Pituitary-Brain Vascular Relations: A New Paradigm

Wislocki's model for brain-pituitary relations emphasizing portal "veins" is reconsidered and revised.

Richard M. Bergland and Robert B. Page

Summary. Vascular casts of the pituitary gland have demonstrated a paucity of veins extending from the adenohypophysis to the systemic circulation and have suggested that some adenohypophyseal venous blood returns to the neurohypophysis. The neurohypophyseal capillary bed may function as a vascular switch and in this article a series of 14 questions are proposed regarding the vascular dynamics of the pituitary. Together these questions raise the larger question, namely, whether pituitary hormones are transported directly to the brain to modify brain function?

Wislocki's description in 1936 of pituitary portal veins (*1, 2*) coincided with another important, but less recognized observation. In that decade it was established that the adenohypophysis did not contain nerves (*3*), even though certain pituitary events, notably reflex ovulation (*4*), were controlled by the brain. Arising out of these two observations was the question, *Are neural hormones carried via portal vessels to the pituitary to modify endocrine function?* This question provided the impetus for the physiological (*5*) and biochemical (*6*) studies that revealed the neurohumoral control of adenohypophyseal function.

As the absence of nerves in the adenohypophysis then emphasized the importance of the pituitary portal system, so the recent discovery of hormones within the brain (*7–16*) now emphasizes the importance of the several routes by which hormones might be transported from the pituitary to the brain (*17*). Coupling this to other recent evidence that pituitary hormones affect neural function (*18*) makes it appropriate to reverse the question initiated by Wislocki, to wit: *Are pituitary hormones transported directly to the brain to modify brain function?* (*17*). This broad question provides a new paradigm for the study of brain-pituitary relationships and raises a series of more focused questions which will be considered in this article.

Historical Review

Wislocki viewed pituitary portal veins as the main bridge between the nervous system and the endocrine system. He concluded that (i) pituitary portal veins, like the hepatic portal vein, separated a primary capillary bed from a secondary capillary bed, (ii) the adenohypophysis, like the liver, received a small amount of arterial blood as well as portal venous blood, (iii) all pituitary venous blood, like hepatic venous blood, flowed directly to the systemic circulation, and (iv) the vascular beds of the pituitary were not connected to the vascular bed of the brain (*1, 2*).

Largely on the basis of his anatomical observations and those of others (*19*), physiologists have long assumed that all hormones produced in the adenohypophysis are released directly into the cavernous sinus and carried through the systemic circulation to distant target organs (*20, 21*). Three kinds of studies have brought this hypothesis into question:

1) Anatomical studies performed in our laboratories supported the observations of Török as cited by Szentágothai (*22*) by demonstrating a paucity of direct venous connections from the adenohypophysis to the cavernous sinus (*17, 23, 24*). This demonstration led us to believe that some venous blood leaves the adenohypophysis by some other route, and in 1976 we suggested that some pituitary portal vessels might serve as alternative efferent routes from the adenohypophysis (*23, 24*).

2) Physiological studies have demonstrated high concentrations of adenohypophyseal hormones within portal blood entering the adenohypophysis and, in the rat, these concentrations were diminished when the infundibular process was removed (*25*). This led to the conclusion that some degree of circular blood flow occurs within the pituitary; blood flows via long portal vessels from the infundibulum to the adenohypophysis, but some adenohypophyseal venous blood is carried via short portal vessels back to the infundibular process and then returns upward to the infundibulum (*17, 25*).

3) Immunohistochemical studies, radioimmune assays, and bioassays have demonstrated the presence of several pituitary hormones within the brain (*7–13*) and within cerebrospinal fluid (*14*). Whether or not these hormones are produced independently by the brain is controversial. Several workers have postulated de novo synthesis of hormones within the brain (*8, 10, 13, 26*), while others have concluded that the hormones found in the brain may have been transported there from the pituitary (*11, 12, 16, 27*).

The neurohypophyseal capillary bed plays a pivotal role in all of these recent observations. (i) It receives some portion of the adenohypophyseal venous blood. (ii) Its continuity (through the infundibulum, infundibular stem, and infundibular process) permits circular blood flow within the pituitary. (iii) It is interposed between the adenohypophysis and the brain and affords the only route by which adenohypophyseal hormones may be transported directly to the brain (*17, 25, 28, 29*).

The neurohypophysis is an extension of the brain and the neurohypophyseal capillary bed, like other vascular beds within the brain, may be controlled by the well-orchestrated regional release of vasoactive substances. Physiologic studies of cerebral vascular beds have emphasized dynamic changes including autoregulation (*30*), regional control (*31*), and the effect of drugs (*32*). However, investigators of pituitary vascular phenomena have focused on blood flow within superficial portal vessels (*33*) and on the rate of blood flow (*34*) and have dis-

Dr. Bergland is an associate professor of surgery (neurosurgery) at Harvard Medical School, and Beth Israel Hospital, Boston, Massachusetts 02215. Dr. Page is associate professor of surgery (neurosurgery) at Pennsylvania State University, Hershey Medical Center, Hershey 17033. Illustrations were drawn by Harriet Greenfield.

0036-8075/79/0406-0018$01.75/0

regarded the possibility of dynamic changes; neither autoregulation, regional control, nor the vascular effects of hormones have been studied.

The importance of the neurohypophyseal capillary bed has been stressed in several anatomical studies in our laboratories (*17, 23, 24, 28, 29*). The use of methacrylate casts in those studies provided better visualization of pituitary blood vessels than was provided by the serial-section techniques of earlier studies (*1, 2, 19*). Vascular casts can be coated with gold palladium and photographed at high power and with great depth of field with a scanning electron microscope. The three-dimensional visualization of all of the arteries, capillaries, and veins which subserve the pituitary has substantially altered the traditional concepts of pituitary vascular relationships.

It is our purpose in this article to review the vascular anatomy of the pituitary and, in turn, to ask several questions concerning the functional implications of these anatomical observations.

