DIODRAST STUDIES OF THE VERTEBRAL AND CRANIAL VENOUS SYSTEMS
TO SHOW THEIR PROBABLE ROLE IN CEREBRAL METASTASES*

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The incidence of cerebral metastases is increasing. In Cushing's series of verified intracranial tumors 3.2 per cent were of metastatic origin but more recent reports variously state the incidence as being from 5 per cent to 20.5 per cent, depending in large part upon the source of material and the number of complete autopsies performed. In a series of 1076 verified intracranial tumors reviewed by the writer the incidence of metastatic tumors was found to be 8.4 per cent. Often the various surgical and physical measures directed at the primary lesion are of necessity incomplete and although the subject gains in comfort and his years of life are extended, the possibility of the development of cerebral metastases before his death is increased.

Cerebral metastatic lesions are blood-borne since no lymphatics are present in the brain. Moreover, their frequent multiplicity and widespread distribution throughout the brain attest to their vascular spread. Frequently, the cerebral involvement is the only point of implantation secondary to a distant primary lesion. This is difficult to explain on a vascular basis and, although other factors are involved, it would seem that the simple mechanics of hematogenic spread of metastases should be considered first.

The commonly accepted route of the vascular spread of tumor cells to the brain is along the arterial tree. The fact that tumors of the lungs are among the largest contributors to cerebral metastases would support such a consideration since their position allows direct passage of tumor cells to the heart and thence to the brain via the arterial system. The manner in which the pulmonary filter is bridged in cases of blood-borne material from the portal system, caval system and general circulation has not been easily explained. Hence the common expression "paradoxical embolism." Of course, instances of congenital heart lesions would answer this question, and cases of patent foramen ovale and ventricular septal defects associated with metastatic lesions have been described. However, cases of cerebral metastases secondary to pathology in the

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pelvis, or of the genito-urinary tract, in the absence of evidence of metastases to the lung and without patent foramen ovale or other congenital cardiac defects, would indicate that other modes of hematogenic spread must exist. Also, the spread of carcinoma of the breast to the brain in the absence of intrathoracic extension would indicate that other vascular routes are present.

Although Willis in 1664 and Bock in 1823 accurately described the vertebral and cranial venous plexuses and although von Recklinghausen in 1885 pointed out the phenomenon of retrograde venous metastases, it remained for Batson in 1940 to postulate the role of the vertebral venous system in the spread of metastases. By the use of various radiopaque substances injected into the venous systems of human cadavers, he demonstrated roentgenologically the ease with which media could pass along the vertebral venous system, its close association with the veins of the body wall, pelvic and shoulder girdles and finally, its continuity with the venous sinuses within the cranium. Similar cadaver studies were repeated by Collis in 1944 and he presented clinical evidence which implicated the vertebral venous system as a mode of spread of cerebral metastases complicating various forms of intrathoracic suppuration.

In 1941, Harris reviewed previously known anatomical facts regarding the spinal and cranial venous systems and emphasized that the anatomical conditions were well documented but that the clinical pathological implications had not been recognized. Recent dissection studies by Anson et al. with attention directed to the pararenal venous system have indicated the close relationship of this venous complex with the vertebral venous system. They pointed out the avenues of possible hematogenic migration through the renal, lumbar, intervertebral veins and vertebral plexuses to the spongy bone of the vertebrae; or, upward along the vertebral venous system to the dural or diploic veins of the cranium.

The pathological evidence that tumor cells in general tend to invade adjacent veins and that their venous spread is a common occurrence has been emphasized by Willis and others. Further, it is known that venous emboli frequently move in a direction opposite to that of their usual flow. This is particularly true in the vertebral veins where there is an absence of valves. There is a tendency toward stasis in the multiple sinuses of this system where there are frequent reversals of blood flow as a result of postural changes and variations in intrathoracic and intra-abdominal pressures.

By the employment of diodrast (3,5-diiodo-pyridone-N-acetic acid and diethanolamine) and newer injection techniques it was believed that (1) the cadaver experiments could be repeated and (2) that similar studies could safely be performed on living subjects to determine whether venous patterns obtained in cadaver studies would be found in the presence of normal circulating mechanisms. To this end, employing a 52% per cent diodrast solution, a series of 12 cadaver studies were made and 22 injections in living humans were performed.
METHODS AND RESULTS

Cadaver Experiments

Twelve cadaver studies were performed. Ten specimens were injected through the deep dorsal penile vein after the method of Batson and in 2 instances the cephalic vein of the upper arm was utilized. All of the subjects were adult males who had died of a variety of causes but in whom there was no evidence of vascular malformation, disease, or trauma that might have resulted in an abnormal venous filling.

