The Brain: An Endocrine Organ and Hormone Target

A different view of the brain from that commonly held emerged from a recent international conference of neuroendocrinologists at Chapel Hill, North Carolina, 14 to 16 May 1974, which attracted more than 300 scientists and clinicians from 12 countries. The discussion focused not only on the median eminence and associated hypothalamic nuclei that are well known as the "hypophyseotropic area" (B. Halasz), but many other regions within the diencephalon, telencephalon, lower brainstem, and even spinal cord were shown to be of neuroendocrine significance as well. Target neurons for sex steroids were reported to exist in selective sites within all of these central nervous system regions in many vertebrate species, such as rat and guinea pig (M. Sar), bird (C. Martinez-Vargas), and tree shrew and squirrel monkey (D. Keefer). Different from the sex steroid "feedback" sites is the distribution of adrenal steroids. While the sex steroids concentrate most heavily in certain neurons of the hypothalamic-preoptic region, the natural glucocorticoids appear mainly in nerve cells of the hippocampus, dorsal, and lateral septum and the temporal-occipital lobe (H. Rees).

Thyroid hormones—or metabolites of them—which are thought to exert relatively little effect on mature brain tissue in contrast to the developing brain, appeared to be localized in nuclei and cytoplasm of neurons almost throughout the entire mature brain (W. Stumpf). Interesting in this context is the earlier use of thyroid hormones for the therapy of certain psychic disorders, although their effectiveness has remained controversial. Nevertheless, thyroid stimulating hormone releasing factor (TRF or TRH) has been suggested recently to be promising in psychiatric therapy for depressed states (A. Prange). The TRF activity could be assayed from extracts not only from the hypophyseotropic area of the hypothalamus but also from forebrain, cerebral cortex, and brainstem (R. D. Utiger). Similarly, TRF release, as indexed by a rise of thyroid stimulating hormone in the plasma, is induced by electrical stimulation of amygdaloid nuclei and the hypothalamic arcuate and ventromedial nuclei (J. B. Martin). In addition, gonadotropin releasing factor is not only extracted from the hypothalamic median eminence region, but also from the preoptic area (S. McCann). With immunohistochemical techniques, now increasingly applied, highest amounts of gonadotropin releasing factor are shown to be present in the median eminence, but it is also present elsewhere, including the vascular organ of the lamina terminalis and the subfornical organ (G. Koslowski). For these so-called circumventricular organs, which lack a blood-brain barrier, much circumstantial evidence suggests that they are involved in hormonal regulations (T. Anand-Kumar), although for most of them the precise function is still unknown. Localization of gonadotropin by the immunoperoxidase technique was reported in neurons of the basal hypothalamus (P. Petrusz), which supports the idea of short loop feedback regulation.

It appears that different hormonal messengers do more than affect the regulation of their own release via feedback to the pituitary and brain. Important other effects on the brain include modulation of behavior, not only as is well known for the sex steroids (R. Lisk), but also for pituitary hormones such as adrenocorticotrophic hormone (ACTH) and vasopressin (van Wiemersma-Greidanus) or melanocyte stimulating hormone and melanocyte inhibitory factor (A. Kastin). Sensory perception in patients is altered in certain endocrine disorders because of the increased or decreased actions of ACTH, adrenal corticosteroids, or thyroid hormones (R. Henkin). Hormones acting on the brain during a certain period of pre- or postnatal development influence irreversibly the functioning of hormone feedback as well as certain aspects of behavior in later life. For instance, infertility or certain forms of homosexuality (D. Dörner) may result from too much or too little of a hormone or drug circulating in the blood before or shortly after birth, depending on species. The existence of sex hormone receptors in the brains of newborns has now been established by P. Sheridan, who presented autoradiographic maps of androgen and estrogen target neurons as a likely substrate underlying known organizational effects of gonadal steroids.

Among the prominent investigators attracted by the conference were three pioneers, Charles Sawyer, John Everett, and Henry Hollinshead, who, 25 years ago at neighboring Duke University, laid the groundwork for the now resurgent field of neurotransmitter-hormone interactions. A special session on this subject was devoted to the anatomical and functional relationships between neurotransmitter circuits and steroid hormone feedback neurons; U. S. von Euler was chairman of this session. Autoradiography and fluorescence microscopy were combined to attack the problem directly (L. Grant) with the use of unembedded freeze-dried sections, which permit the simultaneous localization in the same preparation of tritiated hormones and catecholamine-containing neurons. Of the fluorescing dopaminergic neurons forming the tuberoinfundibular dopamine system 40 to 50 percent were found to show nuclear binding of [^{3}H]estradiol. That such a relationship is likely to be of physiological importance is suggested by data that implicate the tubero-infundibular dopamine neurons in the regulation of gonadotropin release (K. Fuxe). In addition, cholinergic (L. Martini) and serotonergic (C. Kordon) neurons appear to exert, respectively, facilitatory and inhibitory effects on the release of hypophyseotropic hormones.

Terminal distribution areas of noradrenergic pathways were delineated by D. Jacobowitz, and T. Hökfelt reported the use of immunofluorescence techniques for the mapping of "neurotransmitter pathways" by localizing antibodies to dopa decarboxylase, dopamine-β-hydroxylase, and phenylethanolamine *N*-methyltransferase. The tracing of the latter enzyme revealed hitherto unknown adrenalin-containing neural pathways, arising from cells in the medulla oblongata and projecting to the spinal cord, pons, midbrain, hypothalamus, and thalamus.