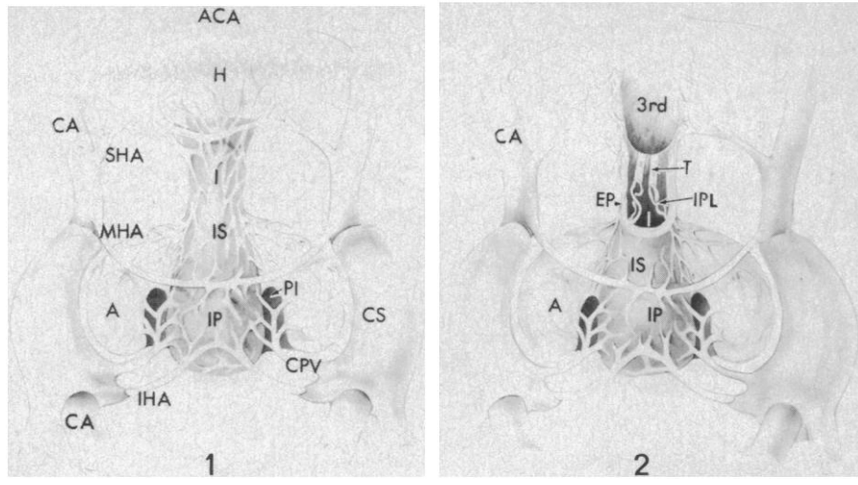


Fig. 1. Diagram of the vascular relationships of the primate pituitary (posterior view). *A*, Adenohypophysis; *PI*, pars intermedia; *H*, hypothalamus; *SHA*, superior hypophyseal artery; *MHA*, middle hypophyseal artery; *IHA*, inferior hypophyseal artery; *CPV*, confluent pituitary vein; *CA*, carotid artery; *ACA*, anterior communicating artery; *CS*, cavernous sinus. The neurohypophysis includes the infundibulum (*I*), infundibular stem (*IS*), and infundibular process (*IP*). Fig. 2. Diagram of the blood vessels of the primate pituitary (posterior view). A portion of the infundibulum has been removed to reveal the relationships of tanycytes (*T*) to the third ventricle (*3rd*) and the internal plexus (*IPL*). *A*, adenohypophysis; *IP*, infundibular process; *IS*, infundibular stem; *I*, infundibulum; *EP*, external plexus; *CA*, carotid artery.

Most often the lateral view (*1, 2*) or the ventral anterior view (*19*) has been employed to demonstrate pituitary vascular anatomy, possibly because those views emphasize the long portal vessels on the anterior surface of the infundibulum. Figure 1 is drawn from a dorsal posterior vantage point, and, even though long portal vessels cannot be seen, this view is superior to the other views because it reveals a number of features basic to any consideration of the dynamics of pituitary blood flow.

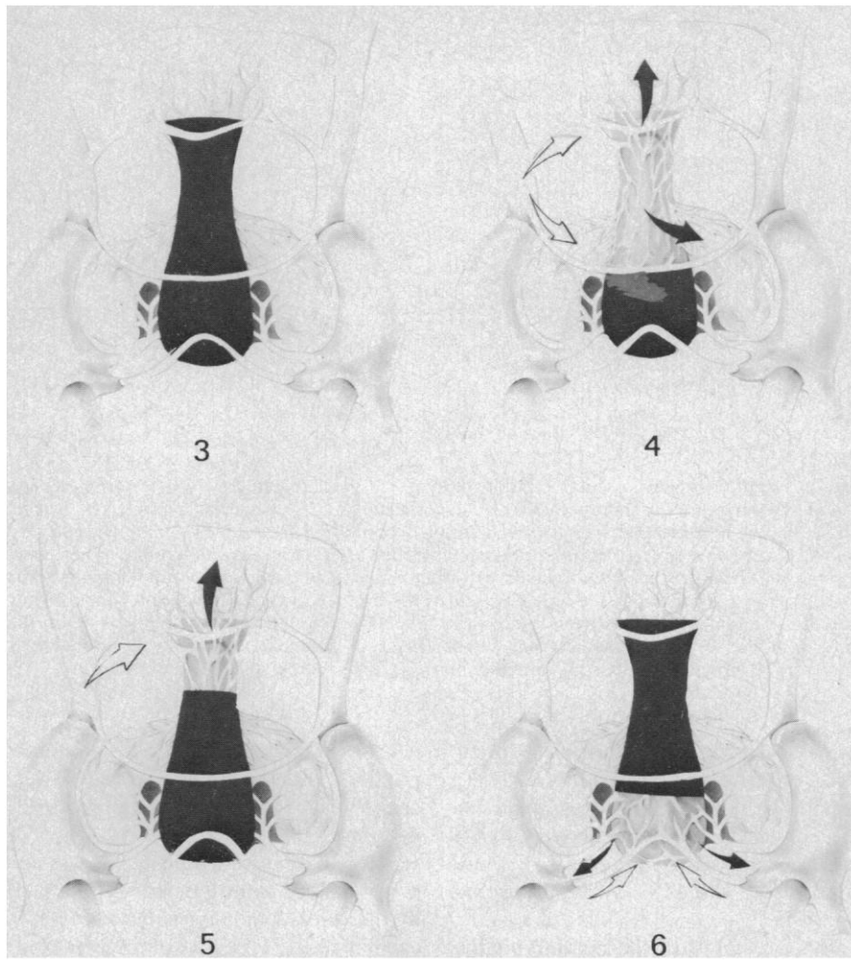
This view (Fig. 1) demonstrates the connections of all of the hypophyseal arteries to the pituitary, to each other, and to the carotid arteries. The adenohypophysis receives no direct arterial supply. Although Wislocki (*1, 2*) and Harris (*35*) both concluded that arteries extended directly to the adenohypophysis, this has not been demonstrated by the study of vascular casts. The neurohypophysis, in contrast, is served by three pairs of arteries. Superior hypophyseal arteries extend to the infundibulum, inferior hypophyseal arteries extend to the infundibular process, and middle hypophyseal arteries extend to the infundibular stem (*17, 28, 29*). In all ten species that we have examined with vascular casts, each of the three kinds of hypophyseal arteries is present. These arteries form numerous anastomotic links between each other, between the right and left carotid arteries, and in some species, between portions of the rete mirabile (*17*). The middle hypophyseal arteries, designated by earlier investigators as either loral arteries (*36*), trabecular arteries (*36*), or arteries of the infundibular stem (*37*), were previously thought to pass through the parenchyma of the adenohypophysis; but vascular casts reveal that these arteries go directly to the neurohypophysis (*17*).

The continuity of the neurohypophyseal capillary bed is apparent only from a dorsal posterior vantage point (Fig. 1). This capillary bed contains numerous short, randomly oriented shunts and extends through all three parts of the neurohypophysis, the infundibulum, the infundibular stem, and the infundibular process (*28*). Numerous capillaries also connect the capillary bed of the infundibulum to the capillary bed of the hypothalamus. There are no venous connections to the systemic circulation from the infundibulum at the upper, rostral portion of the neurohypophysis.

