

## HYPOPHYSIS AND BLOOD PRESSURE

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IN 1894 Oliver and Schäfer<sup>113</sup> discovered that pituitary extracts raised the blood pressure; Howell<sup>78</sup> showed that this action was due to the posterior lobe; and in 1928 Kamm<sup>85</sup> and his collaborators separated the vasopressor and the oxytocic principles.\* It came to be believed early that the pituitary played an important part in the regulation of the arterial pressure.<sup>105</sup> Azam<sup>10</sup> and Delille,<sup>44</sup> a pupil of Renon, attributed the lowered blood pressure, accelerated pulse, etc., of acute infections to an insufficiency of the pituitary, since treatment with the extract corrected these symptoms. Renon even postulated a syndrome of hyperpituitarism with hypertension and bradycardia. But in spite of many theories there were few facts to support them, and in 1932 Dale<sup>41</sup> concluded that it was not possible to say what part the vasopressor principle in the posterior lobe played in the maintenance of normal blood pressure. Nevertheless numerous experimental and clinical observations indicate that there may be a relation between the pituitary and the blood pressure level. We will describe and discuss these observations in this paper.

ARTERIAL BLOOD PRESSURE IN EXPERIMENTAL  
PITUITARY INSUFFICIENCY

*Amphibians.*—The toad's pituitary contains substances which raise the blood pressure of the dog,<sup>72, 76</sup> the cat<sup>64</sup> and the toad.<sup>114</sup> The neuro-intermediate lobe is more active than the principal lobe in this respect.<sup>114</sup> The vascular system of the batrachians is sensitive to the vasopressor substance in the mammalian pituitary,<sup>1, 14, 55, 74, 93, 113, 114, 118, etc.</sup> but Hogben and Schlapp<sup>69</sup> had to use such large quantities to produce effects, that it was not possible to consider them physiological.

A few hours after complete extirpation of the pituitary in the toad the capillaries and arterioles of the skin become dilated.<sup>9, 94</sup> Injection or perfusion of pituitrin, even in doses of 1:1,000,000 re-establishes the capillary tone and larger doses produce a contraction of the arterioles as well. From these facts Krogh<sup>93</sup> deduced that the pituitary, by means of a hormone, had a continuous action on the tone of the capillaries.‡

\*Extensive bibliographies on the vasopressor activity of pituitary extracts will be found in Houssay,<sup>74</sup> Gelling,<sup>57</sup> Trendelenburg.<sup>146</sup> My own work on the subject will be found in my book.<sup>74</sup>

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‡Krogh also brings evidence for the presence of the hormone in the blood of mammals. Thus, in ox serum there is a substance which constricts the capillaries; it is dialyzable, insoluble in alcohol and ether, soluble in methyl alcohol and thermostable.

The removal of the principal lobe produces a similar but transitory alteration,<sup>9, 94</sup> since the normal tone is soon recovered,<sup>94</sup> though in some cases the recuperation may not be complete.<sup>9</sup> In the toad when the nutritional disturbances and asthenia are marked, usually about one month after the lobectomy, the vasodilatation again becomes pronounced. Infundibulotuberal lesions produce only a moderate and passing dilatation.<sup>9</sup> The dilated capillaries are unstable,<sup>94</sup> but react well to thermal stimuli.<sup>9</sup> According to Nogaki,<sup>111</sup> however, the contractile capacity of the vascular system is reduced in the hypophysectomized frog.

Blount<sup>23</sup> produced a state of hyperpituitarism in the larvae of *Amblystoma*, by grafting two extrahypophyseal anlagen. In these animals he observed vasoconstriction, bradycardia, hypertrophy of the ventricle, and sometimes edema. The basal membrane of the glomeruli of the kidney was thickened, the glomeruli were diminished in size and in some the capillaries became obstructed; these lesions are similar to those seen in human hypertension.<sup>23</sup>

