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Reports of Scientific Meetings

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Symposium on Cerebral Blood Flow and Metabolism

The 7th International Symposium on Cerebral Blood Flow and Metabolism was held in Aviemore, Scotland, June 17–20, 1975. The remarkable growth of this organization was exemplified by the presentation of 152 original papers, representing 26 nations and some 500 registrants. The ever-changing complexity in this field of research was again evident as more sophisticated methodologies yield results that challenge old concepts and introduce new ones.

A number of interesting concepts were introduced. Hass (Ontario) showed that prior adrenalectomy protected rats from damage to the blood–brain barrier caused by acute hypertension and that this protection was abolished by the administration of hydrocortisone. Nilsson (Sweden) found that the CBF response to acute hypoxia was not associated with immediate lactic acidosis and concluded that some other trigger must account for vasodilation. Levy (New York) found in gerbils that the no-reflow phenomenon was not an essential process in the development of ischemic brain damage. Grubb (Missouri) demonstrated in man for the first time that following vasospasm induced by subarachnoid hemorrhage there are corresponding regional reductions in CBF and CMR_{O_2}, but he was unable to explain a seemingly paradoxical increase in regional cerebral blood volume. Raichle (Missouri) observed in awake man regional increases in CBF and CMR_{O_2} that were appropriate to the areas of brain being stimulated, thus providing the first direct *in-vivo* human evidence of what has long been assumed, but never proven. Linton (England), Eidelman (South Africa), and Hoff (California) all presented data indicating that the peripheral chemoreceptors and the parasympathetic efferent nerves (VIIth cranial) had little or no significant role in the regulation of CBF responses to CO_2 and to hypoxia. The much-maligned ^{133}Xe inhalation technique for measuring regional CBF was shown in several studies to have good correlation with the carotid injection technique. Indeed, Wyper (Scotland) presented excellent comparative results utilizing a greatly simplified inhalation technique that requires only two minutes of inhalation and two and a half minutes of clearance monitoring.

More than 20 papers were concerned with the neurogenic control of CBF and autoregulation. There now seems to be little question of the existence of two distinct anatomic noradrenergic systems. In addition to the well-recognized sympathetic innervation arising from the superior cervical ganglia, there is a second system that appears to originate primarily in the locus coeruleus. The former is thought to innervate the extraparenchymal vessels (to the level of the conducting vessels in the pia), whereas the latter appears to provide innervation to the parenchymal cerebral microvasculature. Raichle (Missouri) presented data suggesting that the central noradrenergic system may have the unique function of regulating capillary permeability as well as blood flow. Herz (France) demonstrated in cats that a lateral pontine lesion resulted in a significant attenuation of the CBF response to changes in CO_2 in the appropriate hemisphere, whereas autoregulation remained intact. This suggests an unusual differential type of neurogenic control of CBF. Similarly, Capon (Belgium) observed in cats that sectioning of the brain at a high pontine level resulted in loss of the cortical flow response to hypercapnia.

Numerous pharmacologic studies designed to examine the significance of the sympathetic innervation were reported, although the results were often contradictory. Owman (Sweden) reported *in-vitro* evidence that arteries of the brain possess both alpha and beta receptors and that the latter possess the features of a $beta_1$ receptor, thus differing from the usual finding of $beta_2$ receptors in the peripheral circulation. MacKenzie Scott

land) found in baboons that if norepinephrine is administered so as to bypass or cross the blood–brain barrier (by intraventricular injection or acute administration of intracarotid hypertonic urea), cerebral metabolism and CBF significantly increased. Similarly, if endogenous norepinephrine catabolism is inhibited (by an MAO inhibitor), CBF and CMR_{O_2} are increased. Kuschinsky (West Germany) found no evidence in resting pial arteries of a norepinephrine-induced vascular tone, but the vessels did constrict upon microapplication of norepinephrine. Ekstrom-Jodal (Sweden) observed vasoconstriction produced by intravenous administration of norepinephrine during hypoxia, but could not find evidence of a naturally occurring alpha receptor influence that could be blocked and thus further dilate the vascular bed during hypoxia. McCalden (South Africa) presented evidence suggesting that the cerebral circulation is normally protected against sympathetic vasoconstriction by uptake and metabolism of norepinephrine in extraneuronal and possibly neuronal sites. Such a protective effect can be abolished by blocking catechol-o-methyl transferase. Caronna (New York) could find no evidence in reserpinized rats that catecholamine depletion had any effect on CBF, CMR_{O_2}, or autoregulation.