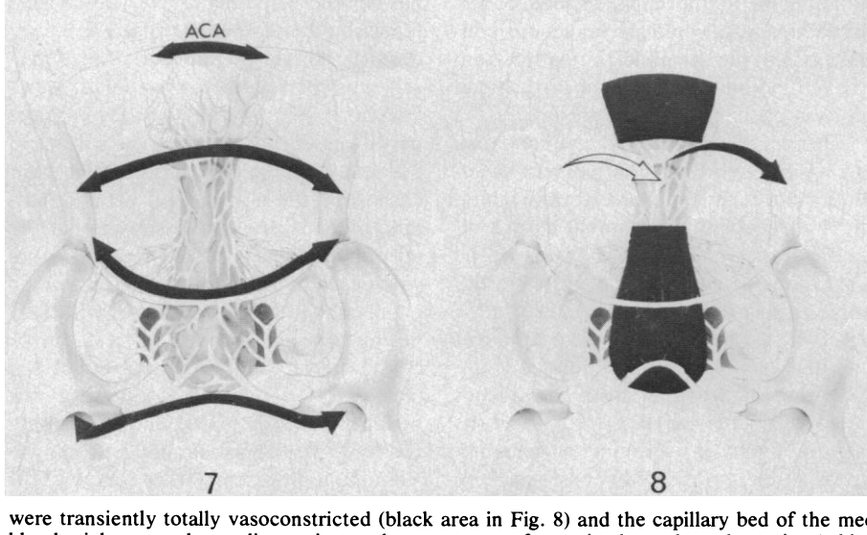
The veins draining the pituitary also are visible only from this posterior vantage point (Fig. 1). There are few lateral hypophyseal veins (*1, 2*) that extend directly from the adenohypophysis to the cavernous sinus. Vascular casts reveal, instead, that the pituitary is linked to the systemic venous circulation by confluent pituitary veins, Y-shaped venous channels that carry blood from the adenohypophysis, the pars intermedia, and the neurohypophysis through a common trunk to the systemic venous circulation (*17*). Thus, the only direct route from the neurohypophyseal capillary bed to the systemic venous circulation is via the neurohypophyseal limbs of the confluent pituitary veins located at the lower, caudal end of the neurohypophysis (*1, 2, 17, 29*).

It is apparent from a posterior vantage point that the neurohypophysis is united to the adenohypophysis by a common capillary bed (Fig. 1). Contrary to common belief there are no pituitary portal veins that separate a primary capillary bed within the infundibulum (or median eminence) from a secondary capillary bed within the adenohypophysis. While large vessels of the rat (*25, 33*) and some other species (*38*) have been designated portal veins (*1, 21, 25*), transmission electron microscopy in several species has demonstrated that these vessels have fenestrated endothelial cells. Therefore, despite their large diameter, these vessels must be regarded as capillaries, not veins (*17, 29*). In many species no large portal vessels are found on the surface of the infundibulum (*29*). Pituitary vascular casts from the primate (Fig. 1) and from nine other species have shown that the adenohypophysis and the neurohypophysis actually are united by a common capillary bed (*17, 29*), not separated by portal veins (*1, 2*).

There is a quantitative imbalance between the capillaries connecting the neurohypophysis to the adenohypophysis and the veins draining from the adenohypophysis into the systemic circulation that becomes apparent only from the posterior view (Fig. 1). The cross-sectional aggregate of the few ade-



Figs. 3 to 6. In these diagrams the theoretical consequences of regional vasoconstriction of the neurohypophysis (black areas) are considered. Total vasoconstriction (Fig. 3) would halt blood flow in all of the hypophyseal arteries. Vasoconstriction of the lower one-third (Fig. 4) would allow flow only in the superior and middle hypophyseal arteries (white arrows), and blood could exit only to the brain or the adenohypophysis (black arrows). Vasoconstriction of the lower two-thirds (Fig. 5) would allow flow only in the superior hypophyseal arteries (white arrow) and blood could exit only to the brain (black arrow). Vasoconstriction of the upper two-thirds (Fig. 6) would allow flow only in the inferior hypophyseal arteries (white arrows) and blood could exit only to the cavernous sinus (black arrows).



Figs. 7 and 8. These diagrams illustrate the phenomenon of flow reversal in hypophyseal arteries. Like the vessels of the circle of Willis, such as the anterior communicating artery (*ACA*), the direction of arterial flow may be reversible; under some circumstances these arteries may carry blood into the carotid arteries (Fig. 7). If the capillary beds of the hypothalamus and the lower neurohypophysis were transiently totally vasoconstricted (black area in Fig. 8) and the capillary bed of the median eminence were simultaneously vasodilated, blood might enter the median eminence by one group of superior hypophyseal arteries (white arrow). Since there are no venous links to the systemic circulation in this region, blood might be forced to exit via other hypophyseal arteries (black arrow) into the carotid artery.

nohypophyseal limbs of confluent pituitary veins is much less than the cross-sectional aggregate of the hundreds of capillaries connecting the neurohypophysis to the adenohypophysis (*17*). Previously it was assumed that all pituitary portal vessels, like the hepatic portal vein, are afferent vessels that carry blood to the adenohypophysis (*1, 2*), but the limited capacity for direct venous drainage to the cavernous sinus may force some portal vessels to serve as alternative routes of exit from the adenohypophysis. Some of the capillaries uniting the neurohypophysis to the adenohypophysis must function as efferent vessels (*17, 25*) from the latter structure.

The vascular relationships of the pars intermedia, too, can be appreciated best from the dorsal posterior vantage point (Fig. 1). The primate pars intermedia, like that of nine other species, is relatively avascular; very few portal capillaries traverse it and the most prominent vessels found within it are confluent pituitary veins (*17*).

If the pituitary is pictured with the posterior portion of the infundibulum removed (Fig. 2), the complex vascular relationships between the pituitary and the ventricular system can be visualized.

Within the infundibulum, vascular structures are seen which are not found elsewhere within the neurohypophysis. A thin outer shell of capillaries, the external plexus (*17, 29*), surrounds a network of numerous capillary coils of different size, shape, and complexity, the internal plexus (*17, 29*), which projects into the inner portion of the infundibulum. Tanycytes, specialized ependymal cells, are stretched between internal plexus vessels (*39*) and the third ventricle. The internal plexus does not receive a direct arterial supply; all of the arterial connections of the infundibulum are to the external plexus (*17, 29*).