Orias has done important work in our Institute, showing that the intermedio-neural lobe plays a considerable rôle in the maintenance of normal blood pressure in the toad *Bufo arenarum* (Hensell). Removal of the principal lobe alone did not alter the blood pressure until the nutritional disturbances and neuromuscular asthenia appeared, when it was found somewhat lower (30 mm. Hg.) than in the controls which had only been craniotomized (39 mm. Hg.). (Fig. 1.) When the whole pituitary was removed, i.e., the neuro-intermediate together with the principal lobe, the blood pressure began to fall within a few hours after the operation. At times there was a transitory reaction in about twenty-four hours, but afterwards the decrease continued and an average blood pressure of 24 mm. Hg. was found one week after operation and of 17 mm. one month later. The injection of extracts of either lobe raised the blood pressure but the neuro-intermediate was the more active. The fall in blood pressure could be prevented by daily implantation of one lobe, either glandular or neuro-intermediate. Neubach (unpublished data) showed that intravenous injection of 3 cc. arterial blood from a normal toad produced a significantly greater increase in the blood pressure of hypophysectomized toads than did the same quantity of blood from hypophysectomized toads.

Several facts indicate that the vasopressor and melanophore dilating activities are due to different substances. The following evidence

may be so interpreted, namely, that after removal of the pituitary the skin blanches before the blood pressure drops; that there are certain differences in the pharmacological and chemical characteristics of the two hormones;<sup>45, 46, 47, 54, 56, etc.</sup> and, of even more significance, that Dietel<sup>45, 46</sup> has isolated a melanophore dilating substance which, far from having a pressor effect, dilates

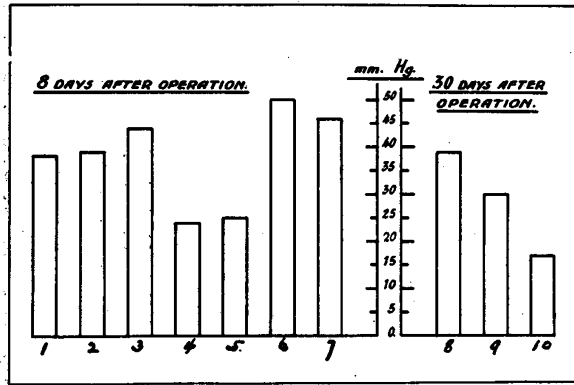


FIG. 1.

Blood pressure of toads in mm. Hg.

Eight days after operation.

1. Controls.
2. Removal of principal lobe.
3. Lesion of tuber cinereum.
4. Hypophysectomy.
5. Hypophysectomy and lesion of tuber cinereum.
6. Hypophysectomy and implantation of neuro-intermediate lobe.
7. Hypophysectomy and implantation of principal lobe.

Thirty days after operation.

8. Controls.
9. Removal of principal lobe.
10. Hypophysectomy.

the capillaries and decreases the blood pressure. He believes it may also have a part in regulating the blood pressure.

**Mammals.**—Braun Menendez<sup>24, 25, 26</sup> measured the blood pressure in twenty-five hypophysec-

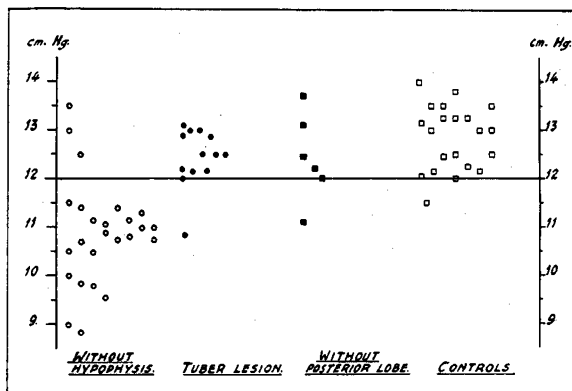


FIG. 2.

Blood pressure of dogs in cm. Hg.

tomized dogs in our Institute. Only three of the operated animals had a normal blood pressure and the average value (108 mm. Hg.), was lower than that found in twenty-one normal controls (127 mm. Hg.). Lesions of the tuber did not modify the blood pressure, the average

being 124 mm. Hg. in thirteen experiments, nor did the removal of the posterior lobe produce a significant decrease, the average being 120 mm. Hg. in four dogs. (Fig. 2.) It must be noted that in these experiments the extirpations were not complete, since the *pars tuberalis* remained in the hypophysectomized animals, and in those whose posterior lobe alone was removed, fragments of the *pars intermedia* were left behind.\*

Braun Menendez<sup>25, 26</sup> was able to demonstrate that the vasomotor reactions were less adequate in the hypophysectomized than in normal dogs. When dogs were bled from the carotid to the extent of 1.5 per cent of the body weight the blood pressure fell 30 to 40 mm. Hg. In six experiments on normal animals the pressure returned to its initial level in 25 to 75 (average 45) minutes, whereas in nine experiments on hypophysectomized animals the initial pressure was not re-established until 75 to 130 (average 95) minutes following bleeding. (Fig. 3.)