A group associated with the laboratory of J. Axelrod introduced a novel biochemical approach which provides for a highly discrete anatomical study of the chemoarchitectonics of the brain: M. Palkovits introduced a "punch-out" dissection technique, which allows for the biochemical analysis of minute amounts of substances in individual hypothalamic nuclei and thus provides information, for instance, on five sub-

divisions of the "arcuate nucleus." This "Palkovits-punch" technique was utilized to study individual hypothalamic nuclei, demonstrating impressive differences in the distribution of monoamine transmitters (M. Brownstein), their synthesizing enzymes (J. Saavedra), and the effects of hormones on the synthesis of monoamines in those nuclei (J. Kizer). The demonstrated possibility of more meaningful and topographically related biochemical analyses will likely impose a new standard for researchers who, because of technical difficulties, were previously satisfied to study the whole brain or cubes of it.

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Transmissible Disease and Blood Transfusion

It is conventional to think of viral hepatitis as the only disease which is transmitted by blood transfusion. Whether other equally serious diseases may be spread in this fashion was the subject under discussion at the sixth annual Red Cross scientific symposium, "Transmissible Disease and Blood Transfusion," held in Washington, D.C., on 8 and 9 May 1974. Four major points were established. First, a large part of transfusion-associated hepatitis may not be related to the two known forms of viral hepatitis, infectious (type A) or serum (type B) hepatitis. Second, viruses of the herpes group and, in particular, cytomegalovirus and Epstein-Barr virus may be of considerable importance in transfusion and transplant therapy. Third, although many more or less exotic diseases, including parasitic diseases, are potentially transmissible by blood transfusion, the problem does not exist for practical purposes or may be overcome by simple surveillance procedures. Finally, even with the advent of new and sensitive test methods for carriers of serum hepatitis, blood obtained from voluntary sources is still much safer than blood from commercial (that is, paid) donors.

The first day of the meeting was devoted to hepatitis, and papers dealt with both the epidemiology and the etiology of the disease. It is clear that screening programs for the hepatitis B antigen are taking effect, and a number of speakers noted the decline in the incidence of posttransfusion hepatitis type B. The problem of posttransfusion hepatitis is by no means solved, however. Robert Purcell (National Institute of Allergy and Infectious Diseases) outlined the discovery of a particle and antibody associated with hepatitis type A. The availability of this apparent marker for hepatitis type A has led to his discovery that most cases of posttransfusion hepatitis which are not hepatitis type B also appear to be unrelated to hepatitis type A. Other speakers confirmed this supposition, and we were encouraged to consider the possibility of hepatitis types C, D, and so on.

There has been substantial progress in the study of the etiology of hepatitis B, and there is now considerable evidence supporting the notion that the Dane particle is the infectious virion of hepatitis B.

J. Gerin (Molecular Anatomy Program, Oak Ridge National Laboratory) discussed the finding of a specific nucleotide polymerase within the inner core of the Dane particle. Inhibition studies indicate that the polymerase requires a DNA primer. Enzyme, primer, and product all appear to be bound to the Dane core particle. The polymerase could be precipitated from serum specimens by prior treatment with serum containing antibodies to hepatitis type B surface antigen (HB_sAg). These findings could provide the basis of a test for hepatitis B infectivity. J. Hoofnagle (Bureau of Biologics of the Food and Drug Administration) presented his recent findings on the occurrence of antibody to the inner core of the Dane particle. It is probable that this antibody to the core is a reliable indicator of ongoing hepatitis B infection in that it is found in almost all HB_sAg carriers and in certain HB_sAg-negative donors who were implicated in cases of posttransfusion hepatitis type B.

Acceptable animal models for hepatitis types A and B have been developed and are now in use by a number of workers in the field. A. W. Holmes (Rush–Presbyterian–St. Luke's Medical Center, Chicago) described his marmoset model for hepatitis A, and L. F. Barker (Bureau of Biologics) dealt with the chimpanzee, a successful, if expensive, model for the study of hepatitis type B.

A wide spectrum of other diseases with potential relevance to blood transfusion were also discussed. D. J. Lang (Duke University) discussed posttransfusion disease associated with Epstein-Barr virus and cytomegalovirus (CMV). Both viruses are widely distributed in the normal population, and serologic or clinical evidence of exposure is frequently found in transplant or transfusion recipients. Lang has been able to show an association between the number of transfused leukocytes and CMV infection in the recipient. It is as yet uncertain whether herpesvirus-associated disease in blood or transplant recipients is a direct result of transfer of virus from the donor, or whether latent host virus is reactivated by the immune stimulus associated with such operations.

Other viruses potentially transmissible by transfusion are arboviruses and the slow viruses, respectively discussed by R. N. Philip (Public Health Service, Rocky Mountain Laboratory) and Louis Herzberg (National Institutes of Health). Each gave a comprehensive review of his field and pointed out that there was little or no evidence of transmission of either virus group by transfusion. We were warned that a significant potential did exist in the case of Colorado tick fever, which has a lengthy viremic phase following clinical symptoms. In endemic areas, subjects with a recent history of tick-associated febrile illness should be deferred from donating blood for 6 months.

Transmission of bacterial and rickettsial disease by blood transfusion is not a serious problem. In common with most other microbial diseases, the potential donor is too unwell to consider giving blood at the time when he is circulating infectious organisms. Bacterial infection as a result of contamination of blood during collection or processing is still a hazard, however.

Finally, the problem of parasitic disease was considered. Transfusion malaria is no longer a significant hazard as current donor-screening practices are sufficient to eliminate potentially infectious donors. Martin S. Wolfe (Office of Medical Services, Department of State) discussed nonmalarial parasitic disease in the context of the symposium. It is clear that American trypanosomiasis (Chagas' disease) poses a serious transfusion problem in South America; but African trypanosomiasis, visceral leishmaniasis, toxoplasmosis, and filarial in-