positive correlation coefficient of +0.9 between the two methods. Eight non-medicated subjects were studied before and after intravenous infusion of mephentermine, 5 of them with continuous spinal anesthesia (third to eighth thoracic levels) and 3 subjects without anesthesia. *Results:* In the normotensive unanesthetized subjects, the intravenous administration of mephentermine (0.1 per cent solution in 5 per cent dextrose, average dose: 24.4 mg.) caused an increase of forearm blood flow; 47 per cent in five minutes, 32 per cent in thirty minutes and 32 per cent in sixty minutes after infusion of the drug was completed. There was a concomitant increase in calf blood flow. Calculated forearm and calf vascular resistance decreased. Vascular distensibility (change of volume per unit of effective venous pressure) obtained from the initial linear portion of the volume pressure curve, decreased in each of the three non-anesthetized subjects. The maximal change in forearm distensibility was 39 per cent and 14.6 per cent in calf distensibility. Spinal anesthesia resulted in 160 per cent increase of calf blood flow, 70 per cent decrease of calf vascular resistance, slight increase in calf venous distensibility. There was 18 per cent decrease in forearm blood flow, 20 per cent increase in forearm vascular resistance and there was no appreciable change in forearm venous distensibility. There was a further decrease of blood flow with an increase in vascular resistance in the forearm segment when mephentermine was administered during spinal anesthesia. Calf blood flow, however, increased significantly in the presence of decreased vascular resistance. *Conclusion:* In view of these findings, it seems reasonable that mephentermine exerts an action on the capacitance vessels, probably mediated through the autonomic nervous system. (Supported by Research Grant HE-06069 from U.S.P.H.S.)

**Distribution and Site of Action of Extradural Analgesic Drugs Using $C^{14}$ Labelled Lidocaine and Mepivicaine in Dogs.** P. R. Bromage, M.B., F.F.A.R.C.S., D.A., and M. F. Burfoot, M.A., B.M., D.A., *Royal Victoria Hospital, Montreal, Canada.* A pilot study (Bromage, P. R., Joyal, A. C., and Binney, J. C.: Science *140:* 392, 1963) revealed that the assay of radioactivity in the neuraxis and its coverings, following the injection of local analgesic drugs tagged with $C^{14}$, is accurately specific for unchanged drug. This work has been continued along lines indicated by trends in this study. *Method:* Mongrel dogs weighing between 15–30 kg. were anesthetized and the subarachnoid and extradural spaces were catheterized. Following injections of the drug, serial samples of cerebrospinal fluid were taken and the spinal cord and its coverings were dissected to yield samples of the extradural and intradural nerve roots, the dura and pia mater and the cord. *Results:* Preliminary results showed a high level of drug in both the extradural and intradural parts of the nerve roots with much smaller amounts in the dura. The level in the pia was also high and the cord contained significant amounts. We postulate that one route of entry into the neuraxis is the passage of drug out of the spinal foramina, by diffusion into the subperineural space and centripetal flow into the cord and cerebrospinal fluid. Cheng has shown (Thesis, McGill University, 1945) as have Brierly and Field (J. Neurol. Neurosurg. Psychiat. *12:* 89, 1949) that a free communication exists between the peripheral nerve and the neuraxis in the subperineural space. Shanthaveerappa and Bourne have described (J. Anat. [Lond.] *96:* 527, 1962) the continuation of the epithelial layer of the pia-arachnoid peripherally as a complete epithelial cell layer that surrounds each fasiculus and nerve fiber to its termination. In addition, they describe this layer as being rich in enzymes. We, therefore, sought evidence to establish whether or not these enzyme systems actively aided or hindered transport of drugs across the membrane. Solutions of dinitrophenol and sodium iodoacetate were injected into the extradural space one hour prior to the injection of the drug under test. The results are as yet indecisive, but in both cases markedly lower levels of drugs were found in both the cerebrospinal fluid and the tissues of the neuraxis and its coverings. Controversy still exists over the respective roles of the epineurineum and perineurium as diffusion barriers. We believe that confusion is due to the postulation of the perineural epithelium described by

Shanthaveerappa and Bourne, for it has not previously been described as investing the fasiculi so completely. *Conclusion:* Our results neither confirm nor deny that local anesthetic drugs diffuse across the dura directly into the cerebrospinal fluid. They do show that their distribution from the extradural space is complex, and that the sites of action are in the extradural and intradural roots, as well as in the neuraxis itself.