The importance of looking at the pituitary from behind and above, rather than from the side or the front, cannot be overemphasized; it is the only view that shows at once all of the vascular interrelationships of the pituitary. This rather

simple observation may be one of the most important things to come from the study of pituitary vascular casts.

The improved understanding of pituitary vascular anatomy provided by vascular casts leads us to pose the following questions concerning pituitary function:

1) How would total vasoconstriction of the neurohypophysis affect pituitary blood flow? There are no published physiological studies that address this question. In theory, if the entire capillary bed of the neurohypophysis were totally vasoconstricted (Fig. 3), blood could not enter the neurohypophysis from either the superior hypophyseal, the middle hypophyseal, or the inferior hypophyseal arteries. Since neither the pars intermedia nor the adenohypophysis receives an independent arterial supply, no blood would enter the pituitary under these conditions.

2) How would regional vasoconstriction of the infundibular process affect pituitary blood flow? Although regional control of neurohypophyseal blood flow has not been studied, several anatomical observations—the architecture of the neurohypophyseal capillary bed (*28*), the arrangement of its arterial supply (*17, 29*), and its options for venous drainage (*17, 28*)—suggest that regional control is likely to occur. Moreover, the capillaries within the neurohypophysis are well innervated (*40*), have an abundance of juxtaposed smooth muscle (*41*), and are bathed by high concentrations of potent vasoconstrictors (*42*) and vasodilators (*43*), some of which are regionally localized.

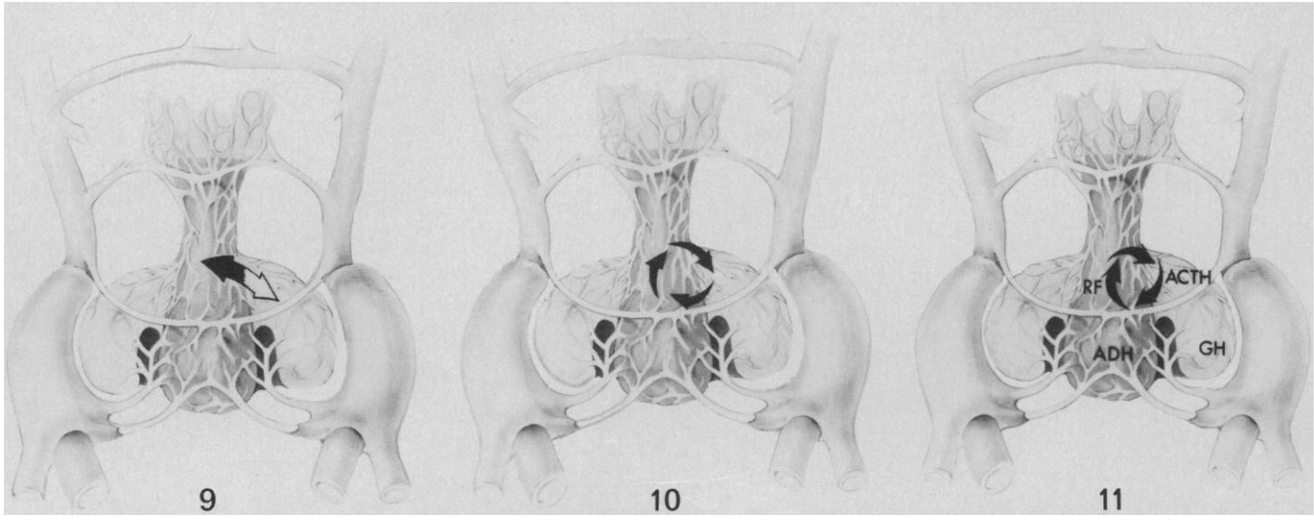
Theoretically, regional vasoconstriction of the infundibular process (Fig. 4) would limit blood flow into the neurohypophysis from the inferior hypophyseal artery, but normal flow would persist in both the superior hypophyseal arteries and the middle hypophyseal arteries. The net effect would be to flush blood from the infundibulum and infundibular stem into the only two efferent routes available: either into the adenohypophysis by connecting portal capillaries or into the brain by the confluent capillaries extending to the hypothalamus. Vasoconstriction of the infundibular process would preclude neurohypophyseal venous blood going directly to the systemic circulation since blood could not enter the neurohypophyseal veins. Adenohypophyseal venous blood could gain entry to the systemic circulation by way of the adenohypophyseal veins.

Regional vascular changes within the neurohypophysis would affect the arterial supply of the neurohypophysis, but, in sequence, the pattern of efferent drainage from the pituitary also would be altered. The three sets of arteries serving the neurohypophysis provide it with the potential of functioning as a vascular switch; switching could not occur if the neurohypophysis were served by a single end artery. Other switching possibilities are considered in questions 3 and 4.

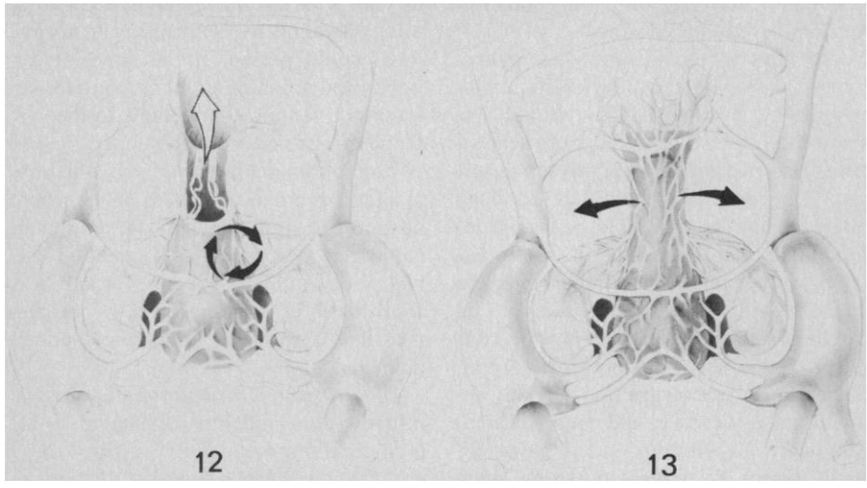
3) How would vasoconstriction of the infundibular process and infundibular stem affect pituitary blood flow? This set of circumstances would limit blood flow from both the inferior hypophyseal artery and the middle hypophyseal artery into the neurohypophysis, but normal flow would persist in the superior hypophyseal artery (Fig. 5). Since there are no direct venous connections to the systemic circulation from the upper, rostral portion of the neurohypophysis, the only available route of venous drainage would be into the hypothalamus via confluent capillaries. Although this question has not been studied directly, blood flow from the infundibulum to the hypothalamus has been observed in anesthetized animals (*44, 45*).