Shortly after death the cadaver was placed on the dissecting table in the usual dorsal recumbent position. The diodrast solution was warmed prior to injection since it was found that this tended to prevent crystallization and enabled the plunger to move through the syringe smoothly. The deep dorsal vein of the penis was isolated just distal to the suspensory ligament of the pubis and a small cannula inserted. A 30 cc. syringe containing the diodrast was connected to the cannula and the injection was made slowly and at a constant rate. This required very little pressure; in fact when the butt of the syringe was elevated the weight of the plunger alone would often cause the diodrast to flow into the vein.

![Fig. 1. Initial injection of diodrast into an adult male cadaver. The cannula is attached to the deep dorsal penile vein.](image-url)
When 30 cc. of diodrast had been injected a roentgen film of the lumbar region and pelvis was exposed with a portable x-ray machine employing a stationary grid. A typical film is shown in Fig. 1, with the cannula in the dorsal penile vein. After 60 cc. more diodrast were injected a venous pattern was obtained (Fig. 2). These illustrations demonstrate the presence of the opaque media in the dorsal vein of the penis and its connections with the pudendal, prostatic and vesical plexuses. The pudendal veins, hypogastric

![Fig. 2. Extensive filling of veins of the vertebræ, genito-urinary system and pelvic girdle.](image1)

![Fig. 3. Appearance of thoracic structures after injection of 150 cc. of diodrast into deep dorsal penile vein.](image2)

veins, obturator veins and iliac veins are well outlined and their numerous anastomoses are evident. The ascending lumbar veins and their rich segmental connections with the intervertebral veins and with the inferior vena cava are shown. The external vertebral veins and, to a lesser extent, the internal vertebral veins are also demonstrated. In the upper lumbar region there is extensive filling of the renal venous plexuses.

After another injection of 60 cc. of the diodrast into the deep dorsal vein of the penis a film of the thoracic region was made (Fig. 3). This shows the further ascent of the opaque media along the vertebral venous system with some filling of the inferior vena cava, the hepatic veins, the pulmonary veins, and the right auricle and ventricle.

In the lower thoracic region the segmental connections of the respective intercostal veins with the vertebral veins can be seen. In the upper portion
of the thorax on the right side the superior portion of the azygos vein is seen where it arches laterally to meet the superior vena cava, which is faintly outlined with a lesser concentration of diodrast. Extending superiorly from the medial aspect of the arch of the azygos vein is the supreme intercostal vein, which connects with the intercostal veins of the first three ribs on the right side. There is some filling of the deep cervical veins and the vertebral veins in the lower portion of the neck.

After a total of 200 cc. of the diodrast had been injected into the deep dorsal penile vein, skull films were obtained. In Fig. 4 there is an accumulation of the opaque media in the superior sagittal sinus and in addition the confluens sinuum is faintly outlined where the transverse sinuses blend into the sagittal sinus.

The lateral view (Fig. 5) demonstrates a heavy concentration of the opaque media in the superior sagittal sinus and many of the superior cerebral veins are filled and blend into the superior sagittal sinus. Beneath it the inferior sagittal sinus is clearly outlined although not as well defined because it is much smaller in size, particularly anteriorly. Posteriorly the straight sinus is well filled and can be visualized as it joins the two sagittal sinuses. The great cerebral vein, the petrosal sinuses and a portion of the basilar plexus of veins are outlined.

In order to visualize better the veins of the shoulder girdle, the breast, and the deep cervical veins, the cephalic vein was injected in the right upper arm just distal to the deltoid muscle where the vein courses along the lateral aspect of the biceps. In Fig. 6 the cephalic vein is outlined in the lower right-hand corner and can be seen curving downward and emptying into the large axillary vein. Following medialward a portion of the subclavian vein is not
visualized but inferiorly the azygos vein can be seen with its component, the supreme intercostal vein, extending upward. On the left side, at approximately the mid-clavicle, the descending left mammary vein can be seen. The transverse cervical vein is outlined on both sides of the neck, as are many of the scapular veins, which are most heavily filled on the side of the injection. On the right side, along the lateral margins of the cervical vertebrae, the deep cervical vein is well demonstrated. Laterally, and not as well filled, the internal jugular veins can be seen as they descend from just within

the superimposed mastoid processes. Intracranially the sagittal sinus is well demarcated and the transverse sinuses can be seen joining it at their point of confluence.

Diodrast Injections in Patients

The procedures were duplicated, in so far as was practicable, in human patients in the presence of normal circulating mechanisms. An exposure of the dorsal penile vein in these subjects was unwarranted; therefore, the injection was made percutaneously into the femoral vein just distal to the inguinal ligament. The advantage of this injection was that under proper conditions the connection between the systemic vessels in the pelvic and lumbar region with the vertebral venous system might be demonstrated.
In 1947 Fariñas and O'Loughlin separately described methods for roentgen visualization of the inferior vena cava with diodrast. The procedure employed in these studies is essentially a combination of their methods with some technical extensions to emphasize the collateral circulation. Femoral vein injections of diodrast were performed in 18 instances.

Prior to the injection of the $52\frac{1}{2}$ per cent diodrast solution, an evaluation of the cardio-hepato-renal status was made and a skin test for drug idiosyncrasy was done. The patient was prepared as for an ordinary kidney-ureter-bladder study in which 35 per cent diodrast is employed. He was placed on the roentgen table in the supine position. The skin of the upper thigh and inguinal region was shaved and prepared surgically with soap and water, and a 1 per cent cephrin solution. A 1 per cent procaine solution was injected first as a skin wheal over the fossa ovalis midway between the anterior superior iliac spine and the pubis and just medial to the pulsating femoral artery. Twenty cc. of the $52\frac{1}{2}$ per cent diodrast solution, which had been previously warmed in a water bath to bring it to body temperature, was drawn into a 20 cc. syringe. With the fingers of one hand palpating the femoral artery, a #18 needle attached to the syringe was inserted through the previously prepared skin into the femoral vein, which is located just medial to the artery. When a small amount of venous blood appeared in the syringe the diodrast was injected as rapidly as possible, approximately 2 cc. per second.
As the injection of 20 cc. was completed, the usual kidney-ureter-bladder exposure was made on a 14 by 17 film. After withdrawing the needle a moderate amount of pressure was employed locally over the point of venipuncture. A film thus obtained is demonstrated in Fig. 7. However, if a moderate amount of pressure is applied by "snuggling down" the x-ray table compression band over a folded piece of toweling placed upon the central and upper abdomen, the return flow in the inferior vena cava is impeded and a very different venous pattern is obtained (Fig. 8).

Fig. 7 demonstrates the normal, unimpeded filling following the rapid injection of 20 cc. of diodrast solution into the right femoral vein. In Fig. 8 the abdominal compression has resulted in an occlusion of the inferior vena cava, and the extensive collateral circulation is demonstrated. The blood has been shunted into the large pelvic veins, the sacral veins are filled and both ascending lumbar veins can be seen, particularly on the right. Also on the right side portions of the vertebral venous complex are noted at the level of the 3rd and 4th lumbar vertebra. The renal calyces and ureters are partially outlined as a result of an injection done about 10 minutes earlier.

In another patient a similar injection into the right femoral vein with abdominal compression applied demonstrated a shunting into the ascending lumbar vein and vertebral veins on the right side (Fig. 9). On another occasion the same subject was injected as previously, abdominal compression applied and a film of the chest and dorsal spine was obtained (Fig. 10). Along the right border of the upper lumbar vertebrae the right ascending lumbar vein and its segmental connections with vertebral veins can be seen. As it is followed upward at the proximal portion of the 12th rib its connections with several of the intervertebral veins of the lower thoracic vertebrae are shown. This plexus of vessels unites to form the lower portion of the azygos vein, which can be seen ascending up to the mid-thoracic region parallel and just to the right of the spinous processes of the dorsal vertebrae.

Upon four occasions the cephalic vein was injected into the anterolateral aspect of the upper arm. An example of normal filling is shown in Fig. 11. The right cephalic vein is shown arching downward into and filling the right axillary vein and the subclavian vein. The right innominate vein is
Partially outlined just to the right of the midline at the lower extent of the film. Crossing the cephalic vein a portion of the transverse scapular vein is demonstrated.

However, when a similar injection is done while the intrathoracic pressure is elevated very little diodrast passes beyond the subclavian vein, and it has "backed-up" into all of the transverse cervical, scapular and deep cervical veins (Fig. 12). Also portions of the left internal and external jugular veins and the vertebral venous system on the left side are shown.

DISCUSSION

The vertebral venous system may be looked upon as a continuous chain of vessels extending from the pelvis to the cranial venous sinuses. The venous pattern obtained in these studies indicates that the ascending lumbar veins, the azygos venous system and the deep cervical venousplexuses can be considered as part of this system (Fig. 13). The venous pressure is relatively low in this system and the circulation is slow and subject to reversals of the direction of flow. The segmental connections at each interspace via the intervertebral veins with all of the adjacent axial structures of the neck, chest and abdomen are evident and an increase in intra-abdominal or intrathoracic
pressure results in an egress of venous blood into the vertebral veins. Hence emboli which have gained access to this venous complex can easily ascend or descend along the vertebral veins. Their direction and ultimate destination depend upon a variety of factors, such as posture and gravity, coughing or straining and the character of the circulation of allied systemic, portal and pulmonary systems.

The spread of bony metastases from carcinoma of the prostate has been found to parallel this vertebral venous pattern and there is pathological

and anatomical evidence that renal tumors may also metastasize by this route.\textsuperscript{2,13} As previously mentioned, the vertebral venous system has been implicated as the mode of spread of cerebral metastatic abscess complicating suppurative thoracic disease.\textsuperscript{7} The close relationship of the cerebral sinuses, the deep cervical veins and the vertebral veins with those of the shoulder girdle and of the breast may be an explanation for the frequency of cerebral and vertebral metastases complicating carcinoma of the thyroid and of the breast.\textsuperscript{1}

Cases of superior sagittal sinus thrombosis complicating puerperal femoral and pelvic thrombosis, in the absence of cardiac or pulmonary path-
ology, have been described by Martin in which the vertebral venous system was regarded as the only logical vehicle of spread. In a review of a group of cases of metastatic abscess complicating thoracic disease it was reported that the cerebral lesion was usually on the same side as the initial thoracic lesion and this was interpreted as evidence of the route of metastases as being via the vertebral veins. Ver Brugghen\textsuperscript{20} presented clinical evidence of the vertebral venous system in the metastatic spread of tumors to the cerebrum.

Bailey has objected to Batson's theory of vertebral venous carcinomatous metastases to the brain because he believes that such growths are rarely found in the spinal canal and because intracranially the metastases are usually found as discrete nodules deep within the brain rather than in the venous sinuses and meninges. In this series of 1076 verified tumors there were 72 cases of carcinomatous cerebral lesions and 15 intraspinal cases of metastatic carcinoma. This number is much less than the number of cerebral lesions but the relative bulk of the spinal cord and its meninges likewise is much less than that of the brain and therefore the chance of metastatic involvement is proportionately less, regardless of the mode of spread. Further, Willis has noted that it is the carcinomas of the lung and of the breast that are most frequently responsible for metastases to the spinal cord as well as to the brain.\textsuperscript{22} As regards the depth of the cerebral metastatic lesions, they often occur at the junction of the cortical gray matter and the white matter, but the deeper structures, such as the basal ganglia, are also frequently the sites of growth.\textsuperscript{18,22} In the retrograde venous filling of diodrast (Fig. 5) it is evident that the internal cerebral veins are filled as well as the external venous sinuses; in fact the internal cerebral veins and the great cerebral vein of Galen are particularly well demarcated. Therefore, according to these studies retrograde venous metastases could occur deep within the cerebrum as well as superficially.

These studies and the clinical correlation give additional credence to the part the vertebral venous system plays in the spread of metastases. It is realized that other factors, such as specific tissue susceptibility, chemical, hormonal and metabolic conditions\textsuperscript{22} play a large part in the final success or failure of tumor emboli to grow in tissue to which they have been conveyed.

CONCLUSIONS

1. The elementary, segmental character of the vertebral venous system and its continuity with the cerebral venous sinuses has been demonstrated roentgenologically by the employment of a 52\% per cent solution of diodrast (3,5-diiodo-pyridone-N-acetic acid and diethanolamine).

2. The close relationship of this venous system with the veins of other axial structures, such as the prostate, kidneys and adrenals, lungs, breast and thyroid, has been demonstrated.

3. The shunting of blood from the systemic circulation into the vertebral venous system has been demonstrated roentgenologically in living subjects.

4. These studies are considered further supportive evidence of possible
routes for spread of metastases via the vertebral venous system from distant primary foci to the cerebrum.

REFERENCES