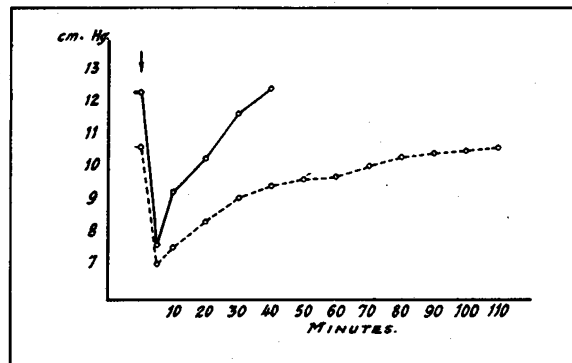


FIG. 3.

Graph showing the effect of hemorrhage on the blood pressure of normal and hypophysectomized dogs.

Solid line—average of five normal dogs.

Dotted line—average of nine hypophysectomized dogs.

At arrow the animals were bled from the carotid artery to the extent of 1.5 per cent of the body weight.

Abscissae—Time in minutes.

Ordinates—cm. Hg.

In the rat, removal of the posterior lobe does not alter the blood pressure significantly, the observed pressures being within the normal range, though somewhat low. Their sensitivity to histamine also is not increased. On the other hand complete hypophysectomy is followed by a decrease in blood pressure and there may be a lowered resistance to histamine.<sup>53</sup> Yamashita<sup>54</sup> also found a lowered blood pressure in the rabbit after partial hypophysectomy.

#### BLOOD PRESSURE IN HUMAN PITUITARY INSUFFICIENCY

In patients with chromophobe adenomas of the pituitary the systolic pressure is usually low.<sup>11, 36, 71, 116</sup> Cushing<sup>36</sup> found it to be below

\*Before Braun Menendez did his work I had measured the blood pressure in a hypophysectomized dog in 1921 and Koster and Geesink<sup>20</sup> did the same in two dogs. Braun Menendez used Biasotti's method, which measures the systolic pressure.<sup>20</sup>

100 mm. Hg. in 11 per cent and below 110 in 46 per cent of his 200 cases, while only two had an abnormally high blood pressure. In craniopharyngiomas it is lower still. Perémy<sup>120</sup> found the blood pressure to be between 78 and 110 mm. Hg. in 20 out of 45 cases of hypophysial tumor.

In many cases of pituitary cachexia there is a low blood pressure, as noted in the papers by Graubner,<sup>59</sup> Calder<sup>30</sup> and others more recently. The vasomotor reactions are also disturbed.<sup>132</sup> After muscular exercise both the systolic and diastolic pressures fall markedly, and the same may happen when the patients resume the erect posture after a period of reclining. This circulatory collapse frequently occurs in such patients and may be corrected by treatment with anterior lobe extract. Nevertheless it cannot be attributed specifically and primarily to the hypophysis, since it is a common occurrence in other types of cases which have a low blood pressure and marked loss of weight. Thus, it has been seen in hypothyroidism and in cases of *tabes dorsalis*. In spite of this, Schelling believes that the pituitary anterior lobe is of importance in the regulation of blood pressure. Ratner<sup>125</sup> found these circulatory disturbances in ten cases, and attributes them to adrenal insufficiency due to a deficient secretion of the pituitary adrenotropic hormone.