Interruption of the sympathetic innervation was reported to have varying and often unexpected effects upon autoregulation. Fitch (Scotland) found autoregulation in baboons following sympathectomy to be preserved to mean pressures of 40 mm Hg, whereas in intact animals autoregulation was lost at 60 mm Hg. In complementary fashion, Kovach (Pennsylvania) found in baboons that hemorrhagic shock (35–40 mm Hg) resulted in heterogeneous cerebral perfusion that could be normalized by prior administration of phenoxybenzamine. In contrast, Gotoch (Japan) reported that pial vessels in cats did not autoregulate normally following ganglionic blockade by hexamethonium. In man, Nanda (Scotland) could find no evidence of altered autoregulation in patients with severe sympathetic dysfunction. On balance, these results suggest that, if anything, sympathetic innervation of the cerebral vasculature may exert a detrimental effect in the circumstance of profound hypotension.

Various vasoactive substances were examined by a number of investigators looking for mechanisms of vasospasm, mechanisms of ischemic vasodilation, or mechanisms of autoregulation. Welch (Texas) reported somewhat remote evidence that 5-hydroxytryptamine may be released during ischemia, resulting in vasoconstriction and progression of infarction. Rubio (Virginia) observed adenosine as well as lactate increases during hypotension in rats and suggests that adenosine may play an important role in regulating vascular diameter, and Wahl (West Germany) demonstrated that adenosine dilates large pial arteries. Flamm (New York) found that cyclic AMP in the walls of vessels in spasm (basilar artery) was significantly depleted, and that dilation with increased cyclic AMP levels could be produced by administration of isoproterenol. Forrester (Scotland) reported that ATP infused in the carotid artery of baboons increased both CBF and CMR_{O_2}. The mechanism for such an effect is unexplained, since ATP is not believed to cross the blood–brain barrier. Olesen (Denmark) could observe no effect in man on CBF following intracarotid injection of naturally occurring vasoactive substances such as histamine, serotonin, prostaglandin E_1, and isoprenaline–propranolol, whereas Yamamoto (Canada) found in dogs that serotonin, prostaglandin E_1, and prostaglandin E_2 all had cerebral vasoconstriction effects. Rosenblum (Virginia) observed by direct application to mouse pial vessels that vasoconstriction could be produced by norepinephrine, serotonin, and prostaglandin $F_{2\alpha}$. These types of studies inevitably result in contradictions and leave the neutral observer in an inconclusive state of mind. Differences undoubtedly are accounted for at least in part by differences in species, drug concentrations, methods of administration, and methods of flow measurement. It appears increasingly unlikely that the "shotgun" approach of an investigator testing a variety of drugs in his favorite animal model will ever unearth basic mechanisms.

Studies in hypertensive animals and man yielded fairly predictable results. With chronic hypertension, autoregulation shifts to the

right so that higher pressures are tolerated without breakthrough (that is, increased flow) or disruption of the blood–brain barrier. The latter is explained by an altered lumen–wall ratio (Johansson, Sweden). Similarly, low pressures are less well tolerated with severe reductions in CBF (Jones, Scotland). In acute hypertension blood–brain barrier disruption appears to occur at the level of the arterioles, due to either opening of "tight junctions" or the occurrence of endothelial breaks (Suzuki, Japan). An alternative explanation, particularly in the late phases of acute hypertension, might be the occurrence of regional hypoxia due to extreme vasoconstriction with subsequent blood–brain barrier breakdown. In the presence of regional ischemia, the induction of hypertension results in increased edema that overwhelms the possible benefit resulting from a transient improvement in collateral flow (Feske, France). This should be differentiated from the beneficial effect of an elevation of pressure in the presence of arterial spasm. Reilly (Scotland) demonstrated in baboons the phenomenon of "false autoregulation" that occurs following acute edema produced by a cryogenic lesion. In this circumstance, the CO_2 response is lost, but autoregulation appears to be intact. The previous explanation that this may be accounted for by elevated brain-tissue pressure appears unsatisfactory, since such pressure increases were not reflected by intraventricular pressure measurements. Thus, the mechanism for this pressure–flow dissociation appears to be independent of intracranial pressure, perfusion pressure, or local brain-tissue pressure.

In the invited guest lecture, Sokoloff (Pennsylvania) presented an elegant method for the simultaneous measurement of rates of glucose consumption in the various structural and functional components of the brain *in vivo*. The method is based upon the use of ^{14}C-deoxyglucose as a tracer, with measurement by quantitative autoradiography. Local glucose consumption is calculated using a derived equation based upon a number of reasonable assumptions. The sensitivity and accuracy of this method were demonstrated in a study of macaque monkeys wherein appropriate regional cerebral increases in glucose consumption were observed following various types of visual stimulation. Shapiro (Pennsylvania), using this method, determined the effects of different anesthetics on local cerebral metabolic rates. Phencyclidine was found to cause variable degrees of regional inhibition of glucose consumption, pentobarbital tended to cause a fairly uniform inhibition (mostly grey matter), and halothane produced a pattern of progressive inhibition from frontal to occipital regions.

