

jority of instances technical errors or the use of rats which showed signs of illness were thought to be responsible for preparations which exhibited poor pressor responses or died prematurely.

*Summary.* A simple method is described for setting up a sensitive pithed rat prepara-

tion suitable for assaying small quantities of pressor substances.

Grateful acknowledgment is made to Mr. C. Wilson whose technical experience in preparing pithed cats has been a valuable aid in the present study.

## 15829

### Effect of Pentaquine in Patients with Hypertension.\*

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The recent observation that pentaquine [6-methoxy-8-(5-isopropylaminoamylamino)-quinoline], a new antimalarial agent, produces postural hypotension in normal man<sup>1,4</sup> raised the question of its usefulness in treating hypertensive patients. The purpose of the present report is to summarize briefly the results of a clinical trial of this compound in a random group of 17 patients with long standing essential hypertension including 3 in the malignant phase of the disease.

*Procedure and Results.* Pentaquine was administered orally in amounts varying from 120 to 240 mg of the base per day, given in equally divided doses every 4 hours. Arterial pressure was measured in the arm by the standard auscultatory method using a mercury manometer. Measurements were made with the patient resting comfortably in the supine position, and also, during and after 5 minutes (or less if syncope intervened) of motionless standing. Mean arterial pressure was calculated as one-half the sum of

the systolic and diastolic blood pressure. The pulse rate was palpated at the wrist or auscultated at the cardiac apex. Patients were hospitalized for at least 3 days prior to treatment, and were maintained on essentially the same regimen before, during and after the period of drug therapy.

In the majority of cases (Table I), after 2 to 7 days of treatment at dosages of 120 to 240 mg per day, a reduction of systolic and diastolic blood pressure occurred, varying from 10 to 40% of the mean arterial blood pressure. At the same time there was usually a further fall in blood pressure in the erect position associated with narrowing of pulse pressure. The pulse rate remained unchanged, or actually decreased in the supine position, and in the majority of patients failed to rise abnormally in the upright position even during marked hypotension.

The development of postural hypotension was not observed in all cases. Four patients exhibited a definite fall in resting blood pressure without the development of a further hypotension when erect. Others maintained a lower resting blood pressure for several weeks after the disappearance of the postural effect. However, one patient exhibited a reduction of blood pressure only in the upright position. In a few patients the depression of arterial pressure first appeared several days after the medication had been discontinued because of toxic reactions.

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<sup>1</sup> Loeb, R. F., *J. A. M. A.*, 1946, **132**, 321.

<sup>4</sup> Craige, B., Jr., Jones, R., Eichelberger, L., Alving, A., Pullman, R. N., and Whorton, C. M., to be published.

TABLE I.  
Summary of Cases.

| Sex | Age | Blood pressure prior to treatment | Dosage pentaquine, mg/day | Supine blood pressure at time of max. fall | Days to return to pretreatment blood pressure | Postural hypotension | Toxic effects   |
|-----|-----|-----------------------------------|---------------------------|--------------------------------------------|-----------------------------------------------|----------------------|-----------------|
| F.  | 50  | 220/120                           | 120-2 days                | 150/90                                     | 12+                                           | +++                  | ++++            |
| M.  | 41  | 210/130                           | 180-3 "                   | 180/118                                    | 2                                             | +                    | +++             |
| F.  | 36  | 240/140                           | 120-3 "                   | Discontinued                               | Severe vomiting and pain                      |                      |                 |
| F.  | 48  | 180/110                           | 120-3 "                   | 140/90                                     | 3+                                            | +                    | ++              |
| M.  | 46  | 200/100                           | 180-2 "                   | No response                                |                                               |                      | ++              |
|     |     |                                   | 240-2 "                   |                                            |                                               |                      |                 |
| F.  | 46  | 230/130                           | 120-2 "                   | 125/88                                     | 6                                             | ++++                 | +++             |
| F.  | 41  | 230/130                           | 180-3 "                   | 150/100                                    | 20                                            | ++                   | ++              |
| F.  | 41  | 220/120                           | 120-14 "                  | No response                                |                                               |                      | Agranulocytosis |
| F.  | 46  | 170/110                           | 120-2 "                   |                                            |                                               |                      |                 |
| M.  | 34  | 170/120                           | 120-2 "                   | 135/110                                    | 7+                                            | 0                    | ++              |
|     |     |                                   | 180-4 "                   |                                            |                                               |                      |                 |
| F.  | 46  | 220/140                           | 120-4 "                   | 180/120                                    | 4                                             | 0                    | ++              |
|     |     |                                   | 60-6 "                    |                                            |                                               |                      |                 |
| F.  | 49  | 240/150                           | 120-3 "                   | 240/150                                    | Postural hypotension 5 days                   |                      |                 |
|     |     |                                   | 180-4 "                   |                                            |                                               |                      |                 |
| M.  | 51  | 200/130                           | 120-3 "                   | 170/90                                     | 30+                                           | 0                    | +               |
|     |     |                                   | 90-7 "                    |                                            |                                               |                      |                 |
| F.  | 49  | 260/135                           | 120-2 "                   | 190/100                                    | 15                                            | 0                    | ++              |
|     |     |                                   | 180-4 "                   |                                            |                                               |                      |                 |
|     |     |                                   | 60-11 "                   |                                            |                                               |                      |                 |
| M.  | 47  | 250/170                           | 120-3 "                   | 140/70                                     | Terminal uremia                               |                      |                 |
| F.  | 34  | 240/140                           | 90-11 "                   | 140/90                                     |                                               |                      |                 |
|     |     |                                   | 120-6 "                   |                                            |                                               |                      |                 |
| M.  | 45  | 230/160                           | 120-2 "                   | 160/100                                    | 12                                            | +++                  | +++             |