#### BLOOD PRESSURE IN ACROMEGALY

The postmortem examination of acromegalics often reveals arteriosclerosis and enlargement of the heart. Numerous instances of increased blood pressure have been reported in these patients<sup>2, 8, 31, 32, 40, 63, 80, 108, 115, 117, 119, 121, 122, 155</sup> and death is frequently due to cardiac insufficiency. Nevertheless the pressure was low (below 120 mm. Hg.) in 30 out of 100 cases of acromegaly studied by Davidoff<sup>43</sup> and in 28 per cent of those seen by Rowe and Lawrence.<sup>129</sup> According to Kylin,<sup>97</sup> in cases of acromegaly occurring in Sweden and collected by Brenning, the blood pressure was normal in young subjects, in only two was it above 140 mm. Hg., but in the patients forty or more years old 11 per cent of the men and 60 per cent of the women had a high blood pressure. Henstell<sup>63</sup> says that paroxysmal hypertension may occur in acromegalics.

#### PITUITARY BASOPHILISM AND THE BLOOD PRESSURE

We owe to Cushing the recognition of a clinical syndrome characterized by adiposity, dorso-cervical kyphosis, amenorrhea or impotence, hypertrichosis, plethoric skin with atrophic striae, high blood pressure, glycosuria, osteoporosis, etc. At autopsy a basophile adenoma of the pituitary is found in a large proportion of the cases in the literature which I have read. The raised

blood pressure was evident and constant in the reports of seventeen cases confirmed by autopsy and in which the blood pressure was recorded.<sup>3, 12, 22, 33, 35, 38, 88, 98, 110, 126, 127, 130, 131, 141, 150, 151</sup> Some of the literature I have not been able to read<sup>16, 58, 142, etc.</sup> and in numerous published cases there was no anatomical verification.

Certain improvements which occur when the pituitary is irradiated favor the theory that it is the prime factor of this disease (Cushing, Jamin, Dattner, Wohl and collaborators, Aub, etc.). Even though the basophile adenoma is not constant (according to Bauer<sup>13</sup> it was found in only fifteen out of twenty-three cases) its frequency is significant since in general it is a rare condition, Susman<sup>140</sup> finding it in only 3 per cent of the 260 pituitary glands which he examined. In some cases adenoma was not present but there was an increase in the basophile cells; this is an equivalent pathological state according to Cushing. In discussing the possible part the pituitary might take in the genesis of raised blood pressure he considers that the hypertension might be due (1) to a specific secretion of the adenoma, (2) to stimulation of the pressor secretion of the posterior lobe by the adenoma, (3) to an action through some other gland. Cushing<sup>38, 39</sup> is inclined to accept the second of the possibilities just mentioned, while Bauer<sup>13</sup> maintains that elevation of pressure is due to adrenal hyperactivity brought about by the pituitary adrenotropic hormone.

Cushing<sup>39</sup> observed that in cases of eclampsia and elevated blood pressure and in certain cases of basophilism with hypertension, there was basophile cell infiltration of the posterior lobe. This might indicate hyperactivity of this lobe, but, according to Spark,<sup>137</sup> this morphological appearance has no significance. He made an extensive study of reported cases and sectioned the pituitary in seventy cases of raised blood pressure, in eleven with a previous history of raised blood pressure and in 108 where the blood pressure was normal; in all types of cases a similar basophilic infiltration was found. Also Butt,<sup>28</sup> in 200 cases, failed to find any correlation between the degree of basophilic infiltration and the presence of arterial hypertension, arteriosclerosis, eclampsia or obesity. On the other hand an increase in the basophile cells of the pituitary has been reported in cases of raised blood pressure<sup>19, 91, 92</sup> and more frequently in adiposity. Kraus<sup>91</sup> found it in 80 per cent of cases of the latter type and believed that the basophilism was secondary to the obesity. In some cases of adrenal tumor the fact that foci of basophile cells without adenoma<sup>18, 100\*</sup> have been found in the pituitary

\*In these cases it may be supposed that pituitary basophilism was the cause of the adrenal adenomas, which later became malignant.

has suggested the possibility that basophilism may be secondary to overactivity of the adrenal. Finally, Leyton<sup>104</sup> found Cushing's syndrome in a case of thymus tumor associated with adrenal hyperplasia.