4) How would vasoconstriction of the infundibulum and infundibular stem affect pituitary blood flow? Under these circumstances blood flow into the neurohypophysis would diminish in the superior hypophyseal artery and the middle hypophyseal artery but normal flow would remain in the inferior hypophyseal artery (Fig. 6). Blood would not flow from the neurohypophysis directly to the brain or to the adenohypophysis. Blood entering the infundibular process would flow into the systemic circulation by the neurohypophyseal limbs of the confluent pituitary veins; retrograde flow through the adenohypophyseal limbs of the confluent pituitary veins into the adenohypophysis is possible, but less likely.

Questions 2, 3, and 4 have considered only the consequences of regional vasoconstriction; entirely different consequences would appear after regional vasodilation. Moreover, the synchronous vasodilation of one part of the neurohypophysis with vasoconstriction of another part would enhance the



Figs. 9 to 11. These diagrams address some of the possibilities of flow reversal in the capillaries that link the adenohypophysis and the neurohypophysis. In any single connecting capillary, the direction of flow may be reversible (Fig. 9). Ventrally capillary flow has been observed going toward the adenohypophysis (*32*), but dorsally flow toward the brain has been observed (*25, 44, 45*), and physiological studies have shown that adenohypophyseal hormones may be carried to the neurohypophysis (*25*). Thus some degree of circular flow must occur within the pituitary (Fig. 10). Hormones such as ACTH and releasing factors (*RF*) released centrally within the pituitary would be more likely to recirculate within the pituitary than hormones such as growth hormone (*GH*) and antidiuretic hormone (*ADH*), which are released peripherally (Fig. 11).



Figs. 12 and 13. These two figures relate to the routes by which hormones may gain access to the cerebrospinal fluid. Tanycytes might transport hormones directly into the third ventricle (Fig. 12). Since the vessels on the surface of the median eminence are not veins, but fenestrated capillaries, hormones might leak directly into the surrounding subarachnoid cerebrospinal fluid (Fig. 13).

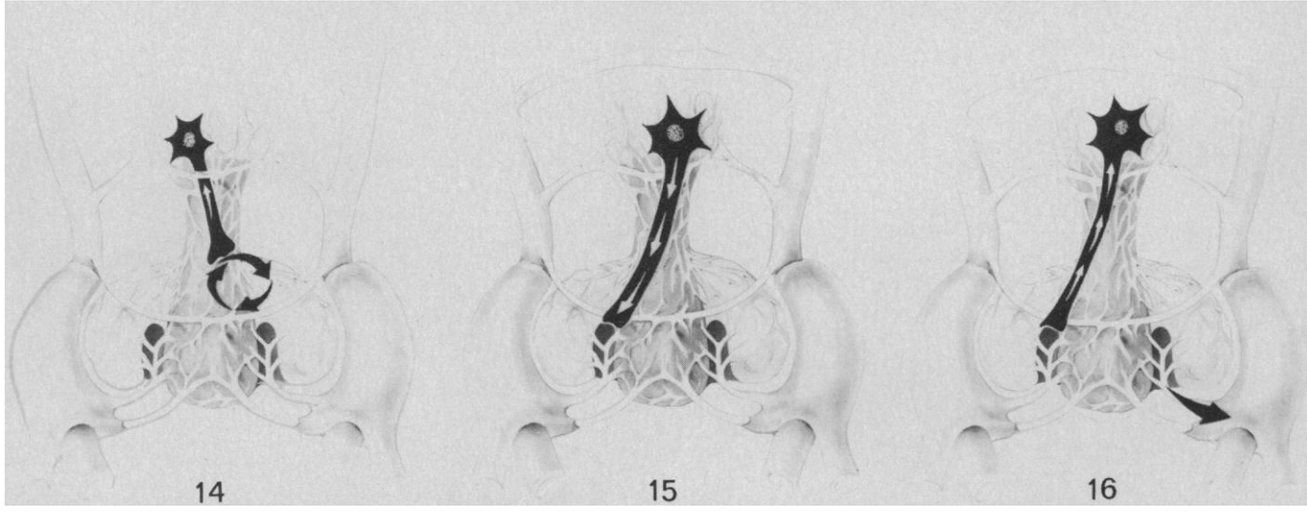
switching effect of each of the many possible permutations.

5) Does blood flow from one carotid to another across hypophyseal arteries? The right and left carotid arteries are connected above the pituitary by anastomoses within the circle of Willis such as the anterior communicating artery and through more circuitous routes by the superior hypophyseal, the middle hypophyseal, and the inferior hypophyseal arteries. None of the hypophyseal arteries are end-arteries; each is a set of anastomotic vessels that has the anatomic potential for flow reversal (Fig. 7). Flow reversal has been verified within anastomotic segments of the circle of Willis and the direction of flow in these vessels is determined by cerebral vascular events, not cardiac events (*30*). The control of the direction of flow within hypophyseal arterial anastomoses must involve complex vascular events within the brain, the pituitary, and the cavernous sinus, and these vessels could under certain conditions carry blood from one carotid to the other instead of to the pituitary. No physiological studies have yet been addressed to this question.

6) Do hypophyseal arteries carry pituitary secretions to the brain via the carotid arteries? Sir Thomas Willis proposed (in 1640) that the rete mirabile may carry blood from the pituitary directly to the brain (*46*), but this ancient proposal has been disregarded. Yet the synchronous vasoconstriction of the lower neurohypophysis and of the hypothalamus might allow this. Under these conditions blood could enter the infundibulum via one group of hypophyseal arteries but could not flow to the remainder of the neurohypophysis or to the hypothalamus. Since there are no veins in this region which extend directly to the systemic circulation, blood could leave only via other hypophyseal arteries (Fig. 8.) The simultaneous vasodilation of the infundibulum might facilitate this phenomenon which could carry hormone-laden blood to the brain via the carotid arteries. In only one study has this possibility been evaluated (*24*).

7) Do some pituitary portal vessels serve as efferent vessels? The limited capacity for venous drainage via adenohypophyseal veins led to the hypothesis that some portal capillaries carry blood from the adenohypophysis to the neurohypophysis (*17*). In anesthetized dogs (*44, 45*) and rats (*25*), this has been observed but the phenomenon has not been studied extensively. As in other capillary beds (*47*), it is likely that the direction of flow is variable within capillaries connecting the neurohypophysis to the adenohypophysis. An individual pituitary portal capillary may serve as an afferent portal vessel but under different conditions might serve as an efferent portal vessel (Fig. 9).