In a session concerned primarily with methodology, the microsphere technique was found to yield presumably erroneously high values for white-matter flow compared with the hydrogen clearance technique, possibly due to streaming of the microspheres into penetrating vessels with preferential trapping (LaMorgese, New York). However, Rowan (Scotland) reported that the hydrogen clearance technique yields white-matter flow significantly lower than that shown by the ^{133}Xe clearance method. Thus, it is not clear in comparing these three methods where the error resides. In two important studies, Raichle and Eichling (Missouri), using cyclotron-produced positron-emitting isotopes in Rhesus monkeys, demonstrated a blood–brain barrier for water that varies with the cerebral blood flow. Thus, erroneous results will result in evaluating blood–brain barrier transport if water is used as the standard. Similarly, CBF measurements may be erroneous when water is used as a tracer. This has resulted in the recommendation that labeled ethanol be used instead as a freely diffusible tracer. However, Raichle demonstrated that longer chained alcohols (presumably because of increased lipid solubility) are more diffusible than ethanol, and showed that butanol was indeed freely diffusible. Eichling demonstrated that in pathologic states the equilibrium partition coefficient for ^{133}Xe varies considerably (presumably due to variable tissue lipid content) and may result in CBF measurement errors of as much as 30–50 per cent. This same group (Ter-Pogossian) described a sophisticated technique for three-dimensional noninvasive measurement of regional cerebral hemodynamics and metabolism. The technique combines tomographic imaging with cyclotron-produced radioisotopes of metabolic substrates and permits virtual elimination of inter-

ference from activity contributed by structures overlying and underlying an area of disease. As already mentioned, the inhalational ^{133}Xe technique was found to compare favorably with the carotid injection technique in three different studies. There was, however, a suggestion that erroneous values may be calculated in low-flow states. This is perhaps only a matter of degree, since the injection technique is also erroneous in very low flow states.

The question of barbiturate-induced cerebral protection during ischemia was the subject of several studies. Gygax (Switzerland) found in cats that induced hypotension to 45 mm Hg did not alter the EEG in animals anesthetized with pentobarbital, whereas marked changes occurred during nitrous oxide anesthesia. Smith (California) found in dogs, following production of a cryogenic lesion, that a five-hour period of pentobarbital anesthesia resulted in less cerebral edema, lower intracranial pressures, and reduced sodium/potassium ratios as compared with awake animals. By contrast, animals anesthetized with 1.9 per cent halothane were worse in all categories. Michenfelder (Minnesota) maintained Java monkeys for 48 hours on pentobarbital anesthesia following occlusion of the middle cerebral artery. Compared with "awake" monkeys, there was significantly less morbidity and mortality, and the frequency and size of infarction were less in the anesthetized animals. Such studies continue to demonstrate a consistent protective effect for barbiturates which in the near future may well justify direct clinical application.

A variety of unrelated studies concerning CBF regulation, anesthetic effects, and CBF in various pathologic states were reported. Severinghaus (California) reported further studies concerned with the nature of the oxygen waves that can be recorded with small electrodes (1–3μ diameter) imbedded in cat cortex. These electrodes record waves that are compatible with a "stop-and-go" type of capillary flow consistent with local and presumably metabolic feedback regulation. Alexander (Wisconsin) reported that both nitrous oxide and halothane appear to slow the movement of glucose carrier through the membranes of the blood–brain barrier, which might account for the changes known to occur in brain glucose concentrations during anesthesia. McDowall (England) tried to determine whether, following administration of althesin in baboons, Pv_{O_2} was the triggering event that might account for the increase in cerebral vascular resistance. However, since Pv_{O_2} decreased coincident with the EEG slowing and CVR increase, no such signal could be identified. Overgaard (Denmark) reported that hydralazine causes a significant elevation in intracranial pressure despite a 20 per cent reduction in MAP and coexisting hypocapnia. They speculate that there is an initial dilation of capacitance vessels, followed by dilation of resistance vessels. A similar effect of nitroprusside on intracranial pressure has also been observed. Symonds (England) and Waltz (California) each reported studies suggesting that a critical cortical flow for maintenance of normal neuronal activity resided somewhere between 16 and 20 ml/100 g/min. Welsh (Pennsylvania) found in rabbits a critical perfusion pressure of 30 mm Hg, below which significant changes in the cerebral energy state occurred. At 40 mm Hg, only EEG changes were observed. Crowell (Massachusetts) reported that occlusion of the middle cerebral artery could be tolerated in monkeys for as long as 8 to 16 hours without infarction, implying that effective medical therapy might be possible in the early hours following acute stroke.

In the closing remarks, Plum (New York) made a plea that future goals of research in cerebral blood flow be directed toward solving the problems of pathologic states since, for the most part, studies concerned with methodology and normal physiology have been exhausted. Lassen (Denmark) also emphasized the importance of studying disease states and pointed to the studies concerned with barbiturate protection as examples of appropriate areas for future research.

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