It is known that the presence of the anterior pituitary is necessary for the development and maintenance of the normal anatomical and functional state of the adrenal cortex.<sup>75</sup> Hypophysectomy causes the atrophy of the reticular layers and of the internal part of the fascicular layers, with preservation or hypertrophy of the glomerular zone, but leaves the medulla unchanged. Adrenotropic extracts of the pituitary may bring about the hypertrophy of the adrenal cortex<sup>15, 34, 50, 51, 75, etc.</sup> and even produce small adenomas<sup>123</sup> and certain symptoms (adiposity, bony alterations, etc.), which Thompson and Cushing<sup>144</sup> consider similar to those of basophilism. Up to now it has not been observed that they cause a rise in blood pressure.

Bauer<sup>13</sup> attributes the symptoms of Cushing's syndrome to hyperactivity of the adrenal cortex, due to an overproduction of the adrenotropic pituitary hormone. He refuses to accept the theory that it originates in the basophile cells, citing the frequency of basophilism in different circumstances and the fact that Sokolow and Gromow<sup>136</sup> found a cortico-adrenal syndrome with raised blood pressure in a child, which was found to have an eosinophile adenoma of the pituitary. The anatomical state of a gland does not give an adequate measure of its function; for this reason a possible overactivity of the pituitary or the adrenal glands cannot be excluded in those cases where no basophile adenoma or adrenal hypertrophy is found. It would be necessary to measure the amount of hormones secreted into the blood. Bauer<sup>13</sup> further draws attention to the fact that the symptoms of Cushing's syndrome are also those of hyperactivity of the adrenals. In chromaffin tumors of adrenal origin the blood pressure is raised permanently or paroxysmally, and in six cases in which the tumor was removed the paroxysms disappeared. It has not been proved that permanent hypertension is due to an excessive secretion of adrenin. Probably cortical overactivity also causes the blood pressure to rise, since there are cases of tumors of the adrenal cortex with high blood pressure and hyperglycemia and in some instances removal of the tumor has cured these symptoms. It must also be remembered that in certain cases of Cushing's syndrome the adrenals are normal, although generally they are hypertrophied or adenomatous.

The adrenal symptoms are predominant in the syndrome of basophilism, but it cannot be affirmed that the hyperactivity of the adrenals is always of pituitary origin, although the large

number of typical and marked cases with basophile adenoma of the pituitary is suggestive. It can only be suspected that the latter is the primary cause in many cases. It is not yet clear whether the raised blood pressure is due to an excess of adrenal or pituitary hormones or to some other cause, since the presence of these hormones in the blood has not yet been confirmed.

#### THE PITUITARY AND RAISED BLOOD PRESSURE IN THE TOXEMIAS OF PREGNANCY AND IN ECLAMPSIA

Since Hofbauer's work<sup>66</sup> it has been maintained that eclampsia may be due to a polyglandular disturbance, with an excess of the posterior pituitary lobe secretion predominating. The principal arguments brought forward and some of the objections raised to them are as follows: (1) There is a certain similarity between the symptoms of eclampsia and those which are produced by posterior lobe extract,<sup>5, 49, 52, 66, 95, 102, 128, 147, etc.</sup> (e.g. tendency to edema, raised blood pressure, capillary spasm, convulsions and coma, pulmonary edema, ionic changes, favorable action of narcotics), but there are also definite differences.<sup>21, 143</sup> (2) There is a certain similarity between the anatomical lesions found in eclampsia (in the liver, kidney, etc.) and those provoked by posterior pituitary extract.<sup>52, 89</sup> However the majority of writers consider these lesions rare and hardly worth mentioning.\* (3) The infiltration of the posterior lobe by basophile cells in eclamptics would cause oversecretion of pituitrin,<sup>39</sup> but Spark<sup>137</sup> proved that the basophile invasion may occur when eclampsia is not present. (4) Dialysis of the serum of eclamptics shows that there is an increase in antidiuretic and blood pressure raising substances<sup>5</sup> but this cannot be pituitary posterior lobe secretion (Theobald<sup>143</sup>). The blood of eclamptics, when injected into the cerebral ventricles, causes oliguria according to Marx.<sup>106</sup> The antidiuretic action, however, has not been confirmed in the careful experiments of Byrom and Wilson<sup>29</sup> or of Hurwitz and Bullock.<sup>81</sup> (5) The melanophore dilating substance is increased in the blood<sup>95</sup> and placenta<sup>49</sup> of eclamptics. Against this are the reports that the blood of eclamptics, in common with that of normal or pregnant women, possesses the property of neutralizing the effects of certain of the posterior pituitary lobe extracts, for example the oxytocic,<sup>53, 145, etc.</sup> the oliguric,<sup>21</sup> the melanophore dilatatory<sup>45</sup> and the pressor.<sup>134</sup>

