SOME ASPECTS OF CARDIOVASCULAR REGULATION IN MAN*†

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Modern medical thought has tended increasingly to the view that illness results from the interaction of plural noxious agents in the environment and multiple defenses of the host. Should the environmental forces be too numerous or highly virulent, or the defenses defective, either genetically or as a result of prior illness, disease results. Such a view of human disease requires that one examine those bodily mechanisms which oppose disease, as well as those which integrate the hosts' defenses. Significant among such mechanisms is the autonomic nervous system.

Essential hypertension and the migraine syndrome, two disorders that we have examined, share three essential features: (1) an exceedingly common occurrence; (2) a mechanism which appears in part to be genetically determined; and (3) an intimate relationship to the autonomic nervous system. We shall limit our remarks largely to the third point in discussing some of our findings and some of our speculations.

In the investigation of hypertensive disease in the United States, the kidney and, more recently, the endocrines have occupied a central position. Americans have inexplicably been loath to examine the autonomic nervous system. Etiologically aimed studies of hypertension have likewise often been inconclusive. Nevertheless, some studies have illuminated this area. Hines' work on the cold pressor reaction has delineated a hyperreactive state.[1] Many have been able to confirm Hines' results, although a few studies have been contradictory.[2] Goldenberg *et al.*[3] postulated a more pronounced blood pressure response to infusion of levarterenol, the effector hormone of the sympathetic nervous system, in hypertensive than in normotensive subjects, an effect in which Judson, Epstein, and Wilkins[4] could not concur. The effect of carotid sinus pressure and of the Valsalva maneuver on blood pressure have been examined without elucidating basic mechanisms in human hypertension. Von Euler and associates[5] have found an increase in urinary catecholamines in only a small minority of hypertensive subjects.

Arising out of a study of minute blood vessel dysfunction in migraine,[6] we have studied the problem of sensitivity to levarterenol and the phenomenon of the acute pressor response in normotensive and hypertensive subjects. In these studies, levarterenol was administered intravenously through a constant infusion pump at rates of either 10 or 20 μg per min. Infusions were made in both normotensive and hypertensive subjects. All were studied under standard conditions, were pharmacologically untreated, and in the postabsorptive state. Blood pressure was measured with a mercury manometer or, as in table 1, was recorded directly intraarterially. Pulse rate was counted from the arterial tracing or determined by electrocardiogram. Twenty-one hypertensives and 17 normotensives were examined; in 10, pressure was measured intraarterially, in the rest, by cuff. The increase in blood pressure calculated as per cent increase over initial pressure exhibited no significant difference in the hypertensive subjects as compared to the normotensive volunteers. However, (table 2) the hypertensive subjects did not respond to the infusion with bradycardia as predictably as did the normotensive subjects. After the single injections of 5 γ levarterenol, as shown earlier by Judson and Wilkins, the hypertensive subjects exhibited less bradycardia than the normotensive subjects. It appears that vagal buffering of the effects of acutely applied vasoconstriction may not be quite as effective in hypertensive subjects, although over-all they exhibit no greater pressor response.

The vascular response to levarterenol, therefore, must be assessed in the absence of autonomic reflex buffers. Accordingly, we decided to explore the direct effects of levarterenol on the small vessels of the bulbar conjunctivae. Lee and Holze[7] and Greisman[8] had shown earlier that the constrictor effects of epinephrine and levarterenol are greater in hypertensive than in

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TABLE 1

Mean arterial blood pressure before and during infusion of 10 γ/min. levarterenol

Normotensives		Hypertensives	
88	110	125	140
90	92	146	158
95	124	168	197
103	139	169	198
118	150	186	208
		175	208

TABLE 2

Pulse rates before and during infusion of 10 γ/min. levarterenol

Normotensives		Hypertensives	
66	58	67	62
91	65	69	47
118	79	53	49
92	74	88	83
81	76	67	63
		63	64

normotensive subjects in the conjunctival and nail fold capillaries, respectively.

