Actions of Certain Drugs Injected into the Ventricular System of Man (Intraventricular Encephalo-Pharmacotherapy)*

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Harvey Cushing1 pioneered many fields of cerebral research, and in a pharmacological approach to the human brain more than 30 years ago he studied the autonomic effects induced by the injection of Pituitrin and pilocarpine into the lateral ventricles of man. A few years later Henderson and Wilson2 observed the response to intraventricular acetylcholine and phystostigmine.

Recently, Feldberg3 carried out an extensive and careful experimental study of different drugs injected into the ventricular system of cats and demonstrated that some drugs may have quite different effects when injected by the usual intravenous route or into the brain.

However, so far, the intraventricular application of drugs has not been tried in an attempt to treat or modify some clinical conditions. During the past year the effects of certain drugs were studied from a therapeutic standpoint and my colleagues and I presented a preliminary report of this procedure, which we have named “intraventricular encephalo-pharmacotherapy.”

Material and Method

For screening and evaluating the main effects induced by intraventricular drugs, 4 patients suffering from irreversible cerebral coma of several weeks’ and months’ duration were studied. In 1 patient coma appeared after a very severe head injury; in another it was produced by cerebral anoxia secondary to anaesthetic cardiac arrest in the course of an operation on the shoulder; in the third it was the result of a probable vascular lesion of the midbrain during pregnancy; and in the fourth it was produced by an obscure lesion of the region of the 3rd ventricle. All of these patients presented signs of decortication and were fed by nasal tube; 3 had had a tracheotomy. The motor, sensory and reflex activity of the head was at least partially preserved. Electroencephalography showed slow activity in 3 and a flat record in the patient suffering from anoxia of the brain. Although these patients had severe lesions of the brain of long duration with great changes in consciousness and were not very suitable for pharmacological studies, they provided the opportunity to start our observations.

In addition to these cases the effect of some intraventricular drugs was recorded in a second group of 14 fully conscious parkinsonian patients before the performance of subcortical stereotaxic lesions. The same burr hole in the skull made for the operation was used for the intraventricular injections which were made through a fine catheter placed in the lateral ventricle several days before the operation.

In the last group of patients there were 3 with intractable facial pain (2 secondary to malignant tumours already operated upon), 1 with epilepsy and 1 with psychosis (before frontal leucotomy was carried out).

In order to make frequent and periodic intraventricular injections for long periods of time a special metal chamber of stainless steel* was devised. This metal chamber has a metal ring on the top with a silicone rubber diaphragm (Fig. 1). After the burr hole is

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* Manufactured by Comercial Quirurgica Conde, Cea Bermudez 67, Madrid.
made in the centre of a small skin flap a hole in the dura mater is opened and the metal chamber is inserted into the bone cavity with a fine plastic catheter at its end which is placed in the frontal horn of the lateral ventricle. Once cerebrospinal fluid flows into the chamber the metal ring with the silicone diaphragm is screwed to the upper ring of the chamber and the whole system is then ready for making injections through the silicone diaphragm with a fine needle. The ventricular catheter is directed towards the 3rd ventricle and the foramen of Monro and its proper situation can be checked radiographically by injecting a small amount of air or a few drops of a radiopaque solution (Fig. 2).

With this method repeated injections were made in cases of coma, pain and epilepsy during long periods of several weeks without complications and with a complete tolerance of the intraventricular device. Usually there was moderate increase of cells in the control studies of the cerebrospinal fluid and only if the catheter was too near the wall of the ventricle was the presence of some blood noted in the fluid with larger increase of cells, but there was no great discomfort for the patient. In some cases the encephalograms also showed transitory slow activity in the region near the intraventricular cannula.

Results

A. Main Effects of Intraventricular Drugs

The effects induced by intraventricular injection of some drugs into the human brain were very diverse. These were mainly autonomic responses, respiratory disturbances with some substances, psychical changes related to stimulant and depressant actions, modifications of the level of consciousness, convulsive activity, etc. Some of these findings have also been recorded in the recent and extensive researches in animals by Feldberg.²

It is important to emphasize that some effects may appear a long time after the intraventricular injection. At the beginning of these studies the injections were repeated too soon. Generally the autonomic effects usually appeared earlier and the stimulant action came before possible signs of nervous depression with some drugs. Also the responses were usually long-lasting and often persisted for several hours. For all these reasons the study of intraventricular drugs requires long intervals between the application of different substances or different doses of the same drug. As a rule the injection was repeated every 24 hours, and the interval was reduced only to attain a therapeutic action.

The doses are also very important and the effect may be quite different and even opposite according to the amount of the