#### THE PITUITARY AND OTHER HYPERTENSIONS

An increase of basophile cells has been seen in the hypophyses of two-thirds of the cases of raised blood pressure,<sup>19</sup> but is even more fre-

\*For the older literature see Houssay<sup>74</sup> and for the more recent Ohligomacher<sup>113</sup> and Scheps.<sup>133</sup>

quent in obesity,<sup>91</sup> and has also been observed in other conditions. Spark<sup>137</sup> declares that the posterior pituitary lobe invasion by basophile cells described by Cushing<sup>88, 89</sup> can exist with equal frequency when there is no raised blood pressure.

Kylin<sup>97</sup> believes that the anterior pituitary lobe is an essential factor in hypertension, because the general and metabolic symptoms are exactly opposite to those of pituitary insufficiency. Pal,<sup>116</sup> and Merle and his collaborators<sup>107</sup> also believe in the pituitary theory and Drouet<sup>48</sup> describes improvement in certain cases of raised blood pressure due to irradiation of the pituitary. The cerebrospinal fluid of patients suffering from raised blood pressure only occasionally contains "minute traces of pituitrin",<sup>79</sup> so an overactivity of the posterior pituitary lobe does not seem to be an etiological factor in the disease. Moehlig<sup>109</sup> has produced arteriosclerosis in rabbits, by submitting them to a diet rich in fats and cholesterol combined with treatment with pituitrin. Volhard<sup>148</sup> has shown that the raised blood pressure due to ligation of the renal artery is produced both in normal and hypophysectomized dogs.

#### PITUITARY, DIENCEPHALON AND HYPERTENSION

It has been known for some time\* that the principal vasomotor centres are in the medulla. Section of the brain stem above the pons does not modify the level of the blood pressure or the vasomotor reflexes and reactions<sup>25, 26, 65, 86, 138, 139, etc.</sup> in acute experiments.

The stimulation of the posterior ventral part of the hypothalamus causes a marked rise of blood pressure,<sup>17, 77, 82, 84, 86, 124, 149</sup> even in the absence of the pituitary and adrenals. (Karplus and Kreidl, confirmed in our Institute.) When the adrenals are present there is also a marked secretion of adrenin, itself capable of raising the blood pressure<sup>77</sup> and the blood sugar.<sup>82</sup> The melanophore dilating substance in the cerebrospinal fluid is also increased.<sup>87</sup> Ergotamine or the extirpation of the sympathetic chain and the splanchnics<sup>82</sup> suppresses the rise in blood pressure. Leiter and Grinker<sup>101</sup> affirm that the rise in blood pressure occurs only when there are muscular or respiratory disturbances, but de Jaegher and Van Bogaert<sup>82</sup> have shown that it may be raised both by mechanical and chemical stimuli which do not evoke muscular activity. According to Hoff and Urban<sup>67</sup> lesions of the mammillary bodies may cause a delayed rise in blood pressure some months after the operation.

It has not been proved that the pituitary takes part in the rise in blood pressure produced by cisternal injection of kaolin or other colloids.<sup>60, 61, 70</sup> Pituitrin causes a rise of blood pressure if it is injected into the cerebrospinal

canal<sup>74, 99</sup> or the cistern.<sup>61, 62</sup> If, however, it is injected into the ventricles there is either a fall in blood pressure followed by a rise<sup>37</sup> or no effect at all.<sup>63</sup>

#### GENERAL SUMMARY

The posterior pituitary lobe contains vaso-pressor substances, which in amphibians play a very important rôle in the maintenance of the blood pressure and arterial and capillary tone. Small quantities of similar substances exist in the principal lobe of the toad, but removal of this lobe causes a lowering of the blood pressure only after asthenia has developed. In the rat, dog and man pituitary insufficiency is accompanied by lowered blood pressure; it is not clear whether this is due to lack of one or both lobes, but it seems more particularly due to lack of the anterior lobe (central or peripheral vascular asthenia).

