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The idea of inserting radium into tumor tissue occurred to many of the pioneers in radiation therapy soon after the discovery of radium. Most authors attribute the suggestion of impaling tumor with radium to Alexander Graham Bell, the inventor of the telephone. H. Strebel of Germany, in 1903, was apparently the first individual actually to apply radium interstitially; his work was closely followed by that of W. Scholtz of Germany, and H. Dominici of France. On March 4, 1904, Dr. Robert Abbe of New York reported the first radium implant in the United States.

In 1920, Claude Régaud compiled the basic principles upon which modern interstitial radiation therapy is based. He advocated the use of low intensity, platinum-encased radium needles and suggested that treatment "is most effective if continuous and extended over a period of 6 to 10 days." Sir Stanford Cade in England, and Maurice Lenz and Charles Martin of this country, introduced these concepts of Régaud into the literature in English. During the third and fourth decades of this century, interstitial radium therapy was used extensively in this country, but the results were far from impressive. The major difficulty seemed to be the failure of therapists to understand the physical and biologic properties of radium. Moreover, no satisfactory clinical method for determining dose was available, nor had any definite method been described for implanting tumor. Therefore every therapist of the time was an artist in the true sense. He could scarcely reproduce his own work on similar patients with similar lesions. Numerous instances of underdosage with residual tumor and overdosage with radionecrosis were clearly evident. To make matters worse, frequently the same patient showed evidence of both overdosage and underdosage i.e., persistent tumor and coexisting radionecrosis. Because of the difficulty in reproducing results, the teacher found it difficult to transmit...
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his knowledge to the pupil. Thus up to World War II, there was in the entire world only a handful of therapists who were skilled at administering radium interstitially. These few were very effective in controlling the disease in their own patients. But the vast majority of radiologists, because of difficulty in learning the method, or because of inability to control the dose, abandoned the procedure. Not until 1934 did an accurate practical method for calculating radium dose become available. In that year Paterson and Parker of Manchester, in their publication entitled *A Dosage System for Gamma Ray Therapy*, elevated interstitial radium therapy above pure trial and error methods.¹

In order to employ radium therapy satisfactorily, the physician must understand very clearly the inverse square law. This law states that the intensity of radiation from a source varies inversely with the square of the distance from the source. This law is immutable and inexorable. It cannot be ignored. If at \( \frac{1}{2} \) cm. from a point source a dose of 6000 r is given, then the dose at 1 cm. from the source will be 1500 r, and at 1½ cm. from the source, approximately 650 r. This very rapid decrease in dose with short increments in distance points out vividly the folly of inserting radium needles into 95 per cent of a tumor and hoping that the inaccessible 5 per cent will be irradiated sufficiently to control the disease. This simply will not happen.

By its very nature a radium implant is a localized treatment, in the same way that surgery is a localized treatment. Only when the tissue is adequately implanted, or through surgical intervention completely excised, can one reasonably hope for a cure. Portions of the tumor beyond the implanted zone will hardly be affected by the implant.

In essence the unique characteristic of a radium implant is its ability to deliver a large dose of radiation to a relatively small volume in a short time. Performed only in selected cases, interstitial radium therapy is usually aimed at cure—in contrast to external radiation, which frequently is aimed at palliation of symptoms. Unavoidable radiation of personnel demands that radium implantation seldom be done with a merely palliative aim. Because of the localized nature of interstitial radium therapy, small volumes of tissue can be raised to exceedingly large doses with safety. This allows certain lesions to receive very large doses which could not be given in any other way. Thus clinicians have universally observed that while squamous cell carcinoma involving the anterior two-thirds of the tongue can seldom be cured by any type of external radiation therapy, it frequently can be controlled by interstitial radium therapy.
Several methods can be used to calculate the dose of an interstitial radium implant. Most radiation therapists now believe that the Manchester system, or as it is sometimes called, the Paterson-Parker system is the most satisfactory. Even the briefest consideration of the inverse square law will make it evident that a homogeneous dose of irradiation throughout the tumor tissue is impossible. The members of the Manchester group have introduced the concept of “the effective minimum dose,” which is 10 per cent above the absolute minimum dose in the irradiated zone. They have suggested that this effective minimum dose should be spoken of as the tumor dose. In other words, when a Mancunian says that the zone of tissue has received a specific tumor dose, he means that no point within the implanted zone has received less than 90 per cent of the stated tumor dose.

In the other systems of calculating radium dose, numerous points of interest are chosen. The doses at these specific points are calculated. But if the therapist does not choose representative points, his calculated dose ratio for the whole implant may be misleading. This possibility is avoided in the Manchester system, in which radium dose is determined by means of two fundamental principles:

1) The radium implantation must be performed according to a geometric pattern.

2) The radium within the geometric pattern must be distributed according to specific, simple rules.

The geometric patterns which are most commonly employed are single plane, two parallel planes, cylinders, cubes, and combinations of planes, cylinders, and cubes. These geometric patterns should be clearly recognizable in radiographs of the implant. The rules for distributing radium within the geometric pattern are specific. These rules are clearly stated in all the current standard textbooks in radiation therapy.

If the two basic requirements for calculation of the implant are met, that is, if the radium is distributed according to specific rules within a geometric pattern, then and only then can the Manchester system of dosage calculation be used. In practice the calculation is a simple arithmetic one. Radiographs of the implanted zone are obtained at right angles using a method described by Meredith and Stevenson. By employing the Pythagorean theorem, one can compute the exact dimensions of the geometric implant. Knowing the precise dimensions of the area or volume implanted and the amount of radium within the implant, one can refer to simple tables to obtain the dose rate.
for the implant. Given the dose rate, one can easily control the dose he wishes to deliver. When the desired dose has been achieved, the radium needles are removed.

The Manchester system offers several distinct advantages:

1) The dose refers to the effective minimum dose and is related to the volume implanted, rather than to a specific point or points within the implanted zone.

2) The rules for implantation are explicit and are easily understood.

3) The calculations are reproducible. When several individuals perform the calculations independently, the dose rates obtained are similar.

4) This method has been clinically proved throughout large areas of the world and has been in use for a quarter of a century. This system of radium dose calculation is uniformly accepted throughout Great Britain and the British Commonwealth. Its superiority is recognized by the French and Scandinavians. There is a growing realization in the United States that this system is superior.

The success or failure of a given implant depends upon three factors: the correct selection of the patient, accurate planning of the implant prior to the procedure, and performance of the implant as planned. From the discussion of the ramifications of the inverse square law, it can be seen that improperly selected tumors cannot be satisfactorily controlled. Precise and accurate planning of the implant prior to the time the physician enters the operating room is essential. If, at examination under anesthesia at the time of the procedure, the tumor is observed to extend beyond its previously conceived limits, the chance for a satisfactory procedure is lessened. Improvisation in the operating room usually results in unsatisfactory implantation.

The principles for the correct selection of tumors suitable for implantation are as follows:

1) The tumor should be moderately radio-sensitive. This usually means a moderately well-differentiated squamous cell carcinoma. Certainly one would not consider radium implantation for lymphosarcoma or lymphoepithelioma nor, on the other hand, would one use it for an adenocarcinoma of salivary gland type.

2) The tumor should be relatively small with well-defined margins. For an implant to be successful the entire volume should be completely encompassed with the zone of irradiation.

3) The tumor should be accessible. Surely, a well-differen-
tiated squamous cell carcinoma of the nasopharynx, because of its inaccessibility, could not be considered a suitable lesion for implantation.

Practically speaking, only a few specific types of tumors in the area of the head and neck will meet all these criteria. The lesions that are suitable for radium implantation are: 1) certain basal and squamous cell carcinomas of the skin; and 2) squamous cell carcinomas involving the anterior portion of the oral cavity.

Most lesions of the skin can be adequately treated by simple excision or external roentgen therapy. Occasionally, certain advanced skin lesions will require radium therapy. Extensive skin lesions which have become fixed to the periostium of the mandible or maxilla without roentgenographic evidence of destruction of these bones, are well treated with radium implantation. Surgical removal of these tumors would usually take a long time for adequate cosmetic results, but frequently a simple single planar implant will suffice and will present a good cosmetic result. Occasionally, tumors will be fixed to or adjacent to the cartilage in the nose. These tumors can often be satisfactorily implanted in a single plane. Here again, if the dose can be controlled accurately, the cosmetic result is good.

Squamous cell carcinomas occurring on the anterior portion of the nasal septum also are well treated by means of a single plane implant, with the needles directed in a plane within the septum. This type of treatment very frequently leads to necrosis and perforation of the septum. But, perforation of the septum does not usually cause grave difficulty, nor does perichondritis in this area usually give rise to symptoms; moreover, by the use of this method the external appearance of the nose is maintained.

Curatively intended interstitial radium therapy is most frequently performed in the anterior portion of the oral cavity. Squamous cell carcinomas of the lip may occasionally be treated with a single or double planar implant, but in most such lesions external radiation therapy, simple excision, or an Estlander type of procedure is usually simpler and yields cosmetically acceptable results. Occasionally, when the musculature around the mouth is extensively involved, radium implantation is indicated. If a surgical excision would require extensive removal of the perioral muscles, the interstitial procedure is simpler and usually obviates extensive plastic repair.

A squamous cell carcinoma of the buccal mucosa can usually be treated by a single planar implant. If the lesion extends
beyond the gingivo-buccal fold to involve the gingiva, the implant cannot be made. The advantages of radium implantation in treating patients with carcinoma of the buccal mucosa are readily demonstrable: In treating these lesions, one can raise the volume of tissue implanted to a very high dose in a short time without delivering significant amounts of radiation to the surrounding structures. One frequently encounters tumors which involve the commissure of the mouth and extend for several centimeters along the buccal mucosa; these lesions also are well treated by single plane implantation.

The most efficacious method of treating squamous cell carcinomas of the anterior two-thirds of the tongue is a matter of great controversy. Many radiotherapists feel that these lesions can be most adequately treated by radium implantation. Most surgeons, on the other hand, consider excision to be the treatment of choice. This is an area in which, I believe, there is honest difference of opinion. Small lesions along the lateral border of the tongue can be controlled by a single planar implant. More extensive lesions of the lateral border will require implantation in two parallel planes with separation of approximately 1.5 cm. More extensive lesions of the tongue will necessitate cylindrical volume implantation. These needles in general are placed through the dorsum of the tongue, perpendicular to the dorsum of the tongue and passing into the root of the tongue, or in the more anterior aspects, into the floor of the mouth.

A few squamous cell carcinomas of the floor of the mouth can be treated by radium implantation, if they are very carefully selected. For example, the lesions of the floor of the mouth which are located in the more posterior aspects, and especially those which approach the frenulum, can be treated satisfactorily by a volume implant with the needles passing through the dorsum of the tongue and down into the floor of the mouth. But those lesions of the floor of the mouth which approach the gingiva and are near the periostium of the mandible, are too inaccessible to permit adequate implantation.

