calcium concentration was raised to 1.8 mM., and the inhibition was greatly increased.

one-third of the normal calcium. This stimulation caused inhibition of the pendular movements to about half their previous size; they remained at this level while the stimulation continued, and while the drum was stopped for five minutes. At the arrow, calcium was added to the bath to bring the concentration up to normal, and the inhibition at once increased to become almost total.

Action of Nicotine.—If the sympathetic impulse first releases acetylcholine and this in turn releases noradrenaline as Burn and Rand have suggested, then the release of noradrenaline by acetylcholine should be affected by calcium in the same way as the release by sympathetic stimulation. This has not yet been fully studied, but it has been shown that nicotine, in the presence of hyoscine, causes an inhibition of the pendular movements of the ileum which increases in proportion to the concentration of calcium. It is therefore reasonably certain that acetylcholine will act in the same way, and indeed some evidence that it does so has already been obtained.

Effect of Magnesium.—Douglas and Rubin found that the addition of magnesium to Locke's solution used to perfuse the adrenal gland reduced the effect of raising the calcium. We likewise observed that the effect of additional calcium in increasing the inhibitory response to stimulation was antagonized by magnesium.

ROLE OF CALCIUM

There are two explanations of the events which lead to the release of noradrenaline at the end of the post-ganglionic fibre.

The first is that the impulse, on reaching the end of the fibre, itself creates a change in the permeability of the fibre membrane to calcium, so that calcium enters the fibre; the extent of calcium entry will depend on the external concentration. When the calcium has entered, it then liberates noradrenaline from the granules. The second explanation is that the nerve impulse first releases acetylcholine and it is this acetylcholine which causes the change in permeability of the fibre membrane to calcium, so that calcium entry can occur.

The significance of the observations is that they indicate that the effect of sympathetic stimulation depends on the concentration of calcium ions. Thus a low concentration of calcium ions in the blood may perhaps be responsible for a low arterial tone, and intravenous infusion of a substance which removes calcium ions, such as the citrate present in blood used for transfusion, may, if given rapidly, cause a fall of blood-pressure. Similarly a high concentration of calcium may be responsible for a high arterial tone.

J. H. BURN, M.D., F.R.S.,
Visiting Professor.

W. R. GIBBONS, B.SC.,
Department of Pharmacology, Washington
University, St. Louis, Mo., U.S.A.

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Medical Memoranda

Pressure Palsy of the Accessory Nerve

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The following report concerns a patient who sustained an injury to the accessory nerve as a result of an unsuccessful attempt at suicide by hanging.

CASE REPORT

A shoe-maker aged 54 who had tried to kill himself by hanging was admitted to hospital. He had been alone for 10 minutes when his wife heard his strangled breathing and rescued him. He was bleeding from the nose, pharynx, and both ears, and there were superficial haemorrhages of the subconjunctivae and skin of the head and neck above the rope burn (Fig. 1). He remained confused for about 10 hours.

There was nothing relevant in the family history. Though he was an over-protected and sickly child, his subsequent life and personality were stable. He was a moderate drinker and his past illnesses were not relevant.

Arterial hypertension was first noted when he was aged 33, and, though he had no symptoms, treatment with reserpine, 0.25 mg. thrice daily, was begun three-and-a-half months before admission. After two weeks his blood pressure was within normal limits and the dose was reduced to 0.25 mg. daily. Four weeks later he was clearly depressed, had lost weight, was sleeping poorly, and was anxious and retarded.

Physical examination after admission revealed no further abnormality. His blood-pressure was 165/105 mm. Hg, a routine urine examination was normal, the blood Wassermann reaction negative,

and radiographs of the chest and cervical spine showed no lesion. His subsequent progress did not indicate intellectual deterioration or change in personality. He had a retrograde amnesia of a few minutes' duration and could not recall events of the 10 hours of clouded consciousness. The reserpine was suspended, he was given imipramine, and had fully recovered from the depressive state eight weeks after admission.

Three weeks after admission, shortly after beginning physical work, he complained of pain in his left shoulder. On examination he complained of pain at about 70° active abduction of his left arm, and could not abduct his arm further. There was asymmetry of the shoulders due to wasting of the left trapezius and lowering of the left shoulder. The body of the scapula was rotated slightly downward and outward. There was moderate weakness of elevation of the left shoulder, but no observable difference in the power of both sterno-mastoids or any other abnormality on full neurological examination.

Electromyography carried out at three-and-a-half weeks and 12 weeks after admission recorded abnormalities that were confined to the left trapezius. The muscle rapidly recovered in bulk so that by the tenth week there was no appreciable difference between the two sides, and no difference in power. The rapidity of recovery, with all areas of the muscle recovering together, indicated a first-degree injury (Sunderland, 1951) of the accessory nerve.

DISCUSSION

Depression is not uncommon as a complication of medication with reserpine for hypertension (Jensen, 1959; Quetsch, Achor, Litin, and Faucett, 1959). The particular interest in this case is the unique paresis of the trapezius. The pain that drew attention to the lesion characteristically occurred when the patient began to do physical work (Hanford, 1933; Norden, 1946; Mead, 1952; Woodhall, 1952).