"POLYCYTHEMIA" ASSOCIATED WITH CEREBELLAR HEMANGIOBLASTOMA

ARTHUR A. WARD, JR., M.D., ELDON L. FOLTZ, M.D., AND LAWRENCE M. KNOPP, M.D.

Division of Neurosurgery, University of Washington, and Neurosurgical Service, Veterans Administration Hospital, Seattle, Washington

(Received for publication December 16, 1955)

In 1943, Carpenter and co-workers reported 2 cases of cerebellar hemangioblastoma with associated "polycythemia vera." They added 3 cases from the literature. Since then, about 22 such cases have been reported in the American literature.\(^{3,4,8,12,21,25}\) Hemangioblastomas of the posterior fossa constitute only 2 per cent of intracranial tumors\(^{5,6,16}\) and those associated with "polycythemia" less than 20 per cent of the total number of hemangioblastomas.\(^{4}\) Thus, the association of "polycythemia" with posterior fossa hemangioblastoma is, to paraphrase Carpenter, an event of the greatest rarity.

Polycythemia rubra vera has been defined as a disease of unknown etiology, characterized by an excessive production of all marrow elements with resultant increase in red blood cell count, total red blood cell volume, white blood cell and platelet counts, and accompanied by increased blood viscosity and decreased velocity of blood flow.\(^{19,33}\) Since quantitative blood studies have been done in only 1 of the reported cases of cerebellar hemangioblastoma,\(^{3}\) it is difficult to determine whether polycythemia vera (as defined above) did, in fact, exist in the remainder. Possibly erythrocytosis, in which the red blood cell count is elevated with no increase in white blood cells or platelets, might be a more appropriate term to use.

We have recently studied 2 patients who had posterior fossa hemangioblastomas with associated erythrocytosis. Both patients were treated surgically, one with subtotal and the other with total removal of the tumor. We believe that the hematologic studies made in these 2 cases are more nearly complete than those reported heretofore.

It has not yet been proved that the relationship between the altered blood picture and the tumor is more than fortuitous. Although the basic physiopathology is unknown, the reduction in the degree of erythrocytosis in some cases following removal of the tumor suggests a cause-effect relationship. We hope that the cases here reported will yield some clue to the mechanisms involved.

CLINICAL DATA

Case 1. W.D., a 45-year-old white male, was admitted to the neurosurgery service on Nov. 3, 1952.

While in the Army in 1941, the development of signs of increased intracranial
pressure and cerebellar dysfunction led to a diagnosis of cerebellar tumor. Ventriculography revealed an "internal hydrocephalus" and was followed by suboccipital craniectomy. No gross tumor was found. Following operation, the patient was relieved of his symptoms for 3 years. Symptoms recurred in 1946 and he then received 2000 r of x-ray therapy to the posterior fossa.

He was next seen in another hospital in 1947 with no change in his clinical picture but with a red blood cell count of 5.38 million. One year later he was re-admitted to that hospital with progression of his signs of cerebellar dysfunction and with a red blood cell count of 6.5 million. He was seen intermittently in the outpatient department until 1949. His discharge note read, "The Tumor Board feels that there is a question of this man ever having had a tumor."

A rapid increase in his neurological deficits prompted admission to this hospital on Nov. 3, 1952.

Examination. The physical findings supported a diagnosis of cerebellar neoplasm. Lumbar puncture yielded clear, colorless fluid under a pressure of 264 mm. of cerebrospinal fluid. There were no cells; protein was 88 mg. per cent. Vertebral angiography revealed a diffuse vascularity of the posterior fossa suggestive of a vascular neoplasm. (Hematologic studies are reported in a later section.)

Operation. On Nov. 19, 1952, a posterior fossa exploration was carried out. An extensive meningocele was encountered on the right and there were three smaller separate ones on the left. Upon exposure of the cerebellum, a large extremely vascular tumor was occupying most of the posterior fossa and involving virtually the entire right cerebellar hemisphere. The neoplasm was gray and had numerous large tortuous venous and arterial channels whose major supply was not identified. Approximately one-third of the tumor was excised from the inferior and lateral portions of the exposed mass.

Postoperative Course. The patient exhibited no over-all improvement in his neurological deficits. He was discharged to a nursing home on Feb. 19, 1953.