**Phlebitis from Plastic Intravenous Catheters.** FREDERICK W. CHENEY, JR., M.D., and JOHN R. LINCOLN, M.D., *Department of Anesthesiology, Maine Medical Center, Portland, Maine.* The incidence of significant phlebitis with the use of plastic intravenous catheters has been said to be about 16 per cent, with bacterial contamination suspect (Erwin, P.: Arch. Surg. *66:* 673, 1953). This study was initiated to determine the incidence and etiologic factors of this phenomenon. *Method:* Intracath (Bard 1514) catheters, 18 gauge, 8–12 inches in length, were inserted, usually in the basilic or cephalic veins of the arms, prior to the induction of anesthesia. The skin was prepared with aqueous Zephiran and the catheter inserted through a no. 14 needle. Three per cent achromycin ointment or a bland ointment was placed over the puncture site. This was covered with sterile gauze and taped securely. A record was kept of all solutions infused through each catheter, concomitant systemic antibiotic therapy, length of time the catheter was in place and the grade of reaction when removed. In addition, the terminal 3–5 inches of each catheter were cultured. All patients who showed no reaction at the time the catheter was removed were re-examined twenty-four hours later and any change in reaction noted. Reactions were classified as grade "A"—no reaction or slight erythema around the site of entrance of the catheter, or grade "B"—significant phlebitis associated with cellulitis, tenderness, or painful thrombosis of the vein. *Results:* Of the 137 cases studied, 60 had grade B reactions. The mean time the catheters were in place was 38.5 hours. A single application of achromycin ointment failed to reduce the incidence of phlebitis. The incidence of grade B reactions varied directly with the time the catheter was in place. The incidence of phlebitis increased from 9 per cent of those whose catheters were withdrawn in the 0–24 hour time period, to 58 per cent of those withdrawn in the 25–48 hour period, to 74 per cent of those withdrawn in the 49–72 hour period. Sixteen per cent of the patients had converted from grade A to B reactions when the twenty-four hour postwithdrawal visit was made. Patients who received heparin, 10 mg./1,000 ml. of infused solution, had their catheters in place significantly longer before the development of phlebitis than those who did not. The incidence of positive cultures was 9.5 per cent (13 of 137 cases) and most of these were staphylococci coagulase negative. There was no correlation of positive cultures with phlebitis. Acromycin ointment did not influence the incidence of positive cultures. No patient with a positive culture had any evidence of systemic symptoms. *Conclusion:* This study suggests that the major factor causing phlebitis and local tissue reactions from plastic intravenous catheters is mechanical rather than bacterial, and that adverse reactions are directly related to the length of time the catheter is in place. No other factor studied seemed to have any influence on the incidence of phlebitis, except heparin, which increases the length of time a catheter may be kept in place without phlebitis.

**Evaluation of Halothane Toxicity by Tissue-Culture Methods Halothane.** GUENTER CORSSEN, M.D., and ROBERT B. SWEET, M.D., *Department of Anesthesiology, The University of Michigan Medical School, Ann Arbor, Michigan.* Clinical studies of anesthetic agents can hardly be relied on to furnish objective evidence of drug toxicity because of the difficulty of evaluating biochemical reactions as well as the impossibility of setting up strict controls. The experimental techniques involved in tissue-culture methods appear to offer a much more efficient means of analyzing the effects of drugs. Recently, such methods were used in a study of the possible cytotoxic effects of halothane, and preliminary results indicated that cultured human liver cells may be affected adversely by this agent. *Method:* In this study, human liver cells under culture