Levarterenol was dissolved in an isotonic ophthalmic buffer at the PH of tears. The least concentration which would blanch conjunctival capillaries was determined and called the threshold, after the manner of Lee and Holze.[7] Bulbar conjunctival arterioles, capillaries, and venules were examined through a slit lamp microscope at a magnification of 47×. It was found that hypertensive subjects exhibited (table 3) much lower thresholds, *i.e.*, the capillaries blanched at much greater dilutions. Such lowered thresholds could conceivably be due to one of two mechanisms: (1) There might be a true hypersensitivity of arteriolar smooth muscle to levarterenol; (2) The hyper-reactivity to levarterenol might represent merely a diameter effect, *i.e.*, vessels already partly narrowed might constrict further more readily than vessels of usual caliber.

Two types of experiments were designed to determine which of the two possibilities was more likely. Twenty γ per min. of levarterenol were infused in five normotensive subjects so that their blood pressure was well into the hypertensive range (table 4). Although the threshold was at its usual levels immediately before such infusions, it fell predictably to threshold levels common in hypertensive subjects. Twenty to 50 γ per min. of histamine, an arteriolar vasodilator, were then infused into four hypertensive subjects so that their blood pressures approached normal levels. During histamine infusion, much more levarterenol (table 5) was required to blanch capillaries than formerly.

When the bulbar conjunctival vessels were irritated and dilated by local installation of soapsuds, much greater concentrations of levarterenol were required to blanch capillaries than previously in the same subjects. Also, when conjunctival vessels were presumably partially constricted by local installation of 1:100,000 vasopressin, much less levarterenol was required to blanch capillaries than earlier in the same subjects. We have interpreted these experiments as follows:

1. There is no basic difference in responsiveness of conjunctival arterioles of hypertensive subjects to levarterenol as compared to normotensive subjects.

2. The minute vessels in any subject, normo-

TABLE 3

Sensitivity to topical levarterenol of bulbar conjunctival capillaries

Normotensives	Hypertensives
1:50,000	1:400,000
1:100,000	1:400,000
1:50,000	1:200,000
1:25,000	1:200,000
1:100,000	1:800,000

TABLE 4

Effects of 20 γ min./levarterenol on BCV sensitivity in normotensive subject

	Before Levarterenol	After Levarterenol
Eye	1:25,000	1:400,000
Blood pressure	128/84	178/112

TABLE 5

Effect of 20 γ/min. histamine on BCV sensitivity in hypertensive subject

	Before Histamine	After Histamine
Eye	1:200,000	1:50,000
Blood pressure	180/116	138/100

tensive or hypertensive, that are partly constricted are more readily constricted further by levarterenol. Those partly dilated require more vasoconstrictor agent to blanch capillaries. The observations of Redleaf anf Tobian[9] with aorta strips had earlier led them to take a similar position.

The unexpectedly high incidence of elevated blood pressure occurring in chronic polio sufferers[10] has been of considerable interest because of the obvious neural damage in this disease. The incidence of casual blood pressures above a diastolic level of 95 mm of Hg was determined in three youthful chronic polio populations; a group of 44 who had pure bulbar disease, a group of 67 with moderate-to-severe bulbospinal involvement, and a third group of 83 with severe bulbospinal involvement and partial respiratory paralysis as well. The latter two populations were matched for age, sex, race and year of involvement. Bulbar involvement, hypertension during the acute phase of the disease, degree of respiratory paralysis, year of involvement (and therefore presumably strain of the virus) were without influence on the incidence of hypertension. Hypertension rose in incidence in each group directly with the amount of skeletal muscle atrophy. About 35 per cent of the respiratory paralysis group, 25 per cent of the simple paraplegic group, and only about 5 per cent of the pure bulbar group exhibited elevated blood pressure. There was a significantly higher incidence of elevated blood pressure among the males as compared to females. Why a person with quadriplegia should be more likely to have an elevated blood pressure than someone with a lesser degree of paralysis eluded us. The work of Roddie[12] may illuminate the issue. He showed that vasodilation in skeletal muscle was a most important buffering mechanism in preventing blood pressure increases during a rise in cardiac output.

With severe skeletal muscle atrophy, there is likely to be a reduced blood supply to such muscles. Therefore, a hypertensive buffering mechanism requiring transient hyperemia of striped muscle would be inhibited. Such a reflex would certainly be under autonomic controls and its inhibition in chronic poliomyelitis indicates its importance in the normal subject. Hemodynamic measurements to test this thesis are under way.