On April 2, 1953, he was returned to the hospital because of sudden coma. Despite frequent periods of apnea, he responded to therapeutic efforts and was awake within 2 hours. However, from this point he deteriorated rapidly and died on the following morning. Cause of death was reported as aspiration pneumonia.

Autopsy. The fresh brain showed a moderate amount of thin bloody subtentorial fluid. There was a firm irregular mass occupying the right cerebellar lobe and a number of large tortuous veins along the right side of the brain stem and pons emerged from the mass. The remainder of the brain was grossly normal except for slight flattening of gyri and narrowing of sulci.

After fixation, the neoplasm was found to occupy almost the entire right cerebellar hemisphere. Some entering veins measured 4 to 5 mm. in diameter. On cut section, the most striking feature was the number of large vascular channels. The tumor was an admixture of grayish-white and reddish-brown tissue with scattered yellow foci, these latter presumably being xanthomas of "foam cells."

The microscopic picture was likewise characterized by striking vascularity. There were many thin-walled vessels of irregular shape with numerous sinusoids and venous lakes. The stroma showed two dominant characteristics—an amorphous eosinophilic matrix and packed masses of foam cells. Pathologic diagnosis: hemangioblastoma (Fig. 1).

Case 2. P.V., a 32-year-old white male, was admitted to the medical service on April 10, 1952.
The patient had experienced 2 months of vertigo and when seen by a private physician had a hemoglobin of 20.3 gm., hematocrit 64 per cent, red blood cells 9.52 million, and white blood cells 12,250. Following four blood donations, these studies were repeated at which time his hemoglobin was 15.6 gm., and red blood cell count 5.61 million. With the development of nausea and vomiting, he was sent to this hospital, where an additional history of progressive occipital headaches was elicited.

Examination. Roentgenograms of the skull were normal. Lumbar puncture revealed clear, colorless fluid under a pressure of 290 mm. of water, containing 61 mg. per cent of protein.

When seen in consultation on July 11, 1952, he had bilateral papilledema of 2 D. and bilateral nystagmus. (Hematologic studies are reported in a later section.)

Operation. On July 16, 1952, ventriculography and suboccipital craniectomy were done. Ventriculography showed a grossly dilated ventricular system including 3rd ventricle and aqueduct. The aqueduct was occluded in its lower portion in a spindle-shaped manner, being displaced forward and to the right. At operation, an egg-shaped mass was found within the 4th ventricle, lying on the dorsal surface of the medulla and extending down to the level of C1. It had separated the cerebellar tonsils and pushed them superiorly and dorsally. The mass extended slightly to the left of the midline and well up into the 4th ventricle. The tumor was adherent to the floor of the 4th ventricle and the dorsal surface of the medulla and overlying cerebellum. It was dark red with many exceedingly large vessels on the surface. The blood contained in the vessels was all bright red. There were multiple vessels feeding the tumor, but the largest source of supply seemed to be from the region of

Fig. 1. Case I. Microscopic appearance of tumor. Hematoxylin and eosin stain, ×240.
the left inferior cerebellar peduncle. Complete removal of the tumor was accomplished.

Postoperative Course. In the 2nd week after operation fever, stiff neck, and lethargy developed. A cyst over the operative site had appeared, but evacuation showed it was sterile and apparently produced by retained necrotic tissue. The lethargy responded in dramatic fashion to anticholinergic therapy and an uneventful physical convalescence followed. Behavioral difficulties necessitated the patient’s transfer to the psychiatric service, from which he was discharged on Dec. 19, 1952.

At 1 year after operation, persisting cerebellar dysfunction could be elicited only on careful neurological examination.

Pathology. On cut section the surgical specimen showed innumerable small and large vascular spaces. The surface of the nodule contained vessels as large as 0.5 cm. in diameter. There was a central cavernous space which appeared to communicate with other surface vessels.

Microscopic section showed an admixture of large vascular channels, some of which had thin walls as though representing veins, and others with rather dense, compact muscular walls suggesting arterial origin. Between these larger channels were compact areas of proliferating young capillaries. In addition, a moderate number of large vacuolated cells were seen suggestive of xanthoma cells. This composite picture was characteristic of hemangioblastoma (Fig. 2).

HEMATOLOGIC STUDIES

Adequate study of the blood picture in a patient with hematological
abnormalities requires more than a routine peripheral blood count. In an
effort to study these cases as completely as possible, a number of determin-
ations utilizing a variety of techniques were done.

Peripheral blood counts were done frequently. Each patient had a total
of 18 preoperative peripheral counts which included red blood cells, hemo-
globin, hematocrit, white blood cells, bleeding time, clotting time, pro-
thrombin time, platelet count and reticulocyte count. Sternal marrow exam-
inations were done. Determinations of the arterial oxygen content, capacity
and concentration were carried out in Case 1. The mean corpuscular values
were also calculated. Unfortunately these latter two studies were not per-
formed in Case 2.

Blood-volume studies were carried out in both cases utilizing three tech-
niques. The {\(I^{31}\)} method is a plasma dilution method using tagged serum.
Both {\(Cr^{31}\)} and {\(P^{32}\)} methods involve the use of tagged red blood cells which

<table>
<thead>
<tr>
<th>TABLE 1</th>
</tr>
</thead>
</table>

Case 1. Peripheral blood counts
(18 preoperative counts; 10 postoperative counts)

<table>
<thead>
<tr>
<th>Red Blood Cells (million)</th>
<th>Hemoglobin (gm.)</th>
<th>Hematocrit (per cent)</th>
<th>White Blood Cells</th>
<th>Platelets (thousand)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>7.09</td>
<td>6.57</td>
<td>21.7</td>
<td>18.2</td>
</tr>
<tr>
<td>Low</td>
<td>5.77</td>
<td>5.32</td>
<td>18.2</td>
<td>16.5</td>
</tr>
<tr>
<td>Average</td>
<td>6.40</td>
<td>5.93</td>
<td>20.1</td>
<td>17.5</td>
</tr>
<tr>
<td>Normal</td>
<td>6.0</td>
<td>5.0</td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>

are injected and later recovered in a blood sample and the red blood cell mass
is calculated from these.\(^{15}\) The {\(Cr^{31}\)} and {\(P^{32}\)} methods are immediately compa-
rable, agreeing within 1 per cent or less.\(^{7}\) The {\(I^{31}\)} method, on the other hand,
generally gives values that are 5 per cent or more higher than the other
two methods. For this reason, the {\(I^{31}\)} values are ignored in evaluating the
results.

Table 1 is a summary of the pre- and postoperative peripheral blood
counts in Case 1. It will be noted that the only abnormalities are in the
erthrocytes and that these values (red blood cells, hemoglobin, and hemato-
crit) are reduced to nearly normal limits following operation. None of the
postoperative figures is the result of blood depletion since continuous and
adequate replacement was carried out during operation in each case.

Bleeding, clotting, and prothrombin times and reticulocyte counts were
normal. Arterial oxygen content, capacity and concentration of Case 1 were
likewise normal. Examination of the sternal marrow revealed hyperplasia of
moderate degree involving both erythrocytic and myelocytic series.

Table 2 compares pre- and postoperative blood-volume determinations
in Case 1. The principal preoperative abnormality is again in the erythro-
**TABLE 2**

*Case 1. Blood volume determinations*

<table>
<thead>
<tr>
<th>Method</th>
<th>Preoperative</th>
<th>Postoperative</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>I$^{31}$</td>
<td>62.5%</td>
<td>59%</td>
<td>47.3%</td>
</tr>
<tr>
<td>Cr$^{51}$</td>
<td>45.5%</td>
<td>45.5%</td>
<td></td>
</tr>
<tr>
<td>Average hematocrit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood volume</td>
<td>10,026 cc.</td>
<td>5,550 cc.</td>
<td>4,450 cc.</td>
</tr>
<tr>
<td>Packed cell volume</td>
<td>6,266 cc.</td>
<td>3,275 cc.</td>
<td>2,450 cc.</td>
</tr>
<tr>
<td>Plasma volume</td>
<td>3,760 cc.</td>
<td>2,575 cc.</td>
<td>2,000 cc.</td>
</tr>
</tbody>
</table>

**TABLE 3**

*Case 2. Peripheral blood counts*

(18 preoperative counts; 32 postoperative counts)

<table>
<thead>
<tr>
<th>Red Blood Cells (million)</th>
<th>Hemoglobin (gm.)</th>
<th>Hematocrit (per cent)</th>
<th>White Blood Cells</th>
<th>Platelets (thousand)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>7.95</td>
<td>6.30</td>
<td>19.4</td>
<td>15.8</td>
</tr>
<tr>
<td>Low</td>
<td>5.29</td>
<td>4.62</td>
<td>15.3</td>
<td>13.2</td>
</tr>
<tr>
<td>Average</td>
<td>6.36</td>
<td>5.34</td>
<td>17.6</td>
<td>14.8</td>
</tr>
<tr>
<td>Normal</td>
<td>6.0</td>
<td>15</td>
<td>15</td>
<td>45</td>
</tr>
</tbody>
</table>

**TABLE 4**

*Case 2. Blood volume determinations*

<table>
<thead>
<tr>
<th>Method</th>
<th>Preoperative</th>
<th>Postoperative</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>I$^{31}$</td>
<td>P$^{51}$</td>
<td>P$^{51}$</td>
<td>Cr$^{51}$</td>
</tr>
<tr>
<td>Cr$^{51}$</td>
<td>45.5%</td>
<td>55%</td>
<td>49%</td>
</tr>
<tr>
<td>Average hematocrit</td>
<td>52.5%</td>
<td>59.6%</td>
<td>50%</td>
</tr>
<tr>
<td>Blood volume</td>
<td>4,777 cc.</td>
<td>3,798 cc.</td>
<td>3,140 cc.</td>
</tr>
<tr>
<td>Packed cell volume</td>
<td>2,508 cc.</td>
<td>2,367 cc.</td>
<td>1,550 cc.</td>
</tr>
<tr>
<td>Plasma volume</td>
<td>2,289 cc.</td>
<td>1,531 cc.</td>
<td>1,600 cc.</td>
</tr>
</tbody>
</table>

**TABLE 5**

*Postoperative reductions in blood values*

<table>
<thead>
<tr>
<th>Percentage Reduction</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average red blood cells</td>
<td>7.4%</td>
<td>16.0%</td>
</tr>
<tr>
<td>Average hemoglobin</td>
<td>12.9%</td>
<td>10.3%</td>
</tr>
<tr>
<td>Average hematocrit (peripheral)</td>
<td>9.9%</td>
<td>16.4%</td>
</tr>
<tr>
<td>Blood volume</td>
<td>19.9%</td>
<td>19.8%</td>
</tr>
<tr>
<td>Packed cell volume</td>
<td>25.2%</td>
<td>25.0%</td>
</tr>
<tr>
<td>Plasma volume</td>
<td>12.1%</td>
<td>12.1%</td>
</tr>
<tr>
<td>Average hematocrit (isotope)</td>
<td>19.8%</td>
<td>8.4%</td>
</tr>
</tbody>
</table>
cytes, and the postoperative levels show a normal range. The normal cited here is an average of figures for males.23

Tables 3 and 4 give comparable data for Case 2. Once again the only abnormalities are in the erythrocytes, the preoperative elevation of red blood cell count, hemoglobin, hematocrit and blood-volume values being reduced to normal following operation. This patient’s bleeding, clotting, prothrombin times and reticulocyte count were normal. The sternal marrow showed erythroid hyperplasia.

Table 5 compares the changes in the blood picture following tumor excision in both cases. Even though Case 2 had a complete tumor excision and Case 1 an incomplete tumor removal, the percentage reductions in the blood-volume values were almost identical for both cases while the postoperative reductions in peripheral counts were less marked.

DISCUSSION

Polycythemia rubra vera frequently causes symptomatology of the central nervous system. In fact Loman and Dameshek14 stated that “in polycythemia vera, symptoms referable to the head greatly outrank in incidence those relating to any other bodily system.” Sloan25 reported in detail 4 cases of polycythemia with neurological symptoms. Lawrence et al.15 found the most frequent symptoms of polycythemia to be headache, dizziness, and visual difficulties. These are often the symptoms of increased intracranial pressure. Hence, as Brockbank2 pointed out, the differential diagnosis is often exceedingly difficult. In fact, some patients with polycythemia have in the past had fruitless explorations for brain tumor3 while others with antecedent polycythemia have been found to have subdural hematoma,8 parietal glioblastoma,19 or metastatic carcinoma of the frontal lobe.19 Oppenheimer17 in 1929 reported the case of a patient with polycythemia vera who had a cerebellar medulloblastoma at autopsy and in whom the polycythemia was the only clinical finding. Still, the combination of brain tumor and polycythemia is a rare one.

Beginning with Carpenter et al.,3 about 22 cases of posterior fossa hemangioblastomas associated with an increase in absolute red blood cell count have been reported in the American literature.4,5,7,12,21,25 Far more cases of hemangioblastoma without increase in red blood cell count have been noted.4,6,16,18,21,24 Although the incidence of this association is not known, it certainly occurs in less than 18 per cent of all cases of cerebellar hemangioblastoma.

The chief difficulty that arises in the evaluation of the published cases lies in the type of hematologic studies performed. The only case in which blood-volume studies were done was that reported by Carpenter et al.3 This patient’s preoperative and postoperative values were similar to ours. Carpenter’s second patient as well as all the others reported had peripheral counts only. Cramer and Kimsey4 discussed polycythemia in some of their cases, stating that in polycythemia the red blood cell count is above 5 million
for females and 6 million for males. Silver and Hennigar\textsuperscript{21} and also Woolsey\textsuperscript{25} similarly diagnosed polycythemia in the absence of any additional studies. As has been pointed out, polycythemia vera is a specific hematologic abnormality which none of the reported patients exhibited. On the other hand, they all had erythrocytosis.

The results of tumor removal in some of the reported patients had a dramatic effect on the red blood cell count. Both patients discussed by Carpenter \textit{et al.}\textsuperscript{3} had preoperative counts of 6.5 million red blood cells or higher with comparable values for hemoglobin and hematocrit. Following operation, each patient had basically normal blood cell counts. Cramer and Kimsey\textsuperscript{4} noted an elevated red blood cell count in some of their patients who proved to have solid or vascular hemangioblastomas at operation. These blood values were reduced after tumor removal. Some of their patients with cystic hemangioblastomas had recurrences. Of these, 63 per cent had an elevated red blood cell count and at re-operation the tumor was found to be either solid or vascular. The blood values likewise were reduced in these cases following removal of the tumor. Woolsey’s\textsuperscript{25} patient had a normal red blood cell count after removal of a cerebellar cyst only, following which the count then rose to 7.89 million. Following re-operation for removal of an obvious hemangioblastoma, it fell to 4.75 million. Thus, removal of the tumor apparently causes a decrease in circulating red blood cells to normal or near-normal levels. This follows the removal of only the solid or vascular types of tumor.

Both cases here reported had solid hemangioblastomas. Case 1 exhibited a postoperative decrease of 7.4 per cent in red blood cell count, 12.9 per cent in hemoglobin, and 9.9 per cent in hematocrit, while comparable reductions for Case 2 were 16.0 per cent, 10.3 per cent and 16.4 per cent respectively. The percentage reductions in blood-volume determinations were more striking. There was a 25 per cent postoperative decrease in packed cell volume in each case, a 19 per cent reduction in blood volume, and plasma volume was decreased 12 per cent. The primary postoperative change was thus in the absolute number of erythrocytes.

It is evident that “polycythemia,” as defined, is a misnomer in these cases. However, in common usage, “polycythemia” refers merely to an increase in red cell levels and thus is semantically justifiable in describing the blood picture in such patients. However, we prefer the term “erythrocytosis.”

The cause for the apparent relationship between erythrocytosis and posterior fossa hemangioblastoma is unknown. Four alternative explanations have been offered:

a) An actual neurogenic focus for the regulation of erythropoiesis. Haynal and Graf\textsuperscript{21} observed polycythemia in 10 patients who had dysfunction of the hypophysial-hypothalamic system. They postulated that in cases of posterior fossa tumor, hydrocephalus caused by obstruction of the 4th ventricle produces hypothalamic dysfunction by pressure. This view, although not
completely shared, was felt to be the most likely by Carpenter et al.\textsuperscript{3} in 1943.

b) The presence of extramedullary erythropoietic centers. In Lindau’s disease, the hemangiomata are not limited to the cerebellum. Tonning et al.\textsuperscript{24} postulated that although the lesions seem to be attributable to a developmental defect, there must also be a persistent alteration in tissue reactivity because new lesions may develop throughout life. They feel that the lesions “represent a fundamental persistent lack of integration between blood vessels and parenchyma.” The continued development of hemangiomata in such organs as liver or spleen would thus be the source of the increase in circulating red blood cells.

c) Erythropoietic centers are stimulated by a disturbance in oxygen balance in the circulating blood caused by arteriovenous shunts in the tumor.

d) The formation of erythroid elements in the tumor itself. Cramer and Kimsey\textsuperscript{4} found that tissue culture of the tumor from one case suggested erythropoietic activity. Sabin\textsuperscript{20} in 1917 described the production of vessels, plasma and red blood cells in the chick. The anatomical description of this developing tissue suggests the structure of the cavernous hemangioblastoma as described by Cushing and Bailey\textsuperscript{6} who were unable to demonstrate red blood cell formation in their series. In the cases that they studied, they mentioned not one patient with increased red blood cell count.

There are valid objections to at least three of these views. Erythrocytosis has not been reported in association with the general group of intracranial tumors, nor with other posterior fossa tumors. Thus it would be difficult to implicate hydrocephalus with resultant pressure dysfunction of the hypothalamus. The possibility of extramedullary erythropoietic centers cannot be ruled out, but the disseminated lesions of Lindau’s disease are usually associated with the cystic hemangiomata. It will be recalled that apparently only the solid tumors are associated with erythropoiesis. This explanation thus does not fit the clinical observations. The arteriovenous shunt postulate is also unsupported by the evidence. Patients with primary intracranial vascular anomalies in which such a shunt exists do not exhibit an associated erythremia. Lawrence and co-workers\textsuperscript{35} stated that there is no known anoxic stimulant to polycythemia vera.

The altered blood picture seen in these cases appears to be associated with only the solid hemangioblastomas, never the cystic variety. When the cystic type undergoes a change to solid type, erythrocytosis may apparently then develop. Such a discrete association suggests that the two are causally related. If so, then production of red blood cells by the tumor is the only one of the four suggested explanations that is tenable.

Recent work by Borsook et al.,\textsuperscript{1} Erslev,\textsuperscript{9} and Grant and Root\textsuperscript{10} postulates the existence of a hormonal factor which has the property of stimulating erythropoiesis. In the experimental animal serum may be secured which, when injected into another animal, results in overproduction of red blood cells.

It may be that some hemangioblastomas secrete such a hormonal factor
"POLYCYTHEMIA" WITH CEREBELLAR HEMANGIOBLASTOMA

which exists in a sufficient concentration to stimulate erythropoiesis. If true, the removal of critical amounts of the tumor could decrease this hormone concentration below the point of erythropoietic stimulation with resultant decrease in blood counts. This explanation obviates the need for finding erythropoietic activity in the tumor itself. Thus cystic varieties of tumor would contain insufficient functioning secretory tissue to produce the necessary amount of hormone for overproduction of red blood cells. With a change to the solid state, the amount of secretory tissue increases and erythropoiesis increases.

We must await further experimental studies to prove this hypothesis that the erythrocytosis associated with cerebellar hemangioblastoma is secondary to an erythropoietic hormone secreted by the tumor.

SUMMARY AND CONCLUSIONS

1. Two cases of posterior fossa hemangioblastoma (solid type) with associated erythrocytosis are presented.
2. Pre- and postoperative peripheral blood counts and blood-volume determinations reveal that the increased red count, hemoglobin, and hematocrit are caused by an increase in erythrocytic elements only and that these values show a dramatic decrease following surgical removal of the tumor.
3. In view of these additional data, it would appear that previous patients reported as having polycythemias did, in fact, have only erythrocytosis.
4. It is postulated that the erythrocytosis associated with solid cerebellar hemangioblastomas may be secondary to an erythropoietic hormone secreted by these tumors.

REFERENCES

A. A. WARD, JR., E. L. FOLTZ AND L. M. KNOPP