8) Does circular blood flow occur in



Figs. 14 to 16. These figures address the phenomena of anterograde and retrograde axonal flow within hypothalamic neurons. Circular blood flow within the pituitary may carry adenohypophyseal hormones to the neurohypophysis. In turn, retrograde axonal flow might transport these hormones to neuronal cell bodies within the hypothalamus (Fig. 14). The pars intermedia is relatively avascular, yet its cells are well innervated; the neurohormones that control this part of the pituitary must be delivered directly by axonal transport, not by portal vessels (Fig. 15). Hormones might leave the pars intermedia by retrograde axonal transport (white arrows) or be carried by confluent pituitary veins (black arrow) to the systemic circulation (Fig. 16).

the pituitary? On the ventral aspect of the pituitary Green and Harris (*33*) observed blood flowing through long portal vessels toward the adenohypophysis. On the dorsal aspect of the pituitary Török (*44, 45*) observed blood flowing through short portal vessels toward the neurohypophysis, and within the neurohypophysis Török (*44, 45*) and Oliver, Mical, and Porter (*25*) observed blood flowing toward the infundibulum. These observations seem at first to be in conflict, but when coupled with the recent demonstration of high concentrations of pituitary hormones in portal blood (*25*) led to the conclusion that some degree of circular blood flow must occur in the pituitary (*17, 25*) (Fig. 10).

9) Which hormones would be most likely to recirculate within the pituitary? Hormones produced by some species primarily in the central portion of the adenohypophysis, such as adrenocorticotropic hormone (ACTH) (*21*), and parvicellular hypothalamic peptides released primarily within the infundibulum, such as releasing factors (*21*), might readily recirculate within the pituitary. Hormones produced primarily in the lateral adenohypophysis, such as growth hormone (*21*) and magnocellular peptides released primarily within the infundibular process, such as antidiuretic hormone (*21*), would be less likely to recirculate (Fig. 11).

10) Do tanycytes transport hormones directly to the brain? Ysbrand van Diemerbroeck postulated (in 1672) that the pituitary transported its secretions into the ventricular system (*48*). In 1914, Cushing also speculated that the neurohypophysis transported secretions into the ventricle (*49*) and in 1932 studied the physiological effects that followed the intraventricular injection of crude pituitary extract (*50*). After tanycytes were discovered stretching from the ependymal surface to internal plexus vessels within the infundibulum (*28, 39*), it was concluded that these cells served as an additional route by which substances might be transported from the brain to the pituitary (*51*). However, internal plexus vessels lack a direct arterial supply, suggesting that blood reaching the base of a tanycyte has already passed through the external plexus and must contain high concentrations of pituitary hormones. This anatomical observation again raises the possibility that the direction of tanycyte transport may be toward the ventricle (*17, 29*) and studies with horseradish peroxidase have supported that postulate (*52*) (Fig. 12). The phenomenon of circular blood flow within the pituitary could provide tanycytes high concentrations of adenohypophyseal hormones as well as neurohypophyseal hormones, both of which could be transported by tanycytes into the ventricle.

11) Are pituitary hormones released directly into the subarachnoid cerebrospinal fluid? The portal vessels on the surface of the infundibulum contain very high concentrations of hormones (*25, 38, 53*). Since these vessels are lined with fenestrated endothelial cells (*29*), these hormones might leak directly into the subarachnoid space (Fig. 13). Many hormones are present within cerebrospinal fluid (*14–16*), but their route of entry into this space is not established.

12) Do hormones exit from the neurohypophysis by retrograde axonal flow? Horseradish peroxidase, introduced into the blood in the cardiac ventricle, is carried by retrograde axonal flow from the capillary bed of the neurohypophysis to the perikaryon of hypothalamic neurons (*54*). Adrenocorticotropic hormone (*8, 11*), prolactin (*9*), and thyroid-stimulating hormone (*12*) have been demonstrated within the hypothalamus and may have been carried by circular flow from the adenohypophysis to the neurohypophysis and, in turn, transported by retrograde axonal flow up to the hypothalamus (Fig. 14). Whether or not hormones actually are transported to the hypothalamus by such a route has not been established.

13) How does the brain control the release of pars intermedia hormones? The relative avascularity of the pars intermedia (*55*) gives rise to this question. This portion of the pituitary is isolated from the phenomenon of circular blood flow, and in contrast to the cells within the adenohypophysis, pars intermedia cells are not bathed in high concentrations of hypothalamic releasing and inhibiting factors. Cells within the pars intermedia are well innervated (*55*), however, so that the release of pars intermedia hormones more likely is controlled by neural information conveyed directly to it by axons rather than by an intermediate vascular portal system (Fig. 15). The method by which the brain controls pars intermedia secretion has not been established (*55*).

14) Do hormones leave the pars intermedia by retrograde axonal transport or by a vascular route? Several 31-K products (endorphin, beta lipotropin, and ACTH) (*56*) have been found in hypothalamic neurons (*8, 10, 27*) and some investigators have concluded that these substances are transported to the brain from the pituitary (*11, 27*). Given the avascularity of the pars intermedia it is unlikely that these substances could be transported from the pars intermedia to the brain by a vascular route. They might be transported from the pars intermedia to the brain by retrograde axonal transport (*17, 54*) (Fig. 16). Since some of these substances are produced by the adenohypophysis (*57*), they might be carried first to the neurohypophysis and then to the brain via a vascular route. Confluent pituitary veins are the predominant vessels within the pars intermedia (*17*), and if pars intermedia hormones exit directly via a vascular route, they would be transported preferentially to the systemic circulation (Fig. 16), not to the brain. To date, no studies have established how hormones leave the pars intermedia.

Conclusion

All the foregoing questions stem from the recognition that the anatomical bridges between the pituitary and the brain are more complex and more numerous than described by Wislocki (*1, 2*) and are anatomically well arranged not only to carry neural information to the endocrine system but also to carry endocrine information to the brain (*17*). The revision of the Wislocki paradigm for brain-pituitary vascular relationships coincides with the realization that the brain has many characteristics of a gland: it contains hormones (*7–13*), it is bathed in hormones (*14–16*), it has hormone receptors (*58*), hormones may serve as its synaptic neurotransmitters (*18*), and hormones modify the brain's main function, behavior (*59*).