Blood pressure responses to psychologic stress have long occupied an important position in the study of these problems. Coming largely under autonomic control, it seems appropriate to comment on some of our current work and opinions. Stress-inducing interviews, psychologic tests, and physiologic measurements have been carried out on groups of hypertensive subjects and on vascular hyper-reactors among medical students with appropriate control groups. Specifically, we have examined the effects of stress and the epidemiology of psychologic test performances in a group of 15 subjects with essential hypertension and a group similar in number, age, sex, and race who had clearly-established hypertension of renal origin. In the latter group, hospital records of renal disease beginning before the hypertension and a renal biopsy were usually the basis of the diagnosis. Blood pressure increase during stressful interviews occurred with approximately equal frequency and magnitude in the two group (table 6). Furthermore, performance and scores of two psychologic tests, the Minnesota Multiphasic Personality Inventory (table 7) and the Rorschach, were surprisingly similar. A study of the response to ganglionic blockade and to topical and intravenous levarterenol during periods of relative tranquility and again during periods of psychologic stress were likewise undertaken. "Tranquility" and "periods of stress" were specifically defined for each subject at the beginning of the period of study.

The blood pressure response to intravenous infusion of levarterenol exhibited no change from tranquil to disturbed periods, indicating probably that the capacity to buffer such responses does not change with stress. However, during periods of agitation, the small blood vessels of the bulbar conjunctiva required significantly lower dilutions to blanch them. This is most readily explicable by assuming an increase in some circulating vasoconstrictor agent whose effects summate with the topical levarterenol. Almost half the time in both groups, there was a so-called "stress reversal"* of the effects of ganglionic blockade. In all these subjects, during tranquil life periods, 6 mg/kg tetraethyl ammonium chloride induced a predominantly depressor response. However, during difficult life periods, the same agent administered in the same way, resulted in an acute rise in blood pressure in almost half the subjects. Such reversal of TEAC effects during stress was

* A term, I believe, coined by Dr. A. A. Brust.

TABLE 6

Blood pressure increase during "stress" interview

	Renal	Essential
Systolic		
Mean	8.2	8.4
SD	6.2	6.7
Diastolic		
Mean	6.0	8.4
SD	5.4	7.1

TABLE 7

Mean M.M.P.I. T-Scores

Scale	Control	Renal	Essential
Hs	63.30	61.50	61.25
D	65.30	64.71	67.75
Hy	64.50	66.64	66.45
Pd	64.50	60.29	64.65
Pa	61.65	56.79	57.75
Pt	55.70	51.50	55.75
Sc	59.55	53.36	55.70
Ma	56.55	53.43	58.60

first shown by Ferris *et al.*[13] about 10 years ago and was also alluded to by Hoobler, Moe, and Lyons.[14]

Reversal of the effects of TEAC was experimentally attempted by administering this ganglionic blocking agent during infusions of 10 γ/min. epinephrine, 10 γ/min. levarterenol, 0.25 mg/min. serotonin, and 5 units/min. angiotonin. Only with levarterenol or with angiotonin was there a predictable reversal of effect (fig. 1). It appears then that the mechanism of the stress reversal of TEAC effect is compatible with an increase in circulating amounts of an agent with hemodynamic effects like levarterenol or angiotonin, *i.e.*, essentially pure vasoconstrictor effects. Wilber and Brust[15] have recently published and previously found much the same potentiation of TEAC with levarterenol but not with epinephrine.

The hemodynamics of the seemingly paradoxical effects of TEAC during levarterenol infusion were studied by means of indicator dilution technique with iodinated human albumin and intra-arterial strain gauge manometer recording of blood pressure. The increased blood pressure induced by TEAC during levarterenol infusion was associated with an increase in pulse rate and

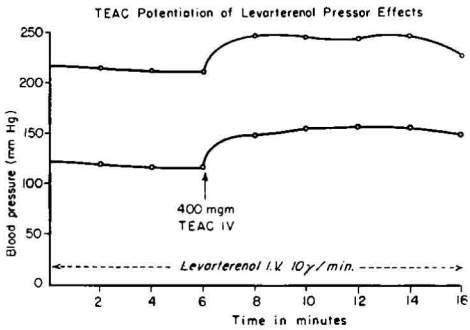

FIG. 1

in cardiac index, and with no change in stroke volume or peripheral resistance.

