I bring you greetings from the United States and from Los Angeles, where I have had the pleasure of receiving many of you as visitors in the past. I hope that many more of you will visit us in the future.

I am reserved about bringing to you these observations made over the past decade because this field has been pursued so effectively by many Japanese workers and is well known to most of you. Indeed, some of you attending this meeting have joined with us in making these studies and much of the information that I bring today will not be new. In general, it will be my purpose to attempt a synthesis of some of the information which has accumulated in our laboratories concerning the influence of the brain, particularly the brain stem, on bodily functions which, when disordered, lead to problems we face in the clinic. These disease entities we call psychosomatic diseases, not an entirely satisfactory term I think; nevertheless, it does indicate the relationship between brain mechanisms and clinical problems.

Much that I shall talk about today will relate to that part of the brain stem which we know by experience to have intimate relationship with the maintenance of balance of visceral function. Additional observations will relate to influences which higher regions of the brain have upon this brain-stem system. Other references will examine relationships which sensory information has upon this central modulation area of brain. Finally the discussion will concern observations which relate to the influence of the state of the brain as a whole on these mechanisms.

A number of investigators in the Brain Research Institute at UCLA have been focusing research interest upon the problems I shall talk about. Earlier I, myself, took an active part, but more recently other responsibilities have prevented me from major participation in these investigations which interest me so much, and the work I shall report to you has in large part been conducted by colleagues, principally Dr. R. W. Porter.

Some ten years ago the relationship between lesions of the brain and complications of the gastro-intestinal tract captured my interest. Lesions, particularly those invading the diencephalon, were found to be associated with diffuse hemor-

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rhage or with non-hemorrhagic perforations of the upper gastro-intestinal system.\(^1\)

In a series of experiments, we were able to reproduce both these pathological disorders in animals by making lesions confined to the anterior or posterior parts of the hypothalamus.\(^1\) Later, by stimulating these regions through electrodes implanted both acutely and chronically, we were able to show that the diencephalic loci activated expressed an active control over function of the gastro-intestinal tract. Single stimulus bursts caused profound changes in gastric secretion and mobility. Repeated bursts over periods of many weeks led to the development of lesions in the stomach and duodenum which were indistinguishable from peptic ulceration in man.\(^2\)

In the same group of animals we found other interesting changes. Many developed ulcerations in their skin and soft tissues during the period of excitation, which lesions would clear up and disappear when stimulation was terminated at the end of the experiment. These observations brought to mind the frequent diagnoses, made by dermatologists, of neurodermatitis, seemingly more common as the years go by. Still another abnormality noted often was a distended pendulous gall-bladder, as if this chronic stimulation had produced a dyskinesia of the musculature of the biliary system.

Later, Dr. Porter found that in chronically stimulated monkeys the arteries develop atheromatous plaques. Since the subjects were young monkeys, the frequent appearance of these atheromatous plaques, particularly in large arteries, prompted the conclusion that disordered neural mechanisms might be causally related to the development of atherosclerotic changes in man.\(^3\)

![Figure 1](image-url)
The cardio-vascular system, as influenced by central nervous system mechanisms, has captured our principal interest in recent years. Dr. Porter and some of his colleagues found that stimuli applied to zones located particularly in the diencephalon caused extensive changes in the heart rate and electrocardiogram (Fig. 1) of the animal stimulated.4

At a more functional level, evidence at hand indicates that these diencephalic regions can be excited by influences coursing cephalically in the brain stem and arising particularly in autonomic receptors. Figure 2, for example, shows that

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**Fig. 2.** Marked change in the EEG occurs (B & C) upon sudden emptying of bladder (see cyto-gram). Recording sites 1, 2, and 3 are from brain stem in region of hypothalamus. (Figure 2 from Porter and Bors, EEG Clin. Neurophysiol., 1962)
sudden release of a distended urinary bladder causes a striking alteration of the EEG being recorded concurrently from brain stem regions which, when stimulated, caused profound cardiac irregularities. It would seem incredible if electrical activity of such nature, approaching epileptiform discharge in magnitude, would fail to cause distortion of the functions subserved by that region of the brain and the distortion in cardiac function unquestionably brought about by this change is unmistakable.

These cardiac irregularities induced by direct diencephalic stimulation are enhanced in severity or evoked at lower threshold by concurrent excitation applied to rhinencephalic structures. It appears, therefore, that higher nervous activity, involving, perhaps, brain structure known to contribute to the emotional stability of the organism, may influence strikingly the excitability of cardiac-regulating brain stem mechanisms.

Influences of other sorts, in addition to those arising in the urinary bladder and other segments of the autonomic system, are capable of producing a variety of changes in the electrical activity of areas of brain stem subserving visceral function and therefore, presumably are capable of altering its function. Dr. Porter found, for example, that when he injected epinephrine intravenously into animals, high voltage activity would appear in the posterior hypothalamus, an area particularly prone to evoke cardiac abnormality. Since the elaboration of epinephrine-like substances is a concomitant of stress, it is useful to conclude that distortions of cardiac activity may be induced commonly through mechanisms such as those described above during various stages of the stress response.