The de novo synthesis of hormones by the brain (*8, 10, 13, 26*) does not preclude transport of pituitary hormones directly to the brain (*11, 12, 16, 17, 27*) by any or all of the routes described in this review. Endorphin and other hormones may be produced in small quantity locally within the brain but transported in larger quantity from the pituitary to the brain on demand.

Are pituitary hormones transported directly to the brain to modify brain function? The answer to this question may provide insights pertinent to memory (*59*), sleep (*60*), pain (*61*), orgasm (*62*), endocrine feedback loops (*21*), cerebral blood flow (*63*), cerebral vascular permeability (*63*), cerebrospinal fluid dynamics (*64*), epilepsy (*65*), headache (*66*), acupuncture (*67*), and mental illness (*68*).

References and Notes

1. G. B. Wislocki and L. S. King, *Am. J. Anat.* **58**, 428 (1936).
2. ———, *Proc. Assoc. Nerv. Ment. Dis.* **17**, 48 (1938).
3. A. T. Rasmussen, *Endocrinology* **23**, 263 (1938).
4. J. C. Hinsey and J. E. Markee, *Proc. Soc. Exp. Biol. N.Y.* **31**, 207 (1933).
5. G. W. Harris, *Neural Control of the Pituitary Gland* (Arnold, London, 1955).
6. R. Guillemin, in *The Hypothalamus*, S. Reichlin, R. J. Baldessarini, J. B. Martin, Eds. (Raven, New York, 1978), pp. 155–194.
7. J. B. Martin, L. P. Renaud, P. Brazen, *Lancet* **1975-II**, 393 (1975); L. Terenius, *Eur. J. Pharmacol.* **38**, 211 (1976); G. Uli, J. Bennett, S. Snyder, *Brain Res.* **130**, 299 (1977); J. Hughes, *ibid.* **88**, 295 (1975).
8. D. T. Krieger, A. Liotta, M. J. Brownstein, *Proc. Natl. Acad. Sci. U.S.A.* **74**, 648 (1977).
9. K. Fuxe, T. Hökfelt, P. Eneroth, J.-Å. Gustafsson, P. Skett, *Science* **196**, 899 (1977).
10. D. T. Krieger, A. Liotta, T. Suda, M. Palkovits, M. J. Brownstein, *Biochem. Biophys. Res. Commun.* **76**, 930 (1977); S. T. Pacold, L. Kirsteins, S. Hojvat, A. M. Lawrence, *Science* **199**, 804 (1978).
11. R. Moldow and R. Yalow, *Proc. Natl. Acad. Sci. U.S.A.* **75**, 944 (1978).
12. ———, *Life Sci.* **22**, 1859 (1978).
13. J. Havrankova, *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **75**, 5737 (1978).
14. L. Terenius and A. Wahlstrom, *Life Sci.* **16**, 1759 (1975); C. Schaub, B. Bluet-Pajot, G. Szikea, C. Lornet, J. Talairach, *J. Neurol. Sci.* **31**, 123 (1977); I. S. Login and R. M. MacLeod, *Brain Res.* **132**, 477 (1977); M. J. Kubek, M. A. Lorincz, J. F. Wilber, *ibid.* **126**, 196 (1977).
15. J. F. Wilber, E. Montoya, N. P. Plotnikoff, W. F. White, R. Gendrich, L. Renaud, J. B. Martin, *Recent Prog. Horm. Res.* **32**, 117 (1976); W. J. Jeffcoate, L. McLoughlin, J. Hope, I. H. Rees, S. J. Ratter, P. J. Lowry, G. M. Besser, *Lancet* **1978-II**, 119 (1978); H. Akil, D. E. Richardson, J. Hughes, J. D. Barchas, *Science* **201**, 463 (1978); K. M. Knigge and S. H. Joseph, *Acta Endocrinol. (Copenhagen)* **76**, 209 (1974).
16. P. D. Pezalla, M. Lis, N. G. Seidah, M. Chrétien, *Can. J. Neurol. Sci.* **5**, 183 (1978).
17. R. M. Bergland and R. B. Page, *Endocrinology* **102**, 1325 (1978).
18. G. Zetler, *Adv. Biochem. Psychopharmacol.* **18**, 1 (1978).
19. J. D. Green, *Am. J. Anat.* **88**, 225 (1951); G. P. Xuereb, M. L. Prichard, P. M. Daniel, *Q. J. Exp. Physiol.* **39**, 199 (1954); J. M. F. Landsmeer, *Advances in Neuroendocrinology*, A. V. Nalbandov, Ed. (Univ. of Illinois Press, Urbana, 1963), pp. 29–67.
20. W. F. Ganong and D. M. Hume, *Proc. Soc. Exp. Biol. Med.* **88**, 528 (1955).
21. J. R. Martin, S. Reichlin, G. M. Brown, *Clinical Endocrinology* (Davis, Philadelphia, 1977).
22. J. Szentágothai, B. Flerko, B. Mess, B. Halasz, in *Hypothalamic Control of the Anterior Pituitary* (Akademiai Kiado, Budapest, 1962), p. 81.
23. R. M. Bergland and R. B. Page, *Proceedings of the Fifth International Congress of Endocrinology*, Hamburg (1976); R. B. Page and R. M. Bergland, in *The Pituitary: A Current Review*, M. B. Allen and V. B. Mahesh, Eds. (Academic Press, New York, 1977), pp. 9–17.
24. R. M. Bergland, S. L. Davis, R. B. Page, *Lancet* **1977-II**, 276 (1977).
25. D. Oliver, R. S. Mical, J. C. Porter, *Endocrinology* **101**, 598 (1977).
26. R. Guillemin, *Science* **202**, 390 (1978).
27. R. Yalow, *ibid.* **200**, 1236 (1978); E. Mezey, M. Palkovits, E. R. de Kloet, J. Verhoef, D. de Wied, *Life Sci.* **22**, 831 (1978).
28. R. B. Page and R. M. Bergland, *Am. J. Anat.* **148**, 345 (1977).
29. R. B. Page, A. E. Leure-duPree, R. M. Bergland, *ibid.* **153**, 33 (1978).
30. N. A. Lassen, K. Hœdt-Rasmussen, S. C. Sørensen, E. Skinhøj, S. Cronquist, B. Bodforss, E. Eng, D. H. Ingvar, *Neurology* **13**, 719 (1963).
31. J. Oleson, *Acta Neurol. Scand. Suppl.* **57**, 1 (1968).
32. M. J. Purves, *Physiology of the Cerebral Circulation* (Cambridge Univ. Press, Cambridge, 1972).
33. J. D. Green and G. W. Harris, *J. Endocrinol.* **5**, 136 (1947).