Lability of blood pressure, a phenomenon presumably in part under autonomic control, has likewise attracted our study. Lability was defined as the standard deviation of five randomly selected, casual diastolic blood pressures obtained under similar circumstances with respect to setting, time of day, and observer.

The subjects previously described with renal hypertension and with essential hypertension were ranked according to the magnitude of the lability number and then according to their scores on the various scales of a psychologic test, the M.M.P.I. There was a significant and positive correlation between lability and the scores on the hysteria, hypochondriasis, and psychasthenia scales of the M.M.P.I. (table 8). As stated earlier, there were no differences in personality traits or responses to stress interviews between the group with renal and essential hypertension. However, in both populations, those subjects whose blood pressure varied the most from day to day exhibited the highest titer of the above-mentioned neurotic traits.

The phenomenon of lability has often been studied in population groups who are not hypertensive. It appears that once the blood pressure remains permanently above some arbitrary level, its variability is no longer considered.

We have examined blood pressure readings immediately before and again at the end of a physical examination in four population groups. Sixteen per cent of 167 male medical students exhibited an initial blood pressure above 140 systolic and/or 90 diastolic. On the second blood pressure examination, only approximately 3 per cent remained above these levels. However,

TABLE 8

n-18	Essential Hypertension Diastolic Lability *vs:*	
Scale	r_s	p
Hysteria	0.71	0.01
Hypochondriasis	0.53	0.05
Psychasthenia	0.42	0.05

only 2.3 per cent of 87 female students examined under similar circumstances exhibited similarly-elevated initial blood pressures. In none of these female subjects was the blood pressure elevated on the second determination. The mean blood pressure was slightly lower in the female group, but this was not sufficient to account for the difference in the two groups. It would appear that the capacity to respond to the stress of a physical examination with a blood pressure above 140/90 occurs much more commonly in males. Herbolsheimer and Ballard[16] at the University of Chicago have shown the same phenomenon. Since blood pressure above the usual arbitrarily defined normotensive levels occurs more commonly in women than in men,[2] the fact that transient hypertension is more common in the males of the groups we examined may indicate that acute blood pressure elevations with stress may not be as closely related to more permanent subsequent elevations as had been thought.

The rise in blood pressure with the stress of a physical examination in a group of 42 men in the fifth and sixth decades of life, by inspection, exhibited roughly the same percentage of fall from the initial to the final determinations as occurred in another group of 57 men in the third decade of life, when both were examined in the same setting by the same observer at about the same time of day.

Let us say that Subject A at age 25 has a basal blood pressure of 125/75. During the stress of a physical examination, because A is the sort of person he is, his initial blood pressure is 150/95. When he rests and is calmed by the examiner, it falls to 140/85. A is called normotensive. Two decades later, because of a less elastic aorta, a fatter upper arm and probably other factors, A's basal blood pressure is 140/90. During the stress of an examination, it rises the same amount it did earlier to 165/110. Again, with reassurance, it falls the same amount as earlier to 155/100. However, now A is considered a mild hypertensive.

It is our thesis that much of what is called essential hypertension represents a superimposition of acute stress-induced pressor responses on the expected rise in blood pressure with age, and that herein lies the real importance of psychologic factors to essential hypertension.

We have postulated that there is a lability factor in blood pressure closely linked with personality which is independent of other factors maintaining elevated blood pressure. The blood pressure of the renal hypertensives fluctuate with acute psychologic stress, yet no one would say that the persistent elevation was caused by distressing life circumstances. The same reasoning in essential hypertension would indicate that psychologic factors are not sole etiologic determinants of the elevated blood pressure in essential hypertension, but may be of great importance in a certain type of person during a period of environmental stress, and of relatively little importance in another person.