Another investigation attempted to assess the role of background excitability of the brain stem in the elaboration of these cardio-vascular abnormalities. In order to examine this problem, Dr. Porter placed a recording electrode in the brain stem of animals. Single pulses arising from stimuli applied to the sciatic nerve could be recorded by this electrode and the appearance of the evoked response would correlate, it was hoped, with various stages of depression induced in the central nervous system by administering sedative or anesthetic drugs. The purpose in attempting to identify stages of brain stem depression electrophysiologically was to see if such changes of excitability here would have any effect upon the cardiac reflex. The cardiac reflex was evoked by stimulating the vagus nerve (Fig. 3).

The results indicated that it was indeed possible to define different levels of excitability in the brain stem by recording techniques employed. Before anesthetics were given, evoked responses of modest amplitude exhibited a latency of 25 to 30 msecs. With light anesthesia this response disappeared almost entirely. With deeper anesthesia, a later evoked response occurred having a latency of 75 or 100 milliseconds and a much higher amplitude than the control response. With still deeper anesthesia, this delayed response disappeared. Dr. Porter found that stimulation of the vagus nerve produced a cardiac reflex that was abnormal during
only one of the stages of depression characterized by the appearance of these evoked responses. The distorted reflex was catastrophic when the vagus nerve was stimulated during the period defined by the appearance of the high-voltage long-latency response in the brain stem. Commonly, in fact, complete cardiac arrest was induced during this period, but such change never occurred at other levels of excitability. Those of you who work in the operating theater are fearful of the cataclysmic occurrence which you sometimes experience when a patient displays cardiac arrest. Presumably such patients are in this same stage of anesthesia reproduced experimentally by Dr. Porter during which some stimulus such as that evoked by intubation elicits profound alteration in cardiac function.

While it seems certain that the mechanisms described here in animals must occur under comparable circumstances also in man, relatively few observations have been made documenting a causal relationship between brain excitability or abnormality and cardiac reflex distortion in the human subject. Recently, how-
ever, Porter has observed two cases which provided interesting support for the extrapolation of laboratory observations to man. In one patient a small tuberculous abscess of the medial thalamus appeared to be responsible for severe paroxysmal auricular tachycardia since, upon recovery of the patient, the cardiac abnormality disappeared. In another patient with a septal glioma, preterminal electrocardiography indicated a coronary occlusion which autopsy failed to confirm.

Reflexes involving blood vessels are known to occur in connection with a number of clinical disorders but only recently have these phenomena become recognized to be of critical importance in connection with ruptured intracranial aneurysms. In a study just completed of 43 patients with aneurysm, Stornelli and French were struck by the consistency with which vasospastic phenomena were triggered by rupturing aneurysms. Locally, near the site of the lesion and often spreading from it to involve the entire intracranial vascular tree, we saw severe vasospasm on the cerebral angiogram. Additionally, in a large percentage of cases, systemic hypertension indicating the presence of visceral vasospasm characterized the acute phase of the disorder. There seems little doubt that these two phenomena, occurring locally on the one hand and remotely on the other, were of reflex origin with “activity” represented by the rupturing lesion serving as the excitatory stimulus.

The cerebral spasm appears to be a protective mechanism which attempts to constrict the leaking vessel and prevent it from bleeding. In so doing, however, vessels distal to the aneurysm are reflexly constricted also with the result that spreading ischemia of brain and resulting edema occur.

The physiological explanation for the occurrence of acute hypertension is
more obscure. Much attention has been focused in the past upon the fact that hypertension is often associated with rupture of an aneurysm but uniformly such hypertension has been considered to have pre-existed in a chronic state. We think the hypertension occurs acutely at the time of rupture and probably results from a stimulus arising in the rupturing or distending aneurysm. One of our patients was known to have been normotensive before rupture: he was observed during two bleeds, and on each occurrence his blood pressure rose to a maximum of 200 mm.Hg. systolic. Upon recovery, he has again normotensive.

These undesirable reflexes appear to be of critical importance both therapeutically and prognostically in this condition. In our experience the presence of these complications of rupture were of foreboding significance, since fatal issue almost always ensued in patients treated operatively when cerebral vasospasm and hypertension were severe. We are searching for a more effective means of blocking these dangerous reflexes during the active stage of the disorder and are satisfied that the success of surgical therapy will be enhanced enormously if undertaken during a quiescent interval.

In summary, I have reviewed some of the observations which we have accumulated in the past which relate to the role of the brain stem in various clinical abnormalities usually described as "psychosomatic" disorders. These brain stem mechanisms were shown to be influenced both by higher nervous activity involving importantly, rhinencephalic structures and by sensory inputs to the brain arising in a variety of visceral sources. It seems useful to conclude that such mechanisms are the seat of a great many disorders and knowledge concerning them will provide increasing enlightenment in the treatment of patients and in the search for better methods of resolving clinical problems.

Now, may I tell you again that it is a great pleasure for me to be here in Japan with so many friends and colleagues. I am honored by your invitation to speak before this distinguished society today.

References

3) Porter, R. W.: Personal communication.