34. W. J. Bryan and T. E. Emerson, Jr., *Proc. Soc. Exp. Biol. Med.* **156**, 205 (1977).
35. G. W. Harris, in *Handbook of Physiology*, Section 1, *Neurophysiology* (American Physiological Society, Bethesda, Md., 1960), pp. 1007–1038.
36. E. M. McConnell, *Anat. Rec.* **115**, 175 (1953); H. Duvernoy, J. G. Koritke, G. Monnier, *Neurovisc. Relat.* **32**, 112 (1971).
37. J. M. F. Landsmeer, *Acta Anat.* **12**, 82 (1951).
38. E. A. Zimmerman, P. Carmel, M. K. Husain, M. Ferin, M. Tannenbaum, A. G. Frantz, A. G. Robinson, *Science* **182**, 925 (1973).
39. F. Knowles, *Prog. Brain Res.* **38**, 255 (1972).
40. J. W. Christ, in *The Pituitary Gland*, G. W. Harris and B. T. Donovan, Eds. (Butterworths, London, 1966), pp. 62–130.
41. R. M. Bergland and R. M. Torack, *Z. Zellforsch.* **99**, 1 (1969).
42. R. Wurtman, in *Hypophysiotropic Hormones of the Hypothalamus*, J. Meites, Ed. (Williams & Wilkins, Baltimore, 1970).
43. R. E. Carraway, L. M. Demers, S. E. Leemar, *Endocrinology* **99**, 1452 (1976).
44. B. Török, *Acta Anat.* **59**, 84 (1964).
45. ———, *Acta Morphol. Acad. Sci. Hung.* **4**, 83 (1954).
46. J. D. Green, in *The Pituitary Gland*, G. W. Harris and B. T. Donovan, Eds. (Butterworths, London, 1966), vol. 1, p. 128.
47. B. W. Zweifach, *Am. J. Med.* **23**, 684 (1957).
48. H. D. Rolleston, *The Endocrine Organs in Health and Disease* (Oxford Univ. Press, New York, 1936), p. 42.
49. H. Cushing and E. Goetsch, *Am. J. Physiol.* **27**, 60 (1914).
50. H. Cushing, *Proc. Natl. Acad. Sci. U.S.A.* **18**, 500 (1932).
51. F. Knowles, and T. C. Anand Kumar, *Philos. Trans. R. Soc. London Ser. B* **256**, 357 (1969).
52. Y. Nakai and N. Naito, in *Brain-Endocrine Interaction*, K. M. Knigge, D. E. Scott, H. Kobayashi, S. Ishii, Eds. (Karger, Basel, 1975), p. 94.
53. J. D. Neill, J. M. Patton, R. A. Dailey, R. C. Tsou, G. T. Tindall, *Endocrinology* **101**, 430 (1977).
54. R. D. Broadwell and M. W. Brightman, *J. Comp. Neurol.* **166**, 257 (1976).
55. B. M. Cox, E. R. Baizman, T.-P. Su, O. H. Osman, A. Goldstein, *Adv. Biochem. Psychopharmacol.* **18**, 183 (1978).
56. R. E. Mains, B. A. Eipper, N. Ling, *Proc. Natl. Acad. Sci. U.S.A.* **74**, 3014 (1977).
57. F. Bloom, E. Battenberg, J. Rossier, N. Ling, J. Leppaluoto, T. M. Vargo, R. Guillemin, *Life Sci.* **20**, 43 (1977).
58. S. H. Snyder, *N. Engl. J. Med.* **295**, 266 (1977).
59. D. de Wied, B. Bohus, W. H. Gispen, I. Urban, Tj. B. van Wimersma Greidanus, in *Hormones, Behavior and Psychopathology*, E. J. Sachar, Ed. (Raven, New York, 1976), pp. 1–14.
60. J. R. Pappenheimer, G. Koski, V. Fencl, M. L. Karnovsky, J. Krueger, *J. Neurophysiol.* **38**, 1299 (1975).
61. A. Goldstein, *Science* **193**, 1081 (1976).
62. A. Goldstein and J. W. Hansteen, *Arch. Gen. Psychol.* **34**, 1179 (1977).
63. M. E. Raichle, B. K. Hartman, J. O. Eichlin, L. G. Sharpe, *Proc. Natl. Acad. Sci. U.S.A.* **72**, 3726 (1975).
64. H. Davson, *Physiology of Cerebrospinal Fluid* (Churchill, London, 1970).
65. F. E. Bloom, J. Rossier, E. L. F. Battenberg, A. Bayon, E. French, S. J. Henriksen, G. R. Siggins, D. Segal, R. Browne, N. Ling, R. Guillemin, *Adv. Biochem. Psychopharmacol.* **18**, 89 (1978).
66. F. Sicuteri, B. Anselmi, C. Curradi, S. Michelacci, A. Sassi, *ibid.*, p. 363.
67. B. Pomeranz and D. Chiu, *Life Sci.* **19**, 1751 (1977).
68. L. Terenius, A. Wahlstrom, L. Linstrom, E. Widerly, *Neurosci. Lett.* **3**, 157 (1976).

Pre-Hispanic Resource Sharing in the Central Andes

Peaceful intergroup exploitation of a unique ecological zone is documented at a settlement in Peru.

Tom D. Dillehay

Group access to resources of different areas can generally be achieved by one or a combination of several means: trade, exchange and market systems, colonization, and warfare or conquest. These means imply either intergroup cooperation in or competition for the exploitation of those resources.

Studies have been made of the Andean method of achieving access to diverse resources in the absence of Western market systems. These studies have profited from the economic model of redistribution developed by Polanyi *et al.* (*1*) and later by Murra (*2*) in his ethnohistorical work on the Inca economy (*3*). Using documentation on late pre-Hispanic (around A.D. 1350 to 1534) ethnic groups in Peru, Murra (*4, 5*) further developed these ideas by proposing the principles of verticality: a nucleus population sends colonies to exploit and control a series of discontinuous ecological zones or "environmental archipelagoes" up and down the highly diversified Andean landscape. This system requires a certain level of political and economic organization and integration to maintain colonies and to ensure redistribution of local products to the nucleus. Colonies from different groups have also been shown to share the same zone.

The author is a professor of anthropology at the Universidad Austral de Chile, Valdivia, Chile.

0036-8075/79/0406-0024$01.75/0