Another aspect of the relationship of psychologic stress to essential hypertension was studied in a group of 14 subjects with brain damage. All had essential hypertension of approximately known duration and severity antedating neurologic symptoms.[17] Figure 2 illustrates a part of this study. In two subjects with damage to the frontal lobes of the brain, the ganglionic blocking agent, TEAC, induced a fall in supine blood pressure. Hypertension may then in some subjects be in part maintained by neurogenic mechanisms in the absence of complete frontal lobe function, such as occurs after frontal lobotomy.

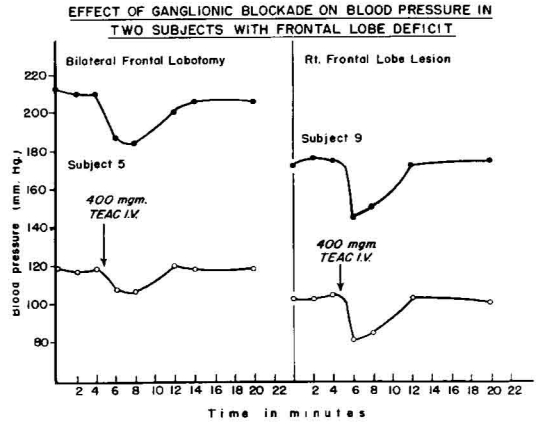

FIG. 2

The thesis has often been advanced that essential hypertension is the outcome and cumulative expression of repeated acute blood pressure rises with psychologic stress. Yet, hypertension of weeks or months duration may occur after a single stressful event as shown by Graham[18] after battle and by Ruskin *et al.*[19] after the Texas City disaster. In following 30 hypertensive subjects at weekly or bi-weekly intervals for from one to two years, we have often observed an elevation of blood pressure persisting for weeks or months concurrently with threatening life events. In each case when the demands of the social environment have remitted, the blood pressure levels fell. Furthermore, as stated earlier, although acute blood pressure elevations with stress occurred more commonly in two groups of young men, essential hypertension as it appears in the fifth, sixth and seventh decades of life is more common in women.

Many psychiatrists, particularly those analytically oriented, have proposed that hypertension is in part a repressed rage reaction, and that chronic "unsatisfactorily" handled feelings of anger are reflected in a sympathetic hyperreactivity. It is true that many hypertensive subjects will admit that they seldom express anger. But if one listens to what they say, the import of repression of rage is differently expressed. They state that they have learned, beginning in childhood, that to express anger is to risk a bodily state which is to them uniquely distressing. When giving vent to rage, they tremble, flush, experience waves of light-headedness, and are assailed by nausea, vomiting and headache. Restlessness and weakness persist for hours or even days, interfering with work and sleep. They state that having experienced the extreme unpleasantness of this feeling state, they prefer to avoid it thereafter. If this be so, then the encouragement of a hypertensive to express his feelings may not be as wise as is commonly thought.

Based on our observations and study, we postulate the following about the relationship between psychologic stress and high blood pressure.

1. Psychologic stress is not etiologically related to hypertension, but may transiently influence the level of blood pressure, whether the disease is renal or essential in origin.

2. The capacity to respond to a stressful event with an increase in blood pressure is in part independent of the capacity to develop persistent hypertension.

3. The autonomic nervous system may contribute to an elevated blood pressure in part independently of cerebral cortical influences.

4. The capacity of subjects to respond to a stressful event with an elevation of blood pressure is approximately the same in the fifth and sixth decades as in the third decade of life.

5. Those hypertensive subjects whose blood pressure varied the most from day to day exhibited the highest titer of certain neurotic traits as assessed by psychologic tests. It is possible that both the personality abnormality and the blood pressure fluctuations are parallel responses to a difficult life situation.