No mention has yet been made of metastatic involvement of the cervical nodes. All the lesions of the anterior portion of the oral cavity are capable of producing cervical lymph node metastases. Such metastases are, in fact, present in most patients with carcinoma of the tongue or carcinoma of the floor of the mouth. Since the radium implantation is directed only at the primary lesion, management of the metastatically involved cervical lymph nodes requires surgical intervention.
Radiation therapists feel that lesions of the posterior portion of the oral cavity and oral pharynx are best managed by external radiation therapy. The use of supervoltage radiation equipment has distinctly enhanced survival rates for patients with tumors originating in these areas. External therapy, however, does not offer complete control of certain of the lesions originating in the posterior portion of the oral cavity. Many squamous cell carcinomas of the tonsillar region invade the adjacent segment of the tongue. These lesions can best be treated with external radiation therapy. After an optimal safe dose has been given, one frequently finds that the disease in the tonsil and soft palate is controlled but the portion of the tumor which had involved the tongue is still palpably present. In such instances, it is usually worthwhile to perform relatively small interstitial radium implants into the palpable residual tumor in the tongue. Squamous cell carcinomas of the base of the tongue are also usually treated with external radiation therapy. The radiation therapy is directed toward the primary tumor and to the lymph nodes on both sides of the neck. Frequently at the completion of the course of external radiation therapy, tumor can still be palpated in the base of the tongue. If there is no evidence of disease in the neck, the residual tumor in the base of the tongue should be implanted with radium needles.

No unusual procedures need be introduced in the preoperative management of the patient who is to receive a radium implant. The history is taken, and physical examination, chest x-ray, biopsy, and essential laboratory work are performed. The physician carefully explains the nature of the procedure and points out that the radium needles will be sutured securely and will remain in the patient's mouth (or wherever the implant is made). The patient must know exactly what to expect, since a perfectly executed implant may be destroyed immediately by a patient's attempts at removing these foreign bodies from his oral cavity.

Among several requests that we make of the anesthesiologist, we ask that if possible, endotracheal anesthesia be used for most of these procedures. For intraoral lesions, we insist that the endotracheal tube be introduced through the nose. With an endotracheal tube inserted through the oral cavity, the chance of performing a geometric intraoral implant is diminished considerably. Occasionally, in patients who represent poor risks, we request a regional anesthesia of the nerve block type; obviously the infiltration type is contraindicated.
The needles are inserted in a geometric pattern sufficient to encompass the entire lesion. Each needle is individually sutured in place with 2-0 silk. The safety cords from the needles are usually tied together and fixed to the skin. The procedure itself usually entails no risk and takes an hour or less to perform. Postoperative care is not complicated. Minimum radium precautions are ordered. This means that the patient is usually placed in a single room and that nursing care is limited to the essentials. Most of these patients can take nourishment by mouth, but nasogastric feeding is instituted in those who cannot maintain an adequate oral intake. For relief of pain, Demerol® is administered intramuscularly every three hours as needed for the first 24 hours. After that period, most patients can usually be maintained with lesser amounts, and many require no further medication for relief of pain. On the second day, radiographs are obtained in order that the optimal dose may be calculated by the physician and checked by the physicist. A specific time for the removal of the implant is decided upon. The removal of the radium needles is a simple matter and is usually performed while the patient is in his hospital bed. Demerol (100 mg.) is given intramuscularly 20 minutes prior to the removal of the needles. The patient is discharged 24 hours after the radium has been removed.

Radium implantation, as has been described, is suitable for selected lesions only. The prognoses as demonstrated by published survival rates have practically no meaning. Naturally, the more rigid the selection criteria, the higher the survival statistics will be. Dr. Ralston Paterson of the Manchester group has reported a 44 per cent five-year survival rate of all patients with localized intraoral lesions treated by radium implantations alone. Stanford Cade has published the following five-year survival statistics for patients treated with radium: those with lesions of the tongue, 23 per cent; floor of mouth, 42 per cent; buccal mucosa, 61 per cent.

The advent of supervoltage therapy had caused many practitioners to believe that the necessity for interstitial radium implantations would be lessened. It is now realized that supervoltage therapy will not appreciably displace radium therapy. Thus far, supervoltage external therapy has not proved superior to interstitial radium therapy for basal and squamous cell lesions of the skin nor for squamous cell carcinoma of the anterior portion of the oral cavity.

In summary, interstitial radium therapy is not new. It is an effective method for treating many potentially curable carci-
nomas in the head and neck region. The method of treatment is successful only in selected patients with localized lesions. Failure frequently results from improper selection. The effectiveness of the radiation therapist in utilizing this technique depends upon his ability to implant the entire lesion in a geometric pattern and upon his ability to control the dose. The most practical way of controlling the dose is by means of the Manchester system for interstitial radium therapy.

REFERENCES

Within recent years many so-called “strokes,” “cerebrovascular accidents,” apoplectic attacks, etc. formerly were assumed to be of intracranial vascular etiology have come to be, which recognized as originating in the extracranial carotid system.

As early as 1905, Chiari drew attention to the frequency of atherosclerotic changes in the region of the bifurcation of the carotid artery in the neck. Although he recognized that these changes were often associated with cerebral symptoms and lesions, he related the symptoms to an associated embolic phenomenon. Hunt in 1914, while studying a number of hemiplegias of vascular origin, noted that not infrequently the carotid arterial pulsation was extremely diminished or absent on the side of the cerebral lesion. He recognized the importance of the collateral circulation in the prevention of the development of cerebral lesions and suggested the term “cerebral intermittent claudication” for the premonitory, transient episodes of cerebral dysfunction that are frequently associated with this entity.

The observations of these two early investigators were for the most part neglected until 1937, when Moniz et al. reported on the use of cerebral angiography in the diagnosis of carotid occlusion. This method assured the detection of carotid artery disease during life. The procedure was rapidly approved in Europe but was slow to gain wide acceptance in this country. Consequently, earlier reports of carotid artery occlusion dealt
primarily with material secured at autopsy. For instance, the pathologic studies of Fisher\(^4\)\(^,\)\(^5\) (1951, 1954) again drew attention to the frequency of extracranial carotid artery occlusion. In 432 consecutive routine autopsies he observed complete occlusion of one or both carotid arteries in 6.5 per cent, and severe luminal narrowing in an additional 3 per cent; thus, a total of 9.5 per cent showed evidence of severe carotid artery disease.

Johnson and Walker\(^6\) (1951) discovered six cases of spontaneous thrombosis of the common or internal carotid arteries during the course of angiography for suspected brain tumors, vascular malformations, or aneurysms; they reviewed another 101 reported cases of angiographically proved thrombosis of the carotid artery. In 40 per cent of these cases, transient episodes of neurologic dysfunction were elicited; sudden, catastrophic onset with immediate severe neurologic deficit was noted in 35 per cent; and 25 per cent revealed a slowly progressive course of neurologic embarrassment simulating that occurring in an expanding intracranial lesion.

Following successful repair of obstructing lesions in the arterial system of the lower extremities, attention was drawn to the possibility of surgical attack on obstruction of the extracranial cerebral vessels. In 1954, Eastcott, Pickering, and Rob\(^7\) reported the first successful repair of a partially obstructing lesion of the carotid artery. Innumerable reports of surgical repair of such lesions have since appeared.\(^0\)\(^–\)\(^22\)

In 1955, Millikan and Siekert\(^8\) defined the characteristics of a partially obstructing lesion, and coined the term “intermittent insufficiency of the carotid arterial system.”

This paper will summarize our surgical experience with obstructing lesions of the extracranial portion of the carotid artery, following a discussion of the clinical features of this entity.

**Clinical Manifestations**

The clinical syndrome follows one of three rather distinct patterns:

1) In most cases symptoms are at first transient and episodic, but over a period of time they become constant. Generalized headache, which occasionally becomes confined to one side, is often the first symptom. This sign may be followed by transient contralateral hemiparesis with greatest involvement of the upper extremity, episodic ipsilateral blindness or visual disturbance (homonymous hemianopsia); sensory disturbances varying from dysesthesias to hypalgesia; dysphasia to aphasia
when the dominant hemisphere is involved; occasionally epilepsy, failing memory, vertigo, etc. Such symptoms usually appear suddenly, last a few minutes to an hour or two, and may clear suddenly or gradually. Generally, these episodes tend to recur with increasing frequency and severity and commonly terminate with sudden hemiplegia and aphasia.

2) Less frequently, the onset of symptoms may be slowly progressive, simulating an expanding mass lesion. Frequently associated with this type of onset is severe headache of some months duration, followed by paresthesias and weakness of the contralateral hand and arm, with gradual spread to the leg. Mental regression, occasional convulsions, and speech impairment slowly appear. The total period of development of this picture may be a year or two.

3) Occasionally the onset may be sudden and catastrophic with loss of consciousness and hemiplegia. Aphasia may be present if the dominant hemisphere is involved. Spontaneous improvement following this type of onset is very slight.

Physical signs of carotid arterial insufficiency are few. A unilaterally diminished carotid pulsation is often observable through palpation over the artery. Groch et al. have expressed the belief that palpation of the carotid artery in the tonsillar fossa is a more reliable technique in establishing whether or not the pulsations are unilaterally decreased. A soft, systolic bruit may be heard over the carotid artery, but this may have doubtful significance. Occasionally a bruit is heard not over the involved artery but over the contralateral vessel. Such an occurrence may be explained on the basis of increased blood flow through the opposite artery. Horner's syndrome, usually in an incomplete form consisting of only mild ptosis and miosis, has been noted by some authors. Ophthalmodynamometry has been used effectively in the diagnosis of carotid artery insufficiency, but not all authors agree about the reliability of this means of evaluating insufficiency. It is well recognized that equality of bilateral retinal artery pressures does not rule out the possibility of carotid arterial disease. When compression of the contralateral artery is employed, subsequent syncope is considered to be a positive result. Electroencephalographic changes—especially those observed by use of a tilt-table—have been reported helpful. Other changes, such as visual field defects, unilateral retinopathy, and asymmetric hypertensive retinopathy, have been cited in a few instances.

The preceding symptoms and signs are extremely helpful in suggesting the probable diagnosis, but angiographic evidence
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is necessary for full confirmation; without adequate radiographic demonstration it is impossible, short of surgical visualization, to determine the exact location, the extent, and most important, the status of the vessel(s) distal to the site of the lesion.

PATHOLOGIC CHARACTERISTICS

The underlying pathologic process in most cases has been atherosclerosis. Other diseases, such as thromboangiitis obliterans and Buerger’s disease, have been implicated, but these are exceedingly rare, and furthermore, the validity of the reported cases has been questioned. Caldwell and Hadden reported eight cases of carotid arterial thrombosis with disastrous cerebral effects following trauma to the neck or region of the tonsillar fossa. Anomalies of the cervical vertebrae may occasionally compress the internal carotid or vertebral artery. Boldrey et al. reported a case characterized by repeated attacks of transient hemiplegia that occurred with turning of the head; surgical exploration revealed that the internal carotid artery was bound down and compressed by the transverse process of the atlas.

Atheromatous occlusive disease generally assumes two distinct patterns of involvement: DeBakey has classified these as a proximal and distal form and has emphasized their segmental nature. In the proximal type, the occlusive process involves one or more of the branches of the aortic arch. In this area, the obstruction may be complete or incomplete; and may be confined to a short segment of the artery near its origin or may be more extensive and involve the major portion of the course in the neck. Because of the large number of distal collateral arteries arising in the chest and neck, the distal portion of the artery remains patent despite complete proximal occlusion.

In the distal form, the occluding atheromatous process usually occurs at the origin of the internal carotid or vertebral arteries. In the earlier stages the obstruction is only partial and remains well localized. At this stage the vessel proximally and distally remains relatively uninvolved. With complete occlusion, however, extension of the process into the intracranial portion of the vessels commonly occurs. For this reason, all but the acute forms of distal obstruction have generally been found to be inoperable. Another peculiar feature of the distal form of obstruction is the tendency for the atheroma to be limited to the internal carotid artery. It may extend into the common carotid artery, but rarely involves the external carotid artery to any significant degree. This fortuitous occurrence often provides a valuable channel of collateral circulation to the intracranial
vessels via anastomosis through the various branches of the external carotid artery and the vertebral artery.32,33

The initial lesion is usually a small, flat, subintimal plaque which slowly enlarges to occlude the lumen. Ulceration of, or sudden hemorrhage into the plaque may hasten the disease process, and may be associated with sudden, disastrous occlusion of the vessel. Fisher's4,5 studies have shown that incomplete atherosclerotic lesions of the internal carotid artery in the neck rarely involve associated arteriosclerosis of the intracranial vessels. DeBakey, Crawford and Fields14 have shown that multiple lesions occur in 43 per cent of cases and may therefore limit the chance of very permanent recovery.

Occlusive disease of the internal carotid artery may occur at any age6-10 but has been reported to occur most often between ages 45–70 years.11 Occlusive disease involving the great vessels from the aortic arch tends to involve a younger age group. Men are more prone to occlusive disease of the internal carotid and basilar arteries, whereas occlusions of the aortic arch are more common in women.

Presentation of Data

The data for this presentation are derived from all patients with occlusions of the carotid artery subjected to surgical exploration between 1955 and 1960 at the University Hospitals and at Veterans Hospital, Minneapolis. Of these 30 patients, all but four have been operated upon by members of the Division of Neurosurgery, University of Minnesota, College of Medical Sciences.

In the majority of cases the clinical history proved extremely valuable in establishing a tentative diagnosis of an insufficiency syndrome. Because of the proximity of the internal and external carotid arteries in the region of the tonsillar fossa, palpation in this area was not found to be a reliable means of determining diminished blood flow in the internal carotid artery. Horner's syndrome has not been observed in this series. Ophthalmodynamometry has not been employed widely in this study.6 The Matas test (compression of the involved artery to test the adequacy of collateral circulation) has been employed. Because of the potential dangers involved, we have not used compression of the contralateral artery as a means of determining insufficiency.

Several techniques of arteriography were utilized: direct,

Hollenhorst's24 report of a 72% significant decrease in retinal arterial pressure on the affected side in cases of proven carotid insufficiency certainly is noteworthy and suggests that this method should be used more frequently.
percutaneous puncture of the carotid artery (used in most of these cases); direct, percutaneous puncture of the subclavian artery; reflux brachial angiography; and aortocerebral angiography (placement of a catheter in the aortic arch from either the brachial or femoral arteries).

Table 1 illustrates the frequency in our series of the three common types of attack in this disease:

1) Sixteen of the 30 patients had transient symptoms. Unilateral partial occlusion of the vessels was found in 11 of these 16 patients. Also in this clinical group there was one case of total occlusion, one of bilateral partial occlusion, and three of a combined lesion (i.e., a total occlusion of one side and a partial obstruction on the opposite).

2) Seven of the 30 patients had progressive symptoms. Of this group, two patients had partial occlusions, three had total occlusions, one had bilateral partial occlusion, and one had a combined lesion.

3) The remaining seven patients were representative of a sudden, catastrophic onset. Of these, one proved to have a partial occlusion, and six had total occlusions.

<table>
<thead>
<tr>
<th>Type of Attack</th>
<th>Number</th>
<th>Partial Occlusion</th>
<th>Total Occlusion</th>
<th>Bilateral Partial Occlusion</th>
<th>Combined Occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient</td>
<td>16</td>
<td>11</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Progressive</td>
<td>7</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Sudden</td>
<td>7</td>
<td>1</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total cases</td>
<td>30</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2 shows the lesions that were demonstrated angiographically. Note the decided tendency for the atherosclerotic plaque to occur on the left side, a tendency which has been reported by other authors. The reason for this phenomenon is not known, though it may be related in some way to hemodynamics. No side effects were noted in any of these patients during or following angiography. As indicated in this table, 23 bilateral and 5 unilateral angiograms were performed. We believe that bilateral angiography should be employed in all cases in which surgical intervention is contemplated. With preoperative knowledge of the health and patency of the contralateral artery, one can decide whether or not a temporary by-
pass shunt should be used and thereby prevent complete occlusion of the one remaining artery.

**TABLE 2**
**Frequency Comparison, According to Side Involved, of Partial and Total Occlusion**

<table>
<thead>
<tr>
<th>Side</th>
<th>Normal</th>
<th>Partial Occlusion</th>
<th>Total Occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td>13</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Left</td>
<td>4</td>
<td>13</td>
<td>6</td>
</tr>
</tbody>
</table>

**TABLE 3**
**Age Incidence and Frequency of Associated Diseases**

<table>
<thead>
<tr>
<th>Age</th>
<th>Number</th>
<th>Heart Disease</th>
<th>Hypertension</th>
<th>Diabetes</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-50</td>
<td>8</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>50-60</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>60-70</td>
<td>12</td>
<td>8</td>
<td>9</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>70-80</td>
<td>6</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>15</td>
<td>19</td>
<td>5</td>
<td>11</td>
</tr>
</tbody>
</table>

Table 3 presents the incidence by age, of carotid arterial occlusion and of associated diseases, including hypertension. Table 4 presents the results of surgical therapy according to the type of occlusion. Of the total group, 15 patients (50 per cent) were improved clinically as a result of surgical treatment; 10 (30 per cent) were unchanged by the surgery, 2 (6 per cent) were worse, and 3 (10 per cent) died. Of 23 partial occlusions, only 19 were subjected to operation; this was because four of these patients had combined lesions, and operation on the totally occluded side was effected. As can readily be ascertained from this table, only partial occlusions are amenable to surgery. The exception to this statement is the case of acute total occlusion occurring only a few hours before surgical treatment is effected.
### Table 4

**Number and Type of Lesions Subjected to Surgical Treatment, and Postoperative Clinical Status**

<table>
<thead>
<tr>
<th>Type of Occlusion</th>
<th>Total Number</th>
<th>Number Operated Upon</th>
<th>Blood Flow Restored</th>
<th>Improved</th>
<th>Same</th>
<th>Worse</th>
<th>Died</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial</td>
<td>23</td>
<td>19</td>
<td>18</td>
<td>13</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>11</td>
<td>1</td>
<td>2</td>
<td>8</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

In the only case of this kind in the series, it was possible to re-establish blood flow five hours after sudden onset of aphasia and contralateral hemiplegia. The second patient who improved after total occlusion was a young woman with a progressive onset of symptoms. At surgical intervention she had an extremely small, nonpulsatile, fibrotic cord representing the internal carotid artery. In retrospect she would have been expected to have improved spontaneously. The slowly progressive onset and the youth of the patient probably were important factors in the development of adequate collateral channels.

The three deaths all occurred within the first week after surgical intervention. One of these three patients was a 76-year-old man who had had paralysis agitans for ten years. He bled from the wound postoperatively, required a tracheostomy, and eventually died of pulmonary complications. Another patient, operated upon after the administration of local anesthesia, had a sudden onset of aphasia and hemiplegia just as the skin incision was being made. Apparently the incomplete obstruction had become complete. Although the blood flow was restored, the patient died one week later. In the third patient a dissecting aneurysm developed in the common carotid artery (below the level of the endarterectomy); the patient became hemiplegic and aphasic, and died.

Of the 13 patients listed as improved, seven have had follow-up angiograms two to four months after surgical treatment. Table 5 reveals the results of these studies. The arteries in six

### Table 5

**Follow-up Angiograms on Patients with Partial Occlusions Who were Improved Clinically**

<table>
<thead>
<tr>
<th>Type</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patent</td>
<td>6</td>
</tr>
<tr>
<td>Occluded</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>7</strong></td>
</tr>
</tbody>
</table>

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patients were found to be patent, and in one patient totally occluded. The period of follow-up was from 2 to 24 months. All, except the two patients treated most recently, were given anticoagulants for six to eight weeks postoperatively, with no apparent untoward effects.

**TABLE 6**

**TYPE AND NUMBER OF OPERATIONS PERFORMED**

<table>
<thead>
<tr>
<th>Type of Operation</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endarterectomy</td>
<td>18</td>
</tr>
<tr>
<td>Endarterectomy + patch</td>
<td>1</td>
</tr>
<tr>
<td>Graft Bypass</td>
<td>1</td>
</tr>
<tr>
<td>Exploration only</td>
<td>10</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>30</strong></td>
</tr>
</tbody>
</table>

Table 6 illustrates the type of operation that was performed. Thromboendarterectomy was employed in 18 cases. Thromboendarterectomy plus a teflon patch was used in one case, and a bypass teflon graft was used once. Since in the remaining 10 cases surgical exploration revealed total occlusion of the vessel, no definitive procedure was effected in these cases. Temporary bypass shunts at the time of surgery were employed in two instances.

All but three of our surgical procedures were performed under general anesthesia. The time of total occlusion of the blood vessel has varied from 10 to 30 minutes, with an average total occlusion time of 13 minutes. Prior to occlusion, 25 mg. heparin was administered intravenously. Following occlusion a heparin solution (10 mg heparin/50 cc saline solution) was instilled directly into the arteries proximal and distal to the occlusion.

All the lesions were atherosclerotic, and the atheroma generally peeled out easily with the attached intima and a portion of the media. Prior to completion of the closure of the arteriotomy, the occluding clamps were released in definite sequence (i.e., common carotid, internal carotid, and external carotid clamps) in order to “flush out” any bits of debris and clot that might have accumulated. After repair was complete the common and the external carotid artery clamps were removed in the hope that any lingering particles of debris or clot could be flushed up the external carotid system. Finally, the internal carotid occlusion was removed. The patients were permitted to walk the following day.
Figure 1 illustrates a carotid angiogram (A) of a patient who entered the hospital with symptoms of transient attacks of insufficiency of the left carotid artery. Two months after carotid endarterectomy the patient was free from symptoms. The carotid angiogram (B) taken at that time revealed that the internal carotid artery was free of luminal constriction, and
the intracranial vessel filling was observed to be excellent.

The restitution of function in cerebrovascular insufficiency depends in part upon the development of an adequate collateral circulation. The latter in turn requires the maintenance of an adequate blood pressure, blood flow rate and adequate vascular
channels. Brain\textsuperscript{36} has stated: "The most important fact about the regulation of the cerebral circulation is its peculiarly close dependence upon systemic blood pressure." Therefore, a major factor in the production of transient cerebral ischemia is frequently the superimposition of a diminished systolic blood pressure upon a cerebral blood flow that is already severely compromised by an occlusive process. The fact that many patients suffering from cerebral vascular occlusive disease experience more serious attacks of insufficiency during sleep or upon sudden assumption of an erect position is readily explained on the basis of hypotension. Herein lies the danger of hypotension during surgical intervention. Attacks of cerebral insufficiency following myocardial infarction may be secondary to hypotension or cerebral embolism or both. As many authors\textsuperscript{36-38} have warned, prolonged bed rest for elderly people and vigorous attempts to reduce blood pressure in hypertensive patients may produce hypotension with concomitant cerebrovascular insufficiency. Conversely, a rise in systolic blood pressure with resumption of physical activity is frequently accompanied by amelioration of symptoms of cerebral vascular embarrassment.

Equally important in compensating for insufficiency is the availability of adequate vascular channels for development of collateral circulation. Of major importance in extracranial carotid insufficiency are the anastomoses between the external and internal carotid arteries. Under normal conditions the external carotid artery does not contribute to the arterial supply of the brain; rather it is primarily concerned with supplying the extracranial structures of the head and neck. But with reduction of the lumen of the internal carotid artery to one-half or less, these collateral channels enlarge and carry an additional arterial blood flow to the brain. Anastomotic channels between the internal and external carotid systems develop in four locations: a) between the ophthalmic and internal maxillary arteries, b) between the ophthalmic and superficial temporal arteries, c) between the ophthalmic and external maxillary arteries, and d) between the occipital branch of the external carotid and vertebral arteries.\textsuperscript{32,33}

The circle of Willis is likewise extremely important in the establishment of an adequate collateral circulation. The anatomic structure of the circle of Willis is "normal" in only 50 per cent of all individuals. The many anomalies which may involve the structure include: absence of the anterior communicating arteries, hypoplasia of the proximal portion of one or both
anterior cerebral arteries, incompleteness of the circle itself, and hypoplasia of one or both posterior communicating arteries, etc. In the presence of such anomalous development, occlusive disease involving one or more of the supplying vessels of the circle of Willis may greatly embarrass adequate collateral circulation. Therefore, in some instances, vascular insufficiency may be predetermined during embryonic stages.32

The effect of a gradually increasing discrete narrowing in the internal carotid artery in the neck will depend upon the efficiency of the collateral circulation to the ipsilateral hemisphere. As has been discussed above, collateral circulation depends on maintenance of an adequate systolic blood pressure and blood flow, the development of collateral channels via the external carotid system, and the developmental anatomy of the circle of Willis. If one or more of these factors are impaired, inadequate oxygenation of a part of the brain may ensue, and transient symptoms will develop. Such instances have been called “hemodynamic crises.”38

When presented with a patient who has had a so-called “little stroke,” one should immediately suspect the possibility of extracranial arterial insufficiency. More than half the patients in our series presented themselves with transient attacks. The diagnosis in those cases with a progressive or sudden onset may be more difficult, but the possibility of an extracranial arterial lesion should be remembered in the differential diagnosis. We have relied upon the presence of a carotid bruit, or decreased pulsation, plus the clinical history in making an initial diagnosis. But we regard angiographic visualization as essential in establishing the definitive diagnosis.

As our data indicate, the best results from surgical treatment are obtained in cases of partial occlusion occurring in patients whose blood flow can be restored at the time of operation. An exception to this statement is the occasional sudden total occlusion that can be treated surgically within a few hours after onset of the neurologic deficit. Our one patient with sudden total occlusion responded favorably, and other authors have noted similarly good results in such individuals. For obvious reasons, patients with long-standing total occlusion of the internal carotid artery cannot be considered candidates for surgical intervention. The initial hope that blood flow could be re-established in some of these patients led to the high number of explorations in known cases of total occlusion. Our poor results in surgical treatment of prolonged total arterial occlusions have been borne out in the findings of other authors.7,12,14,16,19–22
The ideal candidate for surgery is an otherwise healthy individual who suffers from transient and reversible symptoms.

DISCUSSION

The natural history of atheromatous narrowing of a carotid artery is unknown. Some individuals have severe disablement with only slight narrowing of one of the quartet of arteries supplying the brain. On the other hand, many persons survive complete obliteration of one carotid artery for many years without symptoms. Some have even been noted to survive bilateral carotid occlusion. The question may therefore be raised, why should endarterectomy be performed? The answer to this question is threefold: First, the presence of a symptomatic partial obstruction may lead to ischemia and cerebral infarction during periods of hypotension such as occur with sleep. In other words endarterectomy can be performed to prevent transient symptoms from becoming permanent. Second, a partially obstructing lesion may be an embolic source. Lastly, an additional pathway for blood flow to the brain is provided, and although the immediate result may not be significant, it may provide insurance for a future time when one or more of the remaining supplying vessels may become involved with a similar process.

Our follow-up on patients who were improved following operation varies from four weeks to two and one-half years. All of these have continued to be free of their previous symptoms. On this basis it is felt that carotid endarterectomy has a definite place in the treatment of some forms of extracranial vascular disease.

SUMMARY

1. The signs, symptoms, and procedures for diagnosis of extracranial arterial disease in the neck have been described.
2. A series of 30 cases of proven carotid artery occlusive disease has been presented and the surgical treatment discussed. Results of the surgical treatment are given.
3. Some of the factors involved in production of symptoms with cerebral vascular insufficiency have been outlined.
4. We have concluded that carotid endarterectomy is an effective means of treatment in those cases with partially obstructing lesions and transient, reversible attacks.

REFERENCES


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Observations on Myocardial Ultrastructure

Douglas A. Nelson, M.D. and Ellis S. Benson, M.D.

INTRODUCTION

The myocardium has an intricate, detailed structure. The order of magnitude of much of this structure prevents its visualization with the light microscope. The introduction of the electron microscope and subsequent refinement of techniques of tissue preparation have opened this microcosm for exploration and investigation. Its description, now in progress, will be followed by elaboration of the functional significance of its components.

Our interest in the application of the electron microscope to the study of the myocardium stemmed from long-term investigations in our laboratory of the chemistry of this structure in a number of abnormal functional states. Evidence has been presented of abnormalities in the contractile proteins in chronic congestive heart failure in dogs and of postanoxic failure in the resynthesis of adenine nucleotides. The existence of defects in the corresponding structural units (myofibrils and mitochondria, respectively) had to be considered. We have therefore turned to electron microscopy in the hope that this technique would provide insight into these and other unresolved problems of myocardial function.

Relatively few studies of the fine architecture of mammalian myocardium have been made using improved techniques of tissue preparation. Notable among these few are the studies of Van Breeman, Moore and Ruska, Lindner, Muir, Porter and Palade, and Poche. To our knowledge, very few electron

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†Supported in part by research grant No. H1584 C-6, USPHS, and by a grant from the Minnesota Heart Association.
‡Instructor, Department of Laboratory Medicine
§Professor, Department of Laboratory Medicine

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microscopic studies of the human myocardium have been made, presumably because of the difficulty in obtaining biopsy specimens. The present preliminary report deals chiefly with descriptions of myocardial ultrastructure in normal dogs and rabbits and in humans undergoing cardiac surgery. It also includes a few tentative observations of ultrastructural deviations in certain abnormal functional states.

**Materials and Methods**

Adult white rabbits and unselected adult mongrel dogs were used in the study, tissue being obtained from anesthetized animals at thoracotomy. In the case of human subjects, fresh myocardial tissue was obtained from patients undergoing open-heart surgery. Small pieces (each less than 50 mg.) of ventricular myocardium (and in one instance, of atrial myocardium) were obtained by the surgeon from the cardiotomy site or from the resected infundibulum; these were immediately passed to one of us in the operating room and were processed without delay.

In some experiments isolated rabbit hearts were used. They were perfused as Langendorff preparations via the coronary vessels with Tyrode's solution equilibrated with 95 per cent oxygen and 5 per cent carbon dioxide. After a sample of ventricular myocardium had been taken for electron microscopic examination, the perfusion medium was changed either to Tyrode's solution equilibrated with 95 per cent nitrogen and 5 per cent carbon dioxide or to isotonic potassium sulfate. Biopsy specimens of the ventricular myocardium were taken repeatedly at varying intervals up to one hour after the start of the perfusion with test solution.

In all instances the tissue was covered with cold fixative, cut into blocks less than 1 mm. thick, and placed in excess cold fixative within two minutes of excision. Buffered osmic acid (Palade or Caulfield) was the fixative used. Tissue was prepared for sectioning by standard procedures, except that in many instances the polyester resin “Vestopal W” was used instead of methyl and butyl methacrylate as the embedding medium. Glass knives and a Porter-Blum microtome were used for thin sectioning; sections 1 micron thick were cut, stained with Giemsa stain, and observed in the light microscope. Thin sections were mounted on copper grids coated with

*These experiments were performed in Dr. John A. Johnson's laboratory, and we gratefully acknowledge his generous assistance in their conduct. Details of preparation and methods used may be found in a recent paper by Humphrey and Johnson.
formvar. Observations were made using an RCA Model EMU 2 electron microscope with an accelerating voltage of 50 Kv. at direct magnifications ranging up to x17,500 and final magnifications up to x75,000 after photographic enlargement.

RESULTS AND DISCUSSION

A. Observations with The Light Microscope

Under the light microscope the myocardium is seen to be a complex and irregular network of branching and Anastomosing cross-striated myofibers each 6-15 micra wide. Within these are parallel smaller fibers, the myofibrils, which are separated by a granular cytoplasm, the sarcoplasm. The myofibrils have a characteristic striped appearance due to regularly alternating light and dark transverse bands. Because these are in precise register, they give the fiber a cross-striated appearance. The dark bands, birefringent in polarized light, are termed anisotropic or A-bands. The light bands, only weakly birefringent, are called isotropic or I-bands. In the center of each I-band is a thin dark line, the Z-line. The sarcomere is the myofibrillar unit between two Z-lines which contains one A-band and two half I-bands. Dark transverse bands, the intercalated discs, separate the fibers into segments 50 to 120 micra long by crossing them in a stepwise fashion. Each segment bounded by these discs contains at least one central ellipsoidal nucleus. In contrast, the nuclei of skeletal muscle are just beneath the cell membrane.

The structures described above can be seen with the light microscope which has a resolving power of 2,000A. With a resolution approaching 20A in biological materials, the electron microscope reveals a new world of structure.

B. Observations with the Electron Microscope, Normal Hearts

1. Cell Membranes

a) The myofiber is bounded longitudinally by a scalloped cell membrane complex, the sarcolemma. The scalloping is the result of indentations at the levels of the Z-lines in the underlying contracted fiber. Two parallel membranes may be seen (Figs. 1,5): an inner dense plasma membrane, 75-100A thick, separated by a clear 150A space from an outer less dense membrane 100-300A thick. Vesicles, 400-700A wide, may lie just beneath the plasma membrane, especially where adjacent to a capillary. Invaginations of the plasma membrane of similar size are seen among them.

b) In the transverse axis of the fiber, the cell boundary has three variations which are of increasing complexity (In all three the outer layer of the sarcolemma is absent):
Fig. 1. Rabbit, myocardium four minutes after potassium arrest, Vestopal-embedded, stained with phosphotungstic acid, magnification × 18,000

Note contracted myofibrils (MF) with heavy contraction bands at Z-lines, barely visible cross-bridges between myofilaments; scalloped sarcolemma (S) at border of myofiber, extending deeply into cell at arrow; numerous mitochondria (MI) between myofibrils; granules in sarcoplasm especially beneath sarcolemma; fat droplets (F).

1) Two adjacent cells are separated by a regular space, 150-200Å wide, bounded by plasma membranes of the respective cells (Fig. 2). These plasma membranes are continuous at the lateral aspect of the fiber with the inner component of the sarcolemma. Sometimes the intercellular space is absent, and the boundary consists of a single line 150Å thick, presumably composed of the two joined plasma membranes.

2) Occasionally, over a length of about 3500Å, the adjacent plasma membranes are thickened and form, together with
Fig. 2. Dog, normal myocardium, Vestopal-embedded, stained with uranyl acetate, magnification \( \times 16,000 \)

Note intercalated discs (ID) one sarcomere apart replacing Z-lines, joined by simple cell boundary (B) in interfibrillar sarcoplasm; cardiac desmosome (CD) in next interfibrillar space; confluent mitochondria (MI).

an accumulation of electron-dense granular material in the underlying sarcoplasm of each cell, a complex about 1200Å wide (Fig. 2). The intercellular space, 150-200Å wide, remains unmodified. These specializations resemble the desmosomes of the skin and the terminal bars of columnar epithelium.$^{20}$

3) Whenever the transverse cell boundary crosses a myofibril, it does so as an irregular, wavy, dense band about 1200Å wide. The 150-200Å intercellular space is bounded by thickened plasma membranes with subjacent dense granular sarcoplasm into which the myofilaments insert (Fig. 2). This, the most highly specialized cell boundary, is the intercalated disc of light
microscopy. With respect to the myofilaments, it occupies the
place of the Z-line, and the myofilaments do not cross its inter-
space. Intercalated discs do not differ in structure among the
three species studied.

The ultrastructure of the intercalated disc was first deline-
ated by Van Breemen. Having noted that these discs were con-
tinuous with the sarcolemma and their central space was not
crossed by myofilaments, he claimed that they represented
true cell boundaries. Others have confirmed these findings in
a variety of invertebrate and vertebrate species, so that the
myocardium is no longer accepted as an anatomical syncytium.
Interestingly enough, the concept that the intercalated discs
were true cell membranes was held as early as 1866 (see
Cohn); it gained general credence but lost favor in the early
decades of this century, when the theory of a cardiac syncytium
was in ascendancy.

The function of the disc has been the focus of much specu-
lation. Heidenhain (see Cohn) originally proposed that it was
a center for growth of the fiber. Since sarcomere length does
not vary with age, this growth was believed to involve the addi-
tion of whole sarcomeres. Bourne found high succinic dehydro-
genase and alkaline phosphatase activity at the disc and thought
the disc might serve as a booster of the contraction wave spread-
ing longitudinally through the fiber. Weidmann noted an in-
creased permeability to potassium at the disc; he suggested that
the impulse flows unimpeded across the disc and that electro-
physiologically the myocardium may behave as a true syncytium.

2. Contractile Elements

The delineation of the fine structure of striated muscle by
Huxley and Hanson and relationships suggested between this
structure and muscular contraction have been among the major
achievements resulting from electron microscopy. The myo-
fibrils are observed to contain closely packed, parallel myo-
filaments, shown by Huxley and Hanson to be of two types:
1) thick filaments confined to the A-band; and 2) thin fila-
ments which extend from the Z-line through the I-band
into the A-band interdigitating with the thick filaments. The
myofibril on cross section through the A-band shows a hexa-
gonal array of myofilaments. Each thick filament has six thin
filaments arranged symmetrically around it. At very high magni-
fications (circa x500,000) Huxley and Hanson found transverse
bridges connecting the thick and thin filaments. Studies of the
extractability of the thick and thin filaments convinced them
that the thick filaments were composed of myosin and the thin
filaments were mainly actin. These studies, together with earlier X-ray diffraction studies of H. Huxley and investigations of A. F. Huxley, gave rise to the “sliding filament hypothesis” of muscular contraction. This hypothesis states that when muscle shortens, the two sets of filaments slide past each other by interaction at the cross bridges where the energy of contraction is supplied, perhaps by adenosine triphosphate (ATP). When the thin filaments slide into the A-band, then the I-band and H-band disappear, and with extreme contraction the Z-line thickens. Such a thickened Z-line is a contraction band, explained by Huxley as a crumpling of the thick filaments which have met the Z-line.

In attempting to draw comparisons we have studied both skeletal (rabbit psoas) and cardiac myofibrils. With the electron microscope used, we have not been able to attain the level of resolution seen in the work of Huxley and Hanson. Nor have we obtained unequivocal evidence of a double set of filaments in heart muscle, although in some cross-sectional views a suggestion of fine filaments may be seen. Another handicap has been the impossibility of fixing heart muscle at rest length. In psoas muscle this may be accomplished by tying a few parallel fibers at each end to a glass rod before the fibers are cut free from the muscle; the fibers are then fixed at this length.

In the myocardium after fixation the myofibrils are more or less extremely contracted: The I-bands are absent or inconspicuous, the Z-lines are very prominent, and the length of the sarcomere ranges from 1.0 to 1.5 micra, corresponding to the length of the contracted sarcomeres of skeletal muscle. In some myocardial preparations, notably those subjected to experimental anoxia, partially relaxed myofibrils are seen. Figure 3 shows dog myocardium after 48 minutes of coronary perfusion with oxygen-free solution. The cross-banded structure includes H-zones which are the lighter (“heller”) regions in the center of the A-bands. According to Huxley, these zones represent the space between the ends of the thin filaments, and in the darker part of the A-band the two sets of filaments interdigitate. The M-line in the center of the H-zone appears to represent a local expansion of the thick filaments. In some sections, fine lines regularly cross the space between the filaments, giving a longitudinal periodicity of about 200Å (Fig. 1). In cross section the filaments, 100-150Å thick, are in a fairly precise hexagonal array, each about 500Å apart. We cannot be sure whether or not a regular set of thin filaments exists between them.

3. The Sarcoplasmic Reticulum

The sarcoplasmic reticulum, originally visualized by Thin
Fig. 3. Dog, myocardium after 48 minutes of anoxia, methacrylate-embedded, magnification × 18,300

Note partially relaxed myofibrils showing dense A-band, lighter I-band divided by Z-line, light H-zone with central M-line; mitochondria (MI).

and described in more detail by Retzius (see Bennett\textsuperscript{27}) and by Cajal,\textsuperscript{28} was rediscovered by Bennett and Porter\textsuperscript{29} in 1953 with the electron microscope. Porter and Palade\textsuperscript{8} subsequently described this system as one composed of vesicles and tubules communicating intricately to form a tortuous labyrinthine network around each myofibril. Bennett and Porter\textsuperscript{21} recognized at the outset that this network corresponded closely to the particle-studded, membrane-limited system then being described in a number of cell types by Porter\textsuperscript{30} as the endoplasmic reticulum. A rough surfaced type, studded with granules, and an agranular smooth surfaced type of endoplasmic reticulum have been described.\textsuperscript{31} The former, predominant in such cells as the pancreatic acinar cell and the plasma cell, has been shown to be involved in protein synthesis.\textsuperscript{32} The smooth surfaced type is the predominant type in seminal vesicles, leukocytes, and in cells engaged in producing lipid-rich secretions, e.g., the testicular interstitial cells and cells of the adrenal glands.\textsuperscript{33}

The sarcoplasmic reticulum in muscle has been described in
detail by Porter and Palade. In cardiac muscle, anastomosing longitudinal tubules of smooth surfaced sarcoplasmic reticulum surround the fibril. Transversely oriented tubules appear to be in contact with Z-lines and with each other, continuous with the nuclear membrane and probably with the sarcolemma. Indeed, Lindner and Poche depicted double membrane-lined profiles of the transversely oriented tubules and suggested that these were actually parts of the sarcolemma (exomembrane) dipping deeply into the cell. The longitudinal tubules and the transverse tubules meet but may not communicate at the Z-level. These anatomic configurations may represent the “triads” of Porter and Palade.

Our observations of cardiac muscle indicate that the smooth surfaced sarcoplasmic reticulum has a precise relationship to the myofibrils and is probably composed of interweaving transverse components (at the Z-level) and longitudinal components (surrounding the fibrils). (See Figs. 4 and 5.) These do not communicate with each other but may be in external contact at the level of the Z-line in regions reminiscent of the “triads” of Porter and Palade.

Profiles of the longitudinal system in the interfibrillar sarcoplasm are relatively few and narrow. Transversely oriented tubules are wider; they are in register with the Z-line, and appear to be connected with the Z-lines and probably with each other. They are frequently bounded by a double membrane similar to the sarcolemma; their membranes are continuous with the nuclear membrane (Fig. 5), and probably with the sarcolemma (Fig. 1). Our observations agree with those of Poche and of Lindner and indicate that the space within the transverse tubular system may be an extension of the extracellular space.

Adjacent to the nucleus are numerous round and elliptical profiles lined by a single, smooth surfaced membrane (Fig. 4). In this vicinity we have on rare occasions observed parallel membranes enclosing flattened cisternae with dense particles, 150A in diameter, attached to the outer surface. These correspond in appearance to the rough surfaced endoplasmic reticulum.

The hypothesis that the sarcoplasmic reticulum may function as a link between excitation and contraction was originally proposed by Retzius in 1881 (according to Bennett). Evidence to support this hypothesis has recently been discussed by Peachey and Porter. The experiments of A. F. Huxley and R. E. Taylor on local activation of muscle have corroborated this view, since contraction followed stimulation of the sarcolemma.
only at the level at which "triads" had been found by electron microscopy, i.e., at the level of the Z-lines in amphibians or of the junction of the A-band and the I-band in mammalian skeletal muscle.

4. Mitochondria

Early workers observing myocardium with the electron microscope were impressed by the large numbers of mitochondria. Mitochondria are known to be intimately concerned with processes which supply energy to living cells. Green and Hatefi ascribe to them the universal function so essential to bio-energetics of coupling oxidation with the phosphorylation of ATP. Not only do mitochondria contain the enzymes and cofactors responsible for these vital processes, but the preservation of their distinctive structure seems to be essential to the integrity of the overall reaction sequences. Lehninger has recently emphasized the important relationship of shape changes of mitochondria to their function as energy machines, notably, swelling and shrinking processes.

Cardiac mitochondria are oval or rectangular in section, averaging 0.3 x 0.7 micra, but may be considerable larger. They are found between the sarcolemma and the underlying myofibrils, closely packed in columns between myofibrils, and in perinuclear spaces (Figs. 1, 4, and 5). They are usually intimately applied to myofibrils, with long axes parallel to them, and frequently they bracket the transverse elements of the sarcoplasmic reticulum at the Z-level. When intermyofibrillar columns are seen in cross-section, the packed mitochondria may appear roughly hexagonal.

The elongated myocardial mitochondrion is limited by two parallel membranes which enclose a narrow space 50-100Å wide, and the organelle is filled with numerous parallel, densely packed lamellae, the cristae (Fig. 5). Each crista consists of two parallel membranes and an intervening intracristal space, 100-200Å wide, which occasionally is continuous with the space between the inner and outer limiting membranes. The parallel cristae, 200-400Å apart, are usually perpendicular to the long axis of the mitochondrion. In rare instances they branch and anastomose with adjacent cristae. The matrix between the cristae is denser than the sarcoplasm and occasionally contains a few osmiophilic granules 200-300Å wide.

The mitochondria of rabbit myocardium have more delicate and closely packed cristae and appear darker than the mitochondria of canine and human myocardium, perhaps because of
Fig. 4. Rabbit, myocardium five minutes after potassium arrest, Vestopal-embedded, stained with uranyl acetate, magnification $\times 17,500$

Note nucleus (N); contracted myofibrils; mitochondria (MI) in interfibrillar sarcoplasm; dense bodies (DB); prominent profiles of transverse component of sarcoplasmic reticulum (T) at several Z-levels between fibrils and adjacent to nucleus; smaller smooth-surfaced profiles between fibrils (may belong to longitudinal component of sarcoplasmic reticulum) and adjacent to nucleus.

a denser matrix. Those of the dog and human being are indistinguishable.

Swelling of the mitochondrial matrix is more characteristic of specimens embedded in methacrylate than of those embedded in Vestopal W. (cf. Figs. 3 and 4). In Vestopal W, the outer and inner limiting membranes often appear less distinct; in fact, sometimes they are absent, and adjacent mitochondria appear to become confluent (Fig. 2).

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The high population density of mitochondria in the myocardium and of cristae within the mitochondria is approached in few other structures. This feature is characteristic of tissues with a very high oxidative requirement—tissues such as insect flight muscle.⁶

5. The Sarcoplasm

The cytoplasm of muscle, the sarcoplasm, contains a number of structures besides the mitochondria.

a) Fat droplets are moderately dense, homogeneous bodies, 0.3-0.6 micra wide with irregular margins. They usually lie immediately adjacent to mitochondria. Both morphologic and biochemical evidence indicates that fat or fatty acids may be directly oxidized by the mitochondrial.⁵⁻⁴¹

b) Infrequently seen are round or oval dense bodies (dichte Korper, Poche;⁹ cytosomes B, Lindner⁶), 0.2-0.5 micra wide. These are composed of osmiophilic granular material, they may or may not have an enveloping membrane, and they are usually found in the company of mitochondria (Fig. 4).

Granular cytosomes (Poche;⁹ cytosomes C, Lindner⁶) are bodies similar to the dense bodies but contain light homogeneous inclusions. They have the same distribution as dense bodies and mitochondria and are also infrequently observed.

In one of our canine hearts which had undergone prolonged anoxia, we found in contiguity: intact mitochondria, distincing mitochondria, dense bodies, fragmented dense bodies, and a collection of dense cytoplasmic granules 200-300A wide. This finding supports the theory that the dense bodies and perhaps granular cytosomes may be forms of degenerate mitochondria⁹ and suggests that some of the dense cytoplasmic granules may represent further breakdown products.

c) Sarcoplasmic granules vary in number, size (150-400A in diameter), and electron density. They tend to be found between myofibrils, under the sarcolemma and adjacent to the nucleus. They do not seem to be closely related to the sarcoplasmic reticulum. The larger, less dense granules may be particulate glycogen.⁶² Smaller, dense particles, 150A in diameter, may be ribonucleoprotein.⁴²

d) The Golgi apparatus consists of stacks of closely packed profiles of flattened smooth-surfaced cisternae which are associated with numerous empty vesicles in the adjacent sarcoplasm. It is usually found at the nuclear poles in muscle cells and is less well developed than in secretory cells or in cells with a large fluid transport. Some evidence suggests that the Golgi apparatus functions in concentrating secretory products in

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Fig. 5. Rabbit, normal myocardium, Vestopal-embedded, stained with phosphotungstic acid, magnification × 25,000

Note two sections of the nucleus (N); sarcolemma (S); obliquely sectioned myofibrils and Z-lines; small profiles of longitudinal component of sarcoplasmic reticulum (L); larger profiles of transverse component of sarcoplasmic reticulum (T), one of which appears to join the nuclear envelope at the arrow; mitochondria (MI).

some cell types; and Palade has hypothesized that the Golgi cisternae may represent a “membrane depot” for the cell.

6. The Nucleus

The nucleus is oval and centrally located in the cell. It contains finely dispersed granules, 150Å wide, and is enclosed by a membranous envelope. Occasionally a section includes the nucleolus which is round or serpentine in shape and composed of closely packed dense granules, 150Å wide. The nuclear envelope is made up of two parallel membranes, each 75Å thick and separated by a clear space of 100Å. (Figs. 4 and 5), a fact
first appreciated by Hartmann. The outer membrane is seen occasionally to evaginate, especially opposite a Z-line. Nuclear "pores" are seen as gaps of 200-1000Å in the envelope. The space within the gap is slightly denser than the external sarcoplasm, and the underlying nuclear particulate material seems to "give way" for a short distance, forming a clearing. The complex structure of the nuclear pore-complex was described for the liver cell by Watson. When adjacent myofibrils are contracted, the nuclear membrane is markedly indented.

7. Extracellular Components

The capillaries are lined by endothelial cytoplasm averaging 0.1 to 0.2 micra deep, except around the nucleus, which bulges into the lumen. The luminal surface is a single plasma membrane, while on the peripheral aspect, a double membrane encloses a space 150Å wide. The outer membrane, the basement membrane, is less dense and rather poorly defined, and it averages 100Å in thickness.

The endothelial cytoplasm is teeming with vesicles 300-600Å wide. These appear to be formed by invagination of the plasma membrane on either cell surface. The electron density of the vesicular contents is usually less than that of the capillary lumen. Similar vesicles and invaginations of plasma membranes are found in adjacent myocardial cells. The vesicles are thought to function as a principal means of transport of fluid across capillary cells; Moore and Ruska, studying muscle capillaries, found that the number of vesicles was greater in more active muscles. The cytoplasm of the endothelial cell also contains a few mitochondria, a few profiles of rough surfaced endoplasmic reticulum, and scattered free cytoplasmic granules. At the boundaries between adjacent overlapping endothelial cells, the plasma membranes are separated by a uniform 100-200Å space which is slightly denser than the surrounding cytoplasm. Collagen fibrils are seen occasionally, and a fibroblast rarely, in the extracellular space.

C. Observations with the Electron Microscope, Abnormal Functional States

Our examination of the myocardium in abnormal states is still in its early stages, and the results are fragmentary and inconclusive. A few preliminary observations, however, may provide direction for further inquiry.

1. Potassium arrest

In experiments on isolated perfused rabbit hearts which were arrested in diastole by potassium sulfate, we attempted to
determine whether or not sarcomere length and appearance would correspond with that of the relaxed myofibril. No differences in the structure of any of the cell components were observed in biopsy specimens taken before and five minutes after such arrest.

2. Anoxia

Löhr and associates, Mölbert, Bryant et al., and Caulfield and Klionsky have studied the effects of anoxia on myocardial ultrastructure. They described as early changes the swelling and fragmentation of mitochondria and the swelling of elements of the sarcoplasmic reticulum; these changes were observed to become severe within 40 minutes.

Our studies revealed very few changes in isolated perfused rabbit and dog hearts undergoing severe oxygen deprivation for 45 to 60 minutes. In dogs, some mitochondria showed early fragmentation and granular changes of cristae, and some lost their outer membranes. In both rabbit and dog hearts, dense bodies appeared to be more numerous. Significant mitochondrial swelling was not observed in our studies.

Perhaps the discrepancy can be explained through one or both of the following observations: Mitochondrial degeneration can be expressed morphologically in more than one way; our embedding medium was Vestopal W, while that used in the other studies was methacrylate. The answer is being sought in further studies.

3. Human myocardium

Our biopsy specimens of human myocardium were obtained at corrective surgical intervention for congenital and acquired cardiac defects. Though presumably all these hearts were hypertrophied and perhaps had other functional abnormalities, the details of ultrastructure closely resembled those of normal rabbit and canine hearts. The study of this material does not yet permit drawing any firm conclusions, but certain observations may be of interest:

a) The myofibrils (but not the myofilaments) were thicker in some human hearts (maximum width, 3.4 micra) than any seen in rabbits and dogs (maximum width, 1.8 micra).

b) Fragments of large, very dense, coarsely granular bodies similar to the "Pigmentkörner" of Poche were noted in specimens from a few hearts.

c) In some heart tissue from individuals with prolonged cyanosis (chronic hypoxia), we observed what may be an in-
Fig. 6. Human, right ventricular biopsy from patient with Tetralogy of Fallot, methacrylate-embedded, stained with uranyl acetate, magnification × 8,000

Note scalloped sarcolemma (S) at boundaries of branching myofiber; portion of capillary (C); branching, contracted myofibrils (MF); large numbers of swollen mitochondria between myofibrils; occasional fat droplets (F) among mitochondria.

crease in total mass of interfibrillar mitochondria (Figure 6); in these hearts, some capillaries showed a pronounced thickening of the basement membrane.

Conclusions

The myocardium has a richly detailed ultrastructure which is organized in components and systems that are basically similar in rabbits, dogs, and human beings; With the resolution we were able to achieve, we were unable to decide if two sets of myofilaments occur in cardiac muscle, as in skeletal muscle.
(described by Huxley and Hanson). Efforts to fix cardiac muscle in an uncontracted state will continue, and further study of these elements will be attempted with improved techniques and electron optics.

The myocardial sarcoplasmic reticulum was noted to have two components regularly arranged with respect to the myofibrils. The transverse component has a precise relationship to the Z-line and probably to the sarcolemma; its elements are larger than those of the longitudinal components, and it is lined by two membranes similar to those of the sarcolemma. These findings support current concepts of the role of this system as a carrier of excitation across the fiber.

A remarkable feature of the myocardium is its abundant endowment with mitochondria having densely packed cristae. These features are shared with other tissues possessing high oxidative requirements, such as insect flight muscle.

Although not complete, the description of myocardial ultrastructure is now sufficiently detailed to encourage attempts at relating elements of this structure with fundamental components of myocardial function. Some information of this nature may be gained from the study of abnormal functional states, such as anoxia, prolonged hypoxia, acute and chronic myocardial failure, atrophy, and hypertrophy.

Acknowledgements: Dr. J. F. Hartmann made many helpful suggestions and we acknowledge with gratitude his interest and guidance. We acknowledge also the helpful interest of Drs. Richard Varco, C. W. Lillehei, and their associates in the studies of human myocardium. The technical assistance of Miss Marian Sutherland has been much appreciated.

REFERENCES
26. Thin, G.: On the Minute Anatomy of Muscle and Tendon, and


Dr. Ralph T. Knight (right) cuts a ribbon opening the Ralph Knight Anesthesiology Research Laboratory. Dr. F. H. Van Bergen (left) looks on.

The Ralph T. Knight Anesthesiology Research Laboratory was dedicated February 8, 1961 in ceremonies at the University of Minnesota Medical Center. Dr. Knight, Professor Emeritus of Anesthesiology, was on hand to cut a ribbon formally opening the new four-room research facility in Diehl Hall. Many of his former fellows in anesthesiology witnessed the ceremony. Dr. Knight, who headed the University’s Department of Anesthesiology from its inception in 1920 until his retirement in 1954, called the laboratory a “dream come true.”

A reception and dinner honoring Dr. and Mrs. Knight were held during the evening with 153 persons attending. Among the speakers was University President O. Meredith Wilson.

On the occasion of Dr. Knight’s retirement, a fund was started among the men who trained under him. Contributions from his fellows totalling $17,000.00 helped make the research laboratories a reality. They include an animal research area equipped with operating tables and monitoring equipment for measuring physiological responses during anesthesia; a chemistry section; and a metal working shop for developing and testing mechanical apparatus.

Dedication of the Knight laboratory climaxed a three-day course in Anesthesiology held at the University’s Center for Continuation Study.
Departmental News

SURGERY
Dr. Richard C. Lillehei, Assistant Professor, was awarded the Gallie Prize for his work on “Treatment of Acute Irradiation Sickness.”

PHYSIOLOGY
Dr. Maurice B. Visscher, Professor and Head of the Department, spoke on “Graduate Education in Basic Science for University and Non-University Surgeons” at a meeting of the Society of University Surgeons in Kansas City, Kansas on February 9.

Dr. John Trank, recently awarded his Ph.D. in physiology and Instructor in the Department, has left to accept a position as Lecturer in Physiology at McGill University, Montreal, Canada.

Dr. Carlo A. Terzuolo, Professor, lectured on “Action Potential of Spinal Motoneurons” Dec. 30, 1960 in New York City. His address was given before a conference on “Current Problems in Electrobiology,” sponsored by the New York Academy of Science and the American Association for the Advancement of Science.

CHILD PSYCHIATRY
Dr. Elsa-Brita Nordland, Head of the Department of Child Psychiatry at the Karolinska Institute, Stockholm, Sweden, is serving as Visiting Professor of Child Psychiatry at the University of Minnesota March 15 thru July 1, 1961.

Dr. Reynold A. Jensen, Professor and Director of the Division, was a guest of the University of Oregon Medical School Feb. 21-Mar. 1, participating in a postgraduate medicine course. He delivered two lectures titled “Present Concepts of Personality Development in Children,” and “Psychological Factors in the Digestive Disorders of Children.” He also addressed the Black Hawk County Medical Society and Association for the Mentally Retarded March 21 in Waterloo, Iowa on the subject “Medical Responsibility in Mental Retardation.”

LABORATORY OF PHYSIOLOGICAL HYGIENE
Dr. Ancel Keys, Director, lectured on “The Epidemiology of Heart Disease,” and on “Nutritional Aspects of Coronary Heart Disease” on Jan 18 at the University of Michigan.

On January 31st, he delivered a lecture on “The Geopathology of Heart Disease” in Boston as part of the 150th anniversary of the founding of the Massachusetts General Hospital.
PATHOLOGY

Dr. Herbert M. Hirsch was one of 32 new five-year senior fellowship recipients named March 1, 1961 by the U. S. Public Health Service. Made to scientists in 25 universities and schools of medicine, dentistry and public health in 17 states, the fellowships are intended to encourage and support the development of professional personnel for academic and research careers in these and related fields. The Senior Fellowship program, now supporting a total of 256 active fellowships, is not oriented toward a specific disease, but toward basic biomedical and health-related sciences.

PSYCHIATRY & NEUROLOGY

Dr. A. Jack Hafner, Assistant Professor in the Department of Psychiatry, will conduct a follow up study of adolescent psychiatric patients under a first year grant of $2,278 announced March 9 by the National Institutes of Health. His award was among 41 worth $1.3 million given for new research programs in various aspects of aging.

Dr. Frank Morrell, Associate Professor, Division of Neurology, resigned effective March 1, 1961, to become Professor of Medicine and Head of the Division of Neurology at Stanford University School of Medicine, Palo Alto, Calif.

Dr. Carl Koutsky, Assistant Professor, Division of Psychiatry, has been appointed Chief of the Inpatient Psychiatry Service, University of Minnesota Hospitals. He succeeds Dr. Burtrum C. Schiele, who will be devoting more of his time to research in the future.

BACTERIOLOGY AND IMMUNOLOGY

Dr. Herman C. Lichstein, Professor of Bacteriology, has been appointed to the Editorial Board of the Journal of Bacteriology for a five year term beginning in 1961.

Dr. Sidney E. Grossberg, Assistant Professor of Bacteriology, was named project director of a cooperative study on the sequelae to Japanese encephalitis in American veterans experiencing the disease in the Far East. Members of the study group represent seven other medical institutions and agencies.


Officers of the Minnesota Chapter, Student American Medical Association, for 1961 are Edward Staab, President; Jack Sebald, Secretary; and John McMullen, Treasurer, members of the Senior, Junior, and Sophomore classes, respectively. Class Representatives to S.A.M.A. are John Salchert, Senior; Art Anderson, Junior; Ralph Hyden, Sophomore, and Walter Bailey, Freshman.

The Student American Medical Association is organized at the nation's 85 medical schools to represent medical students in national medical affairs. It was fostered by the American Medical Association, but its district organizations and chapters are now autonomous and separate. Members of the Minnesota Chapter are delegates to four Midwest district meetings held each year, and on May 6-7, 1961, will attend the S.A.M.A. National Convention in Chicago.

Seventy per cent of the student body at the University of Minnesota Medical School are members of S.A.M.A.'s Minnesota Chapter. Since establishment nine years ago, the Chapter has carried out a number of programs benefitting the student body in general. These include a regular schedule of Tuesday noon basic science film showings, and the collection of internship evaluation data from Minnesota graduates which is made available to senior students before they apply for internship.

In 1960-61, the Minnesota Chapter published a complete medical student directory for the first time which was distributed to the entire 500-member student body. In addition, the Minnesota Chapter's S.A.M.A. Wives Club is the largest such auxiliary organization in the United States.
Dr. Arnold Lazarow, Professor and Head of the Department of Anatomy, helps medical student Terrence D. Capistrant, right, a Medical Foundation scholarship recipient, evaluate a slide in the Histology course. Dr. Lazarow is President of the Minnesota Medical Foundation.

MEDICAL FOUNDATION OFFERS SCHOLARSHIPS

Applications are being accepted through May 30 by the Minnesota Medical Foundation for scholarship aid under its 1961-62 program. All medical students at the University of Minnesota are eligible to apply.

Most awards made by the Foundation are $500.00, although a few are larger. Applicants are judged on scholastic achievement and financial need, with slightly heavier emphasis on the former. Funds to make the awards are provided by medical organizations, corporations, individuals, foundations, and other friends of the Medical School.

The Foundation anticipates the issuance of approximately $17,000.00 in scholarships for the 1961-62 academic year. Thirty-two medical students are current holders of Foundation scholarships. Since the program was launched in 1949, the
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Foundation has distributed $110,000 in awards to 215 recipients.

Dr. H. Mead Cavert, Assistant Dean of the Medical School, was reappointed chairman of the Foundation’s Scholarship Awards Committee. Committee members include Dr. Herman E. Drill, Dr. Raymond Bieter, Dr. Albert E. Ritt, and Dr. C. D. Creevy.

Others appointed to Foundation committee chairmanships in 1961, announced by Dr. Arnold Lazarow, Foundation President, are: Malvin E. Herz, fund raising; Malcolm B. McDonald, finance; Dr. R. S. Ylvisaker, liaison; Dr. W. W. Spink, editorial; Dr. John A. Anderson, research awards, and Dr. E. B. Brown, membership.

EMERGENCY LOAN FUND REPORT

The Minnesota Medical Foundation is administrator of the Herman M. Johnson Memorial Loan Fund for medical students, established in November 1959 under a grant from the Minnesota State Medical Association.

The $4,000.00 fund, named for a pioneer southwestern Minnesota physician, makes available short term, emergency-need loans without interest to medical students at the University of Minnesota. Loans can be taken up to a maximum of $200.00 and a period of 90 days.

Ninety-eight loans were made during the fund’s first 16 months of operation. As of March 1, 1961, a total of $11,930.04 had been borrowed. In turning the original fund over nearly three times, not a single penny has been lost to delinquent accounts, the Foundation reported.

MARCH OF DIMES SCHOLARSHIPS

Three freshmen students at the University of Minnesota Medical School were recently named recipients of scholarships from the National Foundation. They are Bruce A. Amundson, Climax, Minn., Carl G. Baumann, LeSueur, Minn., and Jon S. Fredlund, Minneapolis.

They are among 197 students presently enrolled at U.S. medical schools who are receiving Health Scholarships from the March of Dimes organization. Awards generally are $500 each.
ALUMNI DEATHS

• 1893
  Dr. George D. Haggard, pioneer physician and last survivor of his medical school graduating class, died February 25, 1961 in Minneapolis at the age of 104 years. He had retired from practice in 1953 at the age of 95, the oldest practicing physician in Minnesota. His medical career spanned 60 years although he was 36 years old before he began practicing.

  He fought typhoid and scarlet fever as a Minneapolis health official and is credited with providing the impetus to the establishment of the city’s first water purification plant following the typhoid epidemic of 1909-10. Practicing in the horse-and-buggy era of medicine, he also is remembered for his “kitchen table” operations.

  Dr. Haggard was president of the 1893 medical class at the University of Minnesota, and was the oldest alumnus of Drake University, where he received a degree in philosophy before he entered medical school. He was born in a log cabin in Goodhue (Minn.) county in 1857, the year before Minnesota became a state.

  He was 1913 president of the Hennepin County Medical Society, and is remembered for an interest in early automobiles which he created and built as a hobby.

  Surviving him are his only child, Mildreth, 74, his housekeeper and companion since Mrs. Haggard died in 1917, and a sister, Mrs. Mattie Semones, Seattle, Wash.

• 1902
  Dr. Marius J. Jensen died August 31, 1960. He was 90 years old, a resident of Minneapolis, and Life Member of the Hennepin County Medical Society.

• 1906
  Dr. John Pettinger Schutt died September 11, 1960 in Bremerton, Wash. He was 85 years old, and was a Fellow of the American College of Surgeons.

• 1907
  Dr. A. Raymond Varco died recently in Minneapolis at the age of 79 years. He was a retired physician and surgeon and member of Nu Sigma Nu medical fraternity. He practiced in Miles City, Mont. before moving to Minneapolis in 1943.

• 1917
  Dr. George L. Merkert died recently in Minneapolis, where he had lived for 58 years. He was on the staff of the Lutheran Deaconess Hospital, Minneapolis, and a member of Phi Rho
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Sigma medical fraternity. He was 68 years old at the time of his death.

♦ 1927

Dr. Milton G. Brown of Roseville, Minn., died recently. He had retired in 1959 because of ill health, and had been a member of the staff of the Hastings, Minn. State Hospital for 11 years. Dr. Brown was a member of Alpha Omega Alpha and Phi Beta Pi medical fraternities.

♦ 1931

Dr. Francis M. Jolin, Grand Rapids, Minn. physician, died December 11, 1960 at the age of 61. He was a native of South Dakota, and had begun his medical practice in 1932 at Coleraine, Minn. He was a co-founder of the Grand Rapids Clinic in 1950, and served in the Medical Corps during World War I.

♦ 1936

Dr. Neil T. Norris died March 3, 1961 at Caledonia, Minn., where he had lived 24 years, and had been in practice. He was 51 years old, and was born at Annandale, Minn.

Memorial Gifts

Memorial gifts to the Minnesota Medical Foundation have been received recently in memory of:

Dr. H. C. Ramstead
Minneapolis, Minn.

John F. Bruzek, Jr.
New Prague, Minn.

Mrs. Crystal Horns
Minneapolis, Minn.

Memorial contributions are a practical means of honoring the memory of a friend or loved one, while helping the Minnesota Medical Foundation in the advancement of medical education and research. Appropriate acknowledgments are promptly sent to both donor and family of the deceased.
Alumni Notes

• 1921
  Samuel N. Litman, Duluth, was named Chief of Staff at St. Luke’s Hospital in Duluth.

• 1924
  Henry E. Bakkila of Duluth was elected Chief of Staff at Miller Memorial Hospital in that city.

• 1926
  E. P. K. Fenger, associate medical director of Glen Lake Sanatorium, has been elected Vice President of the Mississippi Valley Conference on Tuberculosis.

• 1931
  Robert E. Priest, a Vice President of the American Laryngological, Rhinological, and Otological Society, directed a scientific program of the Society’s Middle Section, held Jan. 27-28 in Minneapolis. Speakers included several members of the University of Minnesota Medical School faculty, and the Mayo Foundation faculty.

• 1934
  Curt W. Lundquist, Owatonna physician, has been elected Chief of Staff at the Owatonna, Minn. City Hospital for 1961. Vice President is Dr. Grant E. Olson (Med. ’32), who practices in West Concord, Minn.

• 1935
  Wayne S. Hagen of Minneapolis was elected Vice President of the Franklin (Minneapolis) Hospital Association’s Board of Trustees at the group’s recent annual meeting.

• 1939
  Milton M. Hurwitz, St. Paul cardiologist, was moderator of the February scientific meeting of the Ramsey County Medical Society, titled “The Heart in Industry.” Panelists included Dr. A. C. Kerkhof (Med. ’27), Minneapolis cardiologist, and Dr. William J. Lick (Med. ’42), St. Paul, Consultant to the state Division of Vocational Rehabilitation. Drs. Hurwitz and Kerkhof are past presidents of the Minnesota Heart Association, which sponsored the program.

• 1939
  William E. Proffitt of Minneapolis has been named team physician for the Minnesota Twins baseball club, which will represent this state in the American League beginning in 1961.

• 1941
  Thomas G. Petrick, formerly of Eveleth, Minn., has become
associated with Dr. Harold H. Joffe in the practice of pathology in Virginia, Minn.

• 1943
Ellis N. Cohen of St. Paul has been appointed an associate professor of anesthesiology at the Stanford University School of Medicine, Palo Alto, Calif. He was formerly an associate clinical professor of anesthesiology at the University of Minnesota, and was in private practice in St. Paul.

• 1944
Edmund C. Burke has been elected to the Midwest Society of Pediatric Research. He is an assistant professor of pediatrics in the Mayo Foundation, and has been a member of the staff at the Mayo Clinic since 1952.

• 1950
John B. O’Leary, Lester L. Bissinger (Med. ’46), and R. L. Pedersen (Med. ’46), all Brainerd physicians, are actively serving on medical problems at the new Brainerd, Minn. State School and Hospital.

• 1952
Robert J. Rotenberg was named Chief of Staff-Elect of North Memorial Hospital, Minneapolis, Minn. Since 1955 he has practiced in association with Dr. Samuel Rotenberg at the McNair Medical Clinic, Minneapolis, Minn.

• 1955
S. E. Silvis has begun a residency in internal medicine at the Minneapolis Veterans Hospital. Since 1956 he had practiced at Spring Valley, Minn., in partnership with Dr. Norbert O’Keefe (Med. ’56).
Ray A. Johnson, who practiced in Fergus Falls, Minn., for two years with the Park Region Medical Center, recently moved to join Dr. David Sisler (Med. ’53) and Dr. John Mohrman in their practice in Petaluma, California. His office address is 24 W. El Rose Drive.

• 1957
Alan Goldstein has begun a practice in Chanhassen, Minn., following two years of general practice in Minneota, Minn.

Gene Muchow recently completed two years’ service with the U.S. Air Force, and has rejoined the Austin Clinic, Austin, Minn. in the practice of general medicine.

• 1958
Charles H. Bloom has begun the practice of medicine in Minneapolis at 5736 Nicollet Avenue. He formerly practiced in North Branch, Minn.
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1959

Jerome C. Fluth has gone to Africa to serve as a Baptist medical missionary, taking his wife and two children with him. He expected to work primarily with leprosy, employing the techniques of tropical medicine which he recently studied at Liverpool School of Tropical Medicine.

His address is Jerome C. Fluth, M.D., Bamenda New Hope Settlement, Mbingo, Cameroons Baptist Mission, P.O. Bamenda, Southern Cameroons, West Africa.

MEDICAL ALUMNI ASSOCIATION

Dr. Leonard W. Larson (Med. '21) Bismarck, N. D., physician who is President-elect of the American Medical Association, will be guest speaker at the Medical Alumni-Senior Class luncheon May 4. The traditional event, sponsored by the Minnesota Medical Alumni Association, will be held in Coffman Union's main ballroom on the University of Minnesota campus.

Tickets for the luncheon are available at the Alumni Association office, 205 Coffman Union, according to Dr. Sheldon M. Lagaard (Med. '43), MMAA president. Medical school seniors will be guests of MMAA members.

The annual Homecoming Dinner-Dance of the Association has been scheduled for October 27, 1961, at the Radisson Hotel in Minneapolis. Members of the Class of 1936 will observe their 25th anniversary reunion. Committee members planning the reunion include Dr. Wilfred J. Bushard, Minneapolis, and Drs. Walter Carley, Jerome Hilger, Lawrence Hilger, Norbert J. Lilleberg, and Roger W. Marks, all of St. Paul.

Dr. James Mankey (Med. '43) of Minneapolis is general chairman of the Homecoming Dinner-Dance. He said alumni association awards will be presented during the evening, and noted that the Minnesota-Michigan homecoming football game will be played the following day, Saturday, Oct. 28, at Memorial Stadium.

Dr. Lagaard was re-elected President of MMAA at the group's February Board meeting. Also re-elected were Charles J. Beck (Med. '40), North St. Paul, Vice President; Neil M. Palm (Med. '50), St. Paul, Vice President; James C. Mankey (Med. '43), Minneapolis, Secretary; and Robert Hugh Monahan (Med. '42), St. Paul, Treasurer.
MEDICAL ALUMNI

Send your personal news to the MEDICAL BULLETIN on the form below. Your contribution to "Alumni Notes" will be welcome.

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Class of ________________

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Detach and mail to: The Editor
University of Minnesota MEDICAL BULLETIN
1342 Mayo Memorial
University of Minnesota
Minneapolis 14, Minnesota
Coming Events

University of Minnesota Medical School

List of Continuation Courses for Physicians
1960-1961
University of Minnesota
Center for Continuation Study

May 1-3 . . . . Ophthalmology for Specialists

May 8-10 . . . . Gynecology for General Physicians and Gynecologists

May 11-13 . . . . Surgery for Surgeons

May 15-19 . . . . Proctology for General Physicians

June 1-2 . . . . Psychiatric Emergencies in Medical Practice

1960-61 all year . . Cancer Detection for General Physicