

not exceed a 48-hour week, contrasted with the low figure of 14% for machinists and munition workers. It will be seen that the advice given in the 25th Report from the Select Committee on National Expenditure (Session 1940-1) has been largely ignored. In that report (page 4) hours of work are dealt with and recommendations made. Paragraph V reads as follows: "The investigations already carried out by the Board indicate that over an extended period weekly hours of work should not exceed 60 for men and 55 for women." Applying these standards to Table VII, the percentage of workers in each group exceeding these figures can be tabulated as follows:

	Males	Females
Section A	67	40
Section B	48	20
Section C	24	7
Clerical workers	19	20
Shop employees	19	7

The subdivision of the commercial class, Group III (a), showed that 60% could be grouped under Section (y) (shop employees, etc.) and 40% under Section (x) (office workers, etc.). The conditions of employment and the risk of developing pulmonary tuberculosis in these two sections appear to be very similar. The proportion who were able to return home for their meals showed no appreciable difference, nor was there any distinction between the average housing and sleeping accommodation. The subdivision of the domestic class provided the following information: that 85% of the recorded cases were those of housewives and 15% domestic servants; that the illness of 10% of the married women showed a definite time-relation to pregnancy; and that 55 (20%) of the 270 cases recorded in the group were contacts with tuberculosis in the home.

#### Scholars and Pre-school Children

It is difficult to ascertain to what extent the number of pre-school children and scholars in Glasgow has diminished owing to evacuation during the year under review; but the number has certainly not increased, yet the number of children affected by tuberculosis has risen by over 32%. Our investigations showed that of the notified cases 24% had been contacts with open tuberculosis within the past five years, as against 18% in 1940 and 14% in 1939. Definite contact history was found in 66 of the 258 pre-school children and scholars notified, and it is possible this increase has arisen from the necessity for keeping chronic cases of phthisis at home owing to shortage of hospital beds. It is significant that, although the number of cases of pulmonary tuberculosis in this group has increased by 32% since 1938-9, there is an increase of 90% in the cases showing definite contact with previous open tuberculosis within the past five years.

#### Summary and Conclusions

Our previous study of tuberculosis in Glasgow dealt with the increased incidence of the disease from the outbreak of war up to the end of 1940. It was found that the main increase involved the age groups 15-45 in males and 15-35 in females, the rise being attributed to war conditions, such as long hours, overwork, strain, and curtailed rest.

The present study carries these observations further. It compares the returns for 1941 with those of 1940 and 1938-9. It also includes the results of a detailed investigation into the occupations and working hours of the first 1,600 confirmed cases of pulmonary tuberculosis notified during the year.

The number of notified cases of pulmonary tuberculosis in Glasgow among the young adult cases of both sexes still remains high, but the rate of increase during 1941 has slowed down considerably. On the other hand, the under-15 age groups of both sexes have revealed a very real increase, as has the over-45 age group in males.

The increase among young people of both sexes under 15 years of age is partly accounted for by an increased proportion of home contacts.

Our contention that overwork and long hours are playing a major part in the increased number of recorded cases since the war is supported by the facts embodied in Tables VI and VII, one of the outstanding features of which is that little increase has occurred among the commercial and professional classes, whose hours of work alone remain within reasonable

limits. It will be observed that, whereas less than 20% of the commercial class exceed the recommended maximum hours of work, 67% of the workers in heavy industries and well over 40% in the medium-heavy industries are working in excess of these standards.

The increase in the domestic class may be accounted for by war strain and the fatigue caused by standing in food queues in all weathers. Inquiry shows that nearly 40% of the housewives notified during 1941 were employed in part-time war work in addition to their household duties. This is a new feature, entirely associated with war conditions, which, in our opinion, may account for the increased number of cases in this group.

## ACTION OF PHOLEDRINE AND NEOSYNEPHRIN IN RAISING THE BLOOD PRESSURE

BY

P. C. ELMES

AND

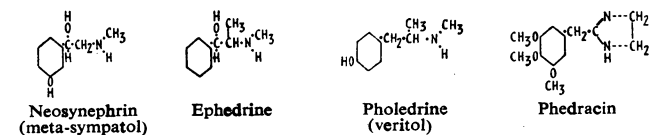
A. A. JEFFERSON

(From the Department of Pharmacology, Oxford)

The use of substances having an action like that of ephedrine for raising the blood pressure still remains limited. Although ephedrine is sometimes injected when a spinal anaesthetic is employed, patients in collapse are ordinarily treated with nikethamide (coramine) or leptazol (cardiazol). Both are medullary stimulants and have no direct action on the heart. There is evidence that in animals they partly restore the blood pressure after previous depression with barbiturate. The effects are, however, seldom definite, and the doses necessary are very large indeed, being almost as great for a cat as the full therapeutic dose recommended for a man. The ability to improve the circulation is presumably due to stimulation of the vasomotor centre, causing vasoconstriction, some rise in blood pressure, and in consequence improved coronary flow.

If the chief effect desired is a rise in blood pressure, a substance which acts *directly* on the heart and blood vessels is clearly preferable. The more widely known agents which act in this way are ephedrine and pholedrine. Two other examples of such compounds on the market are neosynephrin (metasympatol) and phedracin.

The formulae of these substances are as follows:



The properties of ephedrine are well known. Neosynephrin is practically unknown in this country, although it has been employed in America by a number of clinical workers, who find it greatly superior to ephedrine (Bittrich, 1939; Brunner and de Takats, 1939; Johnson, 1937; Lorhan and Oliverio, 1938; Lorhan and Lalich, 1940). In 1938 Jones and Wilson reported on the action of phedracin. They suggested at the time that it might be of use in spinal anaesthesia. Pholedrine (veritol), which was introduced in Germany by Rein (1937a, 1937b), has received only slight attention from clinicians in Great Britain. The many German publications on the clinical use of this compound are in general very favourable, and in this country Dodd (Dodd and Merton, 1939; Dodd, 1942) has recently published the results of its successful clinical use. He recommends that pholedrine, like all other pressor agents, should be used with circumspection and only when absolutely necessary. He employs 4 to 5 mg. intravenously and reports no untoward effects with this dose. Schoenewald, Schweitzer,

and Steel (1940) found that in cats large doses (10 mg.) caused cardiac disturbances; small doses (0.2 mg.) had variable effects when the blood pressure was normal.

### Experimental Investigation

We have compared these four sympathomimetic compounds, under standard conditions in animals with a depressed blood pressure, with the following results:

1. *Effect on the Blood Pressure.*—For each substance a series of five cats was employed; the animals received intravenous chloralose (0.08 g./kg.). The blood pressure was recorded from the carotid artery and enough nembital was given to depress it to about 55 mm. Hg. Artificial respiration was applied throughout and the injections of the pressor agents were made intravenously at approximately hourly intervals. Doses which had previously been found to cause equal rises in blood pressure

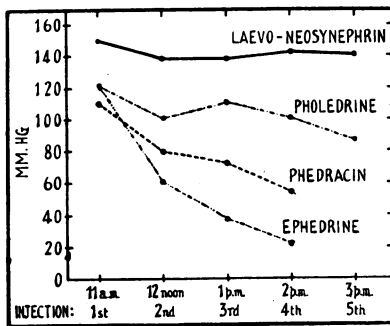


FIG. 1.—Showing the maximum height of the rise in blood pressure produced by successive injections of the four compounds given at hourly intervals. (Ordinate: mm. Hg above the initial level. Abscissa: Time.)

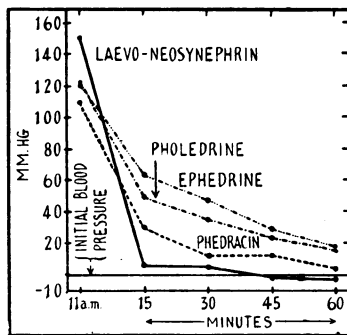


FIG. 2.—Showing the rate at which the blood pressure returns to its initial level after the peak of the first response. (Ordinate: mm. Hg above the initial level. Abscissa: Time.)

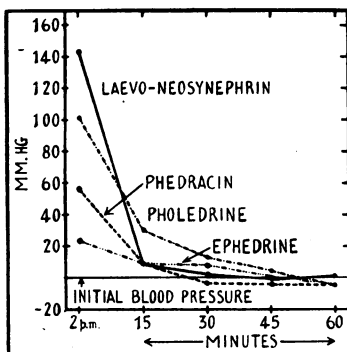


FIG. 3.—Showing the effect on the blood pressure of the fourth injection. Note the severe loss of activity of ephedrine and phedratin when comparing the peak of the response with that of the first injection, shown in Fig. 2. (Ordinate: mm. Hg above the initial level. Abscissa: Time.)

were used. They were: ephedrine hydrochloride 1.01 mg./kg., pholedrine sulphate 0.29 mg./kg., laevo-neosynephrin hydrochloride 0.05 mg./kg., and phedratin hydrochloride 0.79 mg./kg. Under these conditions the blood-pressure responses of the five

cats could be expressed as averages in each series; the results are shown in Figs. 1 to 3. Ephedrine and pholedrine caused the most prolonged rise in blood pressure (Fig. 2), the response to the first dose of each substance lasting for about 45 minutes. Phedratin was briefer in its action (25 minutes), the effect of neosynephrin being the shortest of all (15 minutes). In such a preparation the response to an equivalent rise in blood pressure due to adrenaline does not last longer than about 4 minutes.

Although the result of the first dose of ephedrine was satisfactory, we were never able to see an equivalent effect again in the same preparation, for invariably both the height and the duration of the blood-pressure response to subsequent doses were rapidly and progressively diminished (Figs. 1 and 3). We noticed exactly the same process upon injecting phedratin. However, the response to pholedrine over the first four injections showed little change, and the response to neosynephrin remained constant throughout.

2. *Action on the Heart and Blood Vessels.*—We also compared the action of equipressor doses of these substances on perfused vessel preparations (the rabbit's ear and the dog's hind limb) and on the isolated cat heart perfused through its coronary vessels (Langendorff method). We obtained the following results:

(i) Ephedrine and pholedrine act predominantly on the heart, whereas phedratin acts upon the vessels and neosynephrin upon both the heart and the vessels.

(ii) Ephedrine and pholedrine cause an increase in heart rate (55% and 45% respectively); neosynephrin does not.

(iii) In the experiments on the isolated vessels a regular vasoconstriction was produced by neosynephrin and phedratin. An effect was not always to be seen with ephedrine and pholedrine; a relatively higher dose was required to produce it, and the effect, when it did occur, was prolonged.

These last results are of use in determining the possibility of substituting these substances for adrenaline in local anaesthesia. We investigated the subject by injecting mixtures of procaine and these four compounds into the flank of young guinea-pigs—anaesthesia being tested by the absence of skin reflexes to pin-prick. In the short series which we carried out we did not find ephedrine, pholedrine, or phedratin to be of value. On the other hand, anaesthesia could be prolonged with neosynephrin to within 25% of the duration resulting with adrenaline. These results substantiate the suggestions of others (Tainter and Stockton, 1933; Henderson, 1940) that neosynephrin might find use in local anaesthesia, for it possesses the advantages of being a substance which remains stable in solution and which may be sterilized by heat.

### Discussion

The therapeutic usage of a pressor substance depends in theory upon several factors, among which the following may be considered: (1) the mechanism of the pressor response—namely, whether it is produced by action upon the heart or upon the vessels; (2) the effectiveness of repeated doses; (3) the duration of the pressor response; (4) the existence of any unpleasant side-reactions.

Ephedrine acts mainly upon the heart, but its stimulant action is so violent as to render it potentially dangerous in all conditions in which the heart is not entirely healthy. In animal experiments it soon loses its activity when injected repeatedly, and a reduction occurs in the duration as well as in the height of the pressor response. The routine administration of ephedrine before the injection of a spinal anaesthetic has clearly little to recommend it, especially as an attempted increase in blood pressure above the normal is often the cause of cardiac arrhythmia. The administration of ephedrine very frequently inflicts great subjective discomfort on the patient, and upon these grounds too its use should be carefully controlled.

Pholedrine also exerts its pressor effects through powerful cardiac stimulation, though compared with ephedrine it is less often responsible for irregularities of the heart-beat. When given repeatedly it loses its activity far less rapidly than does ephedrine. The side-effects resulting from its injection into human beings in reasonable doses (4 to 5 mg. i.v.—maximum of 20 mg. i.m.) are slight.

Neosynephrin acts upon both heart and vessels in an extremely favourable ratio. It improves the filling of the heart, it adds to the strength of the beat, and while increasing the heart output often causes slight bradycardia. Though it shows a relatively brief action after intravenous injection into an animal, yet when given intramuscularly, as it very frequently is under clinical conditions, its length of action (30 to 40 minutes) is not greatly different from that of ephedrine or pholedrine (40 to 60 minutes) by the same route. It may be injected repeatedly with no loss of activity. After the administration of neosynephrin the patient rarely complains of even slight discomfort.

Phedracin appears to act almost entirely upon the vessels. It loses its pressor action upon repetition and, like ephedrine, its length of action is reduced. Owing to severe constriction of the skin vessels it may produce an unpleasant feeling of tightness.

### Summary

The importance of using a substance which acts directly upon the cardiovascular system, when it is desired to restore a low blood pressure, is stressed.

Pholedrine, neosynephrin, and phedracin are compared with ephedrine in a series of animal experiments.

It is suggested that neosynephrin as well as pholedrine should be adopted clinically as a substitute for ephedrine.

The results obtained with phedracin do not favour its possible therapeutic use, although it might with advantage be given a further clinical trial.

Neosynephrin may be of value as an alternative to adrenaline in local anaesthetic preparations.

We wish to express our indebtedness to Prof. J. H. Burn for his constant help and encouragement.

### REFERENCES

- Bittrich, N. M. (1939). *Anesth. & Analges.*, **18**, 29.  
 Brunner, R. S., and de Takats, G. (1939). *Surg. Gynec. Obstet.*, **68**, 1021.  
 Dodd, H. (1942). *Lancet*, **1**, 498.  
 — and Merton, G. (1939). *Brit. J. Surg.*, **27**, 78.  
 Henderson, V. E. (1940). *Anesthesiology*, **1**, 323.  
 Johnson, C. A. (1937). *Surg. Gynec. Obstet.*, **65**, 458.  
 Jones, F. A., and Wilson, C. (1938). *Lancet*, **1**, 195.  
 Lorhan, P. H., and Oliverio, R. M. (1938). *Anesth. & Analges.*, **17**, 44.  
 — and Lalic, J. J. (1940). *Ibid.*, **19**, 66.  
 Rein, H. (1937a). *Arch. exp. Path. Pharmacol.*, **187**, 617.  
 (1937b). *Klin. Wschr.*, **16**, 700.  
 Schoenewald, G., Schweitzer, A., and Steel, G. C. (1940). *Lancet*, **1**, 544.  
 Tainter, M. L., and Stockton, A. B. (1933). *Amer. J. med. Sci.*, **185**, 832.

## A DEPRESSION-HYPOSEXUAL-ALOPECIA SYNDROME

BY

CLIFFORD ALLEN, M.D., M.R.C.P., D.P.M.

Squadron Leader, R.A.F.V.R.

AND

CARLYLE CARLYLE-GALL, M.R.C.S., L.R.C.P.,  
D.P.M.

Squadron Leader, R.A.F.O.

Some years ago one of us (C. A.) treated a case of complete alopecia in a man of middle age. This man complained of deep depression, with very marked hypochondriacal trends, accompanied by absolute loss of sexual interest. The alopecia was complete and all hair-bearing areas were denuded, so that it was impossible to find any remaining hair. The lack of sexual interest occurred synchronously with the fall of hair, and the patient not only was impotent but showed no interest in his wife or other women. Nor had he developed any abnormal form of sexual interest. This case progressed in spite of treatment, and when last heard of the patient had entered a mental hospital, as his depression had become severe enough for him to contemplate suicide. (Unfortunately, owing to the exigencies of the war, his notes are not available to us, nor is it possible to follow up his case.)

### Record of a Recent Case

The present case is that of a man aged 33. He came from a normal family. His father died at the age of 64 from a perforated gastric ulcer, and still retained his hair at that age. His mother is still alive, is healthy, and has normal hair. She suffers from occasional attacks of migraine, but has no other symptoms of illness. He has five brothers; one died from a gastric ulcer, and another was operated on for the same reason. (One might suspect from this, and the fact that the patient also has gastric symptoms, that the family is an anxious one and that emotional disturbances tend to cause malfunction of the intestinal tract.) He had five sisters, but one died from pneumonia and one was murdered by her husband. The patient himself has had little other than the usual children's illnesses, except that he has suffered from typical migraine ever since he can remember: his eyes "half black out," then he sees bright lights and zigzags, and finally develops a severe headache which ends with nausea and sometimes actual vomiting. After the attack his head feels sore, but there is a general sense of well-being.

The patient was called up in November, 1940, and joined the R.A.F. He felt well and passed Grade I. A week later he was vaccinated, and seems to have reacted allergically to this. The first night he felt very chilled and his arm was excessively painful. He was faint next day and noticed that both arms had swollen—the oedema reaching down to his hands. He reported sick; but his condition was evidently not considered serious, and his arm was merely re-dressed. Then he complained of a sore throat and feelings of general malaise. This lasted about 14 days and then gradually passed away, although he never felt as well as he had done before. At the beginning of January, 1941, the hairdresser drew attention to a small area on the vertex of the head where there was no hair, and about the same time he himself noticed that there was a diminution of his sexual interest. Eleven weeks after the vaccination he attempted intercourse, but although he had been sexually deprived for some time he had an excessively delayed orgasm—so much so that his wife commented on it. He did not feel depressed at that period. With the passage of time the baldness developed in a patchy way, mainly over the posterior of his scalp. It then spread to the sides, and over the frontal regions the hair grew more and more sparse. He became quite bald. His eyebrows disappeared and he noticed large bare areas on his face, starting on each side of the chin and slowly spreading all over the lower face to coalesce with glabrous areas on the opposite side. This became so pronounced that he had to shave only once weekly instead of twice, as was his custom. The hair on his chest dropped out and a large amount of the pubic hair disappeared also. (This was mainly over the "male" abdominal distribution.) The only area unchanged appears to have been the axillary hair, none of which seems to have been affected even at the worst period. Simultaneously with the appearance of the extensive alopecia he felt depressed. That this was not the result of brooding on his condition but was related to his general feeling of malaise is shown by the fact that he stated definitely: "I felt depressed because I felt ill."

By June, 1941, he had reached the climax of his condition: his hair was absent except in the axillae, he was extremely hypochondriacal, was depressed, and was devoid of all sexual feeling. At this time he had an attack of abdominal pain, which he described as heartburn, but for which no organic cause was discovered. His sleep was poor and he ate little. He was transferred to an R.A.F. hospital in August, 1941, and has slowly improved since then. He was allowed home on short leave at intervals during September, October, and November, 1941. He felt little sexual desire with his wife, and when he did attempt intercourse—he felt he should do so to "prove his manhood"—his orgasm was delayed. The depression was sufficient to make him weep frequently, and he was unable to concentrate on anything. He could not write letters, and eight holes at golf exhausted him. He became excessively worried over his condition and has remained anxious about it ever since.

The condition appears to have followed his vaccination, but psychological factors may be important also—these being the fact that he was in some financial difficulty when he was conscripted into the R.A.F. and while away from home his wife developed a trivial mealtime boil; but he was given a wrong idea of her state, and seems to have thought she was in danger of her life. Curiously enough, during his illness he suffered less from migraine than usual, having only three attacks during the whole of his service in the R.A.F.

In February, 1942, this man was still suffering from considerable alopecia and depression, and, as it was considered