That other hormones besides catecholamines are implicated in autonomic responses to noxious stimulation was shown in the following studies. When 1 cc of saturated NaCl solution was instilled intranasally into either hypertensive or normotensive subjects, a predictable reaction occurred. There was an elevation in blood pressure of the order of 30 mm systolic and 15 mm diastolic. There was a pronounced facial flush and a hyperemia of the conjunctivas. The increase in blood pressure could be prevented by the prior administration of 400 mg TEAC with the patient in the supine position. The hyperemia of the bulbar conjunctivas could be prevented by the prior topical administration of 1:1000 tripellenamine, an antihistaminic agent. There is suggestive evidence that the hyperemia of the head-end may be induced by local liberation of histamine. A sympathetically-induced vasoconstriction and local histamine liberation would thus be part of an integrated response to noxious stimulation of the nasal mucosa. It is interesting to speculate that the mechanism of this response may be similar to the so-called diencephalic flush in which an acute blood pressure elevation and head-end vasodilatation occur together. A flush and acute elevation of blood pressure occurring together have also been reported as part of the carcinoid syndrome.[20]

A series of interviews with the previously described medical students confirmed the remarkable coincidence of blushing and blood pressure elevations. On 23 occasions, medical students blushed while their blood pressure was being measured at intervals of one minute. In every

case, when a blush occurred, it was associated with an increase in diastolic pressure of 10 mm or more.

The consideration of histamine, of vasodilatation, and of serotonin in human cranial vessel function leads us to a discussion of some features of headache.

The frequency with which headache occurs in hypertensive states had led us to an investigation of this phenomenon. The mechanism, symptomatology and incidence of headache occurring in a population of 30 hypertensive subjects and in a control population of thirty normotensive subjects were examined. The frequency of occurrence of migraine and of muscle-contraction headache was approximately the same in the two groups. There was, however, a third type of headache which occurred almost exclusively in the hypertensive group. It occurred on waking, was commonly occipital in location, unaffected by vasoconstrictor agents, of moderate intensity, and usually terminated an hour or so after waking. Such headaches were almost entirely limited in their occurrence to hypertensive subjects with Grade II or III retinopathy. Migraine and muscle-contraction headache, on the other hand, were more common in the relatively milder hypertensive subjects. Successful antihypertensive pharmacotherapy was associated with a decrease in the frequency and severity of this kind of headache, but without effect on migraine or skeletal muscle-contraction headache. It appeared (fig. 3) that in some cases, the headache was closely associated with an acute rise in blood pressure and probable passive dilation of intracranial vessels which occurred immediately after waking. In other subjects, such an association could not be demonstrated. CO_2 retention, occurring during sleep, has been shown to be of appreciable magnitude, sufficient to induce cranial vasodilation and therefore, also, may be pertinent to this type of headache.[21]

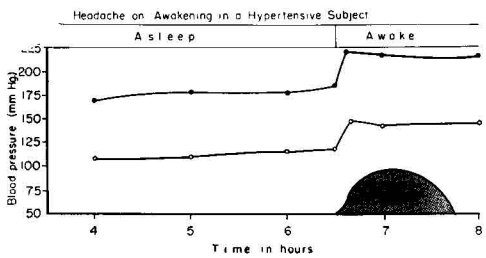

FIG. 3

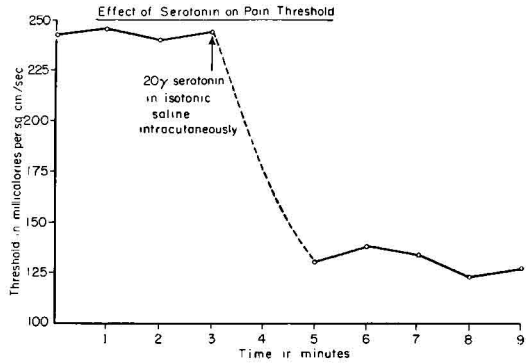

FIG. 4

Finally, I should like to say something about a substance which has been very much à la mode in the last six years, namely serotonin. The fact that this agent was a neurohumor in certain species, a pain-initiator, and exhibited smooth-muscle effects antagonized by ergotamine tartrate, led to an exploration of its relevance to the migraine syndrome. The lowered deep-pain thresholds in those scalp areas involved with migraine are a predictable occurrence. Attempts were made to see if serotonin (after the pain of the initial injection subsided) had the capacity to lower deep-pain thresholds. That it did so is shown in figure 4.

As small an amount of serotonin as 0.05 mg contained in 0.2 cc of sterile saline injected intradermally predictably lowered both superficial and deep-pain thresholds, and was associated with vasodilation in the skin surrounding the site of injection.[22]

Attempts were then made to induce headache with serotonin. Three subjects were immersed in water at 109° to 110°F. until temporal artery dilation was evident. At that time, 0.05 mg serotonin in 0.2 cc isotonic saline was injected periarterially into the scalp on one side, and 0.2 cc sterile isotonic saline on the other without the knowledge of the subject or the person who made the injections as to which contained saline and which contained serotonin. After these injections, a low-intensity headache occurred within 5 min. in two subjects and within 8 min. in a third subject about the site of the infection of the serotonin and persisted for 1½ to 4 hr.

The combination of a naturally occurring pain-threshold-lowering agent and the vasodilation induced by immersion in hot water had the capacity to induce headache.

TABLE 9

Features of the migraine syndrome compatible with serotonin effect

1. Local edema and hyperemia
2. Local lowering of deep pain thresholds
3. Therapeutic effectiveness of ergotamine tartrate
4. Occurrence of flushing and/or mottled cyanosis
5. Occasional diarrhea, urinary frequency

TABLE 10

Features of the migraine syndrome not readily explainable by serotonin effects

1. Arterial dilation
2. Venous dilation

The following features of the migraine syndrome are compatible with the known effects of serotonin (table 9). Two features of the headache attack, however, are incompatible with serotonin effects (table 10).

Since it is possible that what is called migraine represents a number of closely allied disorders rather than a single pattern of dysfunction, attempts were made to induce headache with intravenous infusions of serotonin and to use a brominated derivative of lysergic acid as headache prophylaxis. The intravenous administration of serotonin in doses of 0.2 to 2 mg per min., induced in 4 of 13 migraine patients, a headache indistinguishable from their usual head pain. Such headache was not induced in the same four subjects by infusion of isotonic salt solution, and in three of the four, headache occurred a second time when the same amount of serotonin was infused again.

With respect to BOL prophylaxis, the administration orally of 0.25 to 0.5 mg of BOL daily to the same 13 patients for a period of 6 weeks resulted in almost no headache in the four subjects in whom serotonin induced headache and had a slight, but not significant, favorable effect in the other nine. When a lactose placebo was administered to the four subjects for another month, a total of 11 headache episodes were reported by three of the four members of the group. It appears, then, that in a small percentage of subjects with the so-called migraine syndrome, the mechanisms of the headache may be closely linked with serotonin.

Finally, I should like to draw this long discussion to a close by returning to a point made earlier about autonomic nervous system functions.

Subject at one end to the varied influences of the cerebral cortex and at the other regulating a multitude of visceral and vascular functions, the autonomic nervous system reveals to its students a complex, dynamic and fascinating view of disease.

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DISCUSSION OF PAPER BY RAYMOND F. GRENFELL, M.D.

My congratulations to Dr. Ostfeld for his excellent paper on hypertension.

I have been working with the problem of hypertension for several years and I felt that there was a need for a double-blind study in this field in order to properly evaluate various agents and learn their true effectiveness. Consequently, about two and one-half years ago the hydrogenated ergot alkaloids composed of dihydroergokryptine methanesulfonate, dihydroergocristine methanesulfonate and dihydroergocornine methanesulfonate (Hydergine) and other agents have been employed in a double-blind study.

Some interesting observations have been made. In the intramuscular administration of Hydergine a dosage schedule previously devised by me was used. This consists of an injection three times a week for two weeks; two times a week for two weeks; once a week for two weeks; one injection every ten days for two injections; and a maintenance dosage of one injection every two weeks. An analysis at this time by Dr. James G. Hilton, who is working with me in this study, reveals a significant decrease in the systolic and diastolic blood pressure for as long as 47 weeks in those receiving a placebo. In contrast, a statistically significant decrease in the diastolic pressure remains in the Hydergine treated group until the present time. Thus, a heretofore unexpectedly long period of placebo effect is demonstrated and a base line has been established which will permit the evaluation of other agents. At present, we are conducting a similar study at the University of Mississippi Medical Center using various oral agents with the goal being to determine their true effectiveness and to establish a base line for oral antihypertensive agents.

Dr. Ostfeld has shown how the blood pressure can be elevated by psychologic factors, while we have shown that an intramuscular placebo given every two weeks will cause a statistically significant decrease in the systolic and diastolic blood pressure.