The existence of raised blood pressure in acromegaly has not been well established, since the blood pressure is frequently normal in these cases. On the other hand hypertension is a constant and prominent symptom in the pituitary basophilism syndrome of Cushing, though whether this is due to pituitary or adrenal hypersecretion or to a secondary or associated factor, is not yet clear.

The evidence put forward to demonstrate that hyperactivity of the posterior pituitary lobe is the causal factor in eclampsia and in essential hypertension is contradictory and inconclusive.

In contradistinction to the medulla the diencephalon is not essential for the maintenance of blood pressure in acute experiments, nor has it been proved that increase in blood pressure due to lesions or stimulation of this region is accompanied by hypersecretion of the posterior pituitary.

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## MERCURIN SUPPOSITORIES AS A DIURETIC IN THE TREATMENT OF EDEMA\*

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**I**N the treatment of edema, particularly chronic or recurrent edema, diuretic drugs frequently are of great service. Of these the organic mercurial salts have come to be used extensively because of their effectiveness in increasing urine output and their relative freedom from toxic effects. Salyrgan (mersalyl) enjoys a widespread popularity and has been found to be effective even when given repeatedly over a long period of time.<sup>1,2</sup> During the past few years another preparation, mercupurin, introduced in Europe under the name of novurit, combining both a mercurial salt and theophylline, has been given enthusiastic recognition.<sup>3,4,5</sup> The disadvantages in the use of these drugs are (1) that they must be given either by intravenous or intramuscular injection, (2) that by the former route they are liable to injure the vein or surrounding tissues, and by intramuscular administration are irritating and painful and (3) that their repeated use requires frequent attendance of doctor to patient, or of patient to doctor or clinic, which necessity often curtails their employment. If either drug or any other preparation equally effective could be administered by the patient, himself, under supervision, there would be a saving both in time and money and added convenience of no little measure.

It has been shown in certain European clinics that the mercurial component of mercupurin, the sodium salt of trimethylcyclopentane-dicarboxylic acid-methoxy-mercuryhydroxide-allylamide, is effective as a diuretic when administered by rectum in suppository form.<sup>6,7,8</sup> This preparation has recently been introduced in this country under the name of mercurin suppositories. During the past eight months at the Peter Bent Brigham Hospital we have had the opportunity of using mercurin suppositories in twenty-five patients with edema.‡ They have been found to be an effective and safe diuretic, producing results comparable with those obtained by

the intravenous injection of salyrgan or mercupurin. These results are published with the feeling that this preparation offers a distinct advance in diuretic therapy, particularly in the convenience it affords to both doctor and patient.

### PLAN OF TREATMENT

All but five of the patients with whom this report deals had cardiac failure with edema. Most of them were observed for a time at bed rest on the hospital wards. Following a period of several days' observation to allow for adequate digitalization or a spontaneous diuresis, they were given one gram of ammonium chloride three or four times a day. This therapy, introduced by Keith and his associates<sup>9</sup>, has been shown to enhance the action of mercurial diuretics by the mild degree of acidosis which it produces.<sup>10</sup> After two to four days of this régime, the patients were given the suppositories usually the first thing in the morning following a cleansing enema. Use of the suppositories or other diuretics was repeated at intervals of four to six days, the patients, meanwhile, continuing on a daily dosage of three or four grams of ammonium chloride.

Each suppository, made of cocoa butter base, contains 500 milligrams of the mercurial salt of mercupurin ( $C_{14}H_{24}O_5NHgNa$ ) without any added theophylline. This is approximately five times the amount of mercury contained in one cc. of mercupurin or salyrgan.

### RESULTS

The diuretic response to the suppositories was very satisfactory, comparing favorably with that observed after intravenous administration of mercurial salts. The increased urine flow began in one to three hours after the suppository was given and was passed, as a rule, by the end of twelve hours, so that the patients were not kept awake the following night voiding urine. Occasionally the increased urine flow lasted twenty-four hours or longer. That the absorption of the material by the rectal mucosa may occur very promptly was indicated by one patient who had a bowel movement twenty minutes after insertion of the suppository, yet who

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