The last 3 patients were in the malignant phase of essential hypertension.

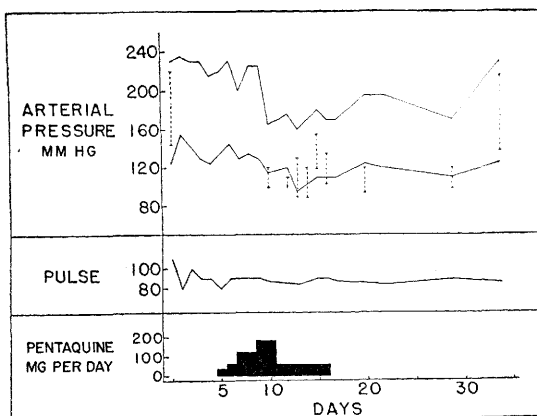


FIG. 1.

Typical response to pentaquine. The vertical broken lines represent arterial pressure readings after 2 minutes in the upright position.

The effective dose varied markedly, one patient requiring 120 mg per day given for

2 days, while several failed to respond to doses as high as 240 mg given for 5 days. Fig. 1 illustrates the typical response of a patient with essential hypertension.

The lowering of blood pressure was often preceded and accompanied by abdominal pain and tenderness, back and chest pain, frequently girdle in character, facial pallor, anorexia, nausea and vomiting, constipation or diarrhea, loss of weight in a few patients, and rarely by fever. Nausea and vomiting and/or abdominal pain were occasionally sufficiently severe to necessitate discontinuation of treatment. Impotence was noted in 2 male patients. Methemoglobinemia and moderate hemolytic anemia occurred in earlier cases but were later successfully controlled by the simultaneous administration of 1 grain of methylene blue with each dose of pentaquine. Cyanosis without signs of cardiac

failure or significant methemoglobinemia appeared in a few patients.

In addition to these toxic effects, agranulocytosis developed in one patient after 2 weeks of continuous therapy, and prolonged menses appeared in another, accompanied by evidence of increased capillary fragility. Both patients recovered uneventfully following cessation of therapy and treatment with penicillin in the case of agranulocytosis. There were no other severe reactions in the group.

Following cessation of full doses of the drug the blood pressure gradually returned to its previous level over a period of several days to several weeks. In most cases the hypotensive effect was not prolonged by the administration of 50 to 60 mg of pentaquine per day. The depression of blood pressure and postural hypotension recurred, however, when the drug was again administered in full doses.

The patients with a malignant phase of essential hypertension as manifested by neuroretinitis, impairment of renal function, high diastolic blood pressure, weight loss and other signs of rapidly progressing disease, responded to pentaquine similarly as patients with uncomplicated essential hypertension, except that they uniformly required lower dosage (120 mg per day). Coincident with the fall in blood pressure there was considerable regression of the pathological changes in the fundi, relief of headaches and cessation of gross hematuria, but apparently no improvement in renal function as measured by clinical and clearance tests.

Hemodynamic studies using Hamilton manometers for recording arterial pressure and the ballistocardiograph for measuring cardiac output, before and after the hypotensive effect had been achieved, indicated that pentaquine caused a reduction of sympathetic vasopressor reflexes similar to that occurring after surgical sympathectomy.<sup>2</sup> This lack of responsiveness was most apparent in those cases which exhibited marked postural hypotension. Measurements of the skin temperature in the extremities under control con-

ditions also indicated a depression of sympathetic activity.<sup>3</sup> Pressor responses to epinephrine and ephedrine were unimpaired, but epinephrine did not prevent collapse in the erect position. Marked postural hypotension and collapse were prevented, however, by the use of a tight abdominal belt similar to that worn following lumbodorsal splanchnicectomy. There were no consistent changes in either the electrocardiogram or in the cardiac output.

*Discussion.* The most interesting effect obtained with pentaquine in hypertensive patients resembled that found in certain normal subjects,<sup>4</sup> namely the appearance of postural hypotension. In addition, hypertensive patients often exhibited a reduction in resting blood pressure. The frequent occurrence of toxic symptoms at first suggested that the hypotensive effect was merely a reflection of toxic debility. However, there was no uniform relation between the appearance of other toxic symptoms and of the hypotensive effect. Furthermore, the hypotension was frequently maintained for several weeks after the disappearance of all other toxic symptoms, and in such instances was associated with considerable subjective improvement. These results indicate that while the drug is too toxic in the dosage necessary to produce a fall in blood pressure, its toxic and hypotensive qualities may not be inseparable.

The preliminary studies suggested that the mode of action of pentaquine upon the vasomotor system is to depress sympathetic nervous reflexes. Its activity differed from that of certain other sympatholytic agents such as the tetraethylammonium salts in that the depression of blood pressure was more prolonged and was not accompanied by a marked quickening of pulse rate. This maintenance of a normal heart rate indicates that its depressor effects include the cardiac accelerator mechanisms. That pentaquine did not block the reactivity of the vascular system to pressor agents was shown by the continued effectiveness of epinephrine and ephed-

<sup>2</sup> Wilkins, R. W., and Culbertson, J. W., unpublished data.

<sup>3</sup> Mixter, G., Jr., and Freis, E. D., unpublished data.

drine. It is of interest that Moe and Seevers<sup>5</sup> reported central impairment of sympathetic reflexes in dogs treated with plasmochin, a closely related 8-aminoquinoline.

*Summary.* 1. The administration of pentaquine in high dosage to patients with essential hypertension frequently produced a significant reduction in resting arterial blood pressure, usually accompanied by the development of postural hypotension. This depressor effect occurred abruptly after several days of therapy and receded gradually over

a period of several days to several weeks following cessation of therapy.

2. Patients with malignant hypertension exhibited a similar response, but did not require as high dosage. With the fall in blood pressure there was some regression of neuroretinitis, headache and gross hematuria; but no significant improvement in renal function.

3. Pentaquine appeared to exert its effects primarily through a sympatholytic action.

4. Toxic reactions to the drug were too frequent and severe to consider its use practicable in the treatment of essential hypertension.

<sup>5</sup> Moe, G. K., and Seevers, M. H., *Fed. Proc.*, 1946, **5**, 193.

### 15830

#### Hemagglutination with Newcastle Disease Virus (NDV).

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Newcastle disease of fowl, an acute infection associated with severe intestinal, respiratory and nervous symptoms, was first recognized as a distinct entity by Kraneveld<sup>1</sup> in the Dutch East Indies and by Doyle<sup>2</sup> in Newcastle, England. Doyle gave the disease its present name and demonstrated that the causative agent is filterable.

Recently there has been increased interest in the virus which causes Newcastle disease, especially because of its capacity to cause hemagglutination.<sup>3</sup> In addition, although the western hemisphere was thought to be free of the disease, Beach<sup>4</sup> showed that there is an immunological similarity between classical Newcastle disease virus (NDV) and the virus of avian pneumoencephalitis, a disease which

is of frequent occurrence in this country. The potential human pathogenicity of the virus for man was indicated in 1943 with the report of an accidental laboratory infection.<sup>5</sup> This resulted in a brief, mild illness associated with conjunctivitis and general symptoms. In 1946 2 similar laboratory infections<sup>6</sup> and a small epidemic of conjunctivitis among women who had been exposed to infected fowls were reported.<sup>7</sup>

Burnet<sup>3</sup> has raised the possibility of "an affinity between NDV and the influenza virus group" chiefly on the basis of hemagglutinating capacity, infectivity for the chick embryo and apparent particle size. However, no immunological relationship could be demonstrated, and recently Bang<sup>8</sup> and others<sup>9</sup> have shown by electron microscopy that NDV

\* Aided by a grant from the Welt Fund of Mt. Sinai Hospital, New York.

<sup>1</sup> Kraneveld, F. C., *Nederl. Indisch. Blad. Diergeneesk.*, 1926, **38**, 448.

<sup>2</sup> Doyle, T. M., *J. Comp. Path. and Therap.*, 1927, **40**, 144.

<sup>3</sup> Burnet, F. M., *Austral. J. Exp. Biol. and Med. Sci.*, 1942, **20**, 81.

<sup>4</sup> Beach, J. R., *Science*, 1944, **100**, 361.

<sup>5</sup> Burnet, F. M., *Med. J. Austral.*, 1943, **2**, 313.

<sup>6</sup> Anderson, S. G., *Med. J. Austral.*, 1946, **1**, 371.

<sup>7</sup> Yatom, J., *J. A. M. A.*, 1946, **132**, 169.

<sup>8</sup> Bang, F. B., *Proc. Soc. Exp. Biol. and Med.*, 1946, **63**, 5.

<sup>9</sup> Cunha, R., Weil, M. L., Beard, D., Taylor, A. R., Sharp, D. G., and Beard, J. W., *J. Immunol.*, 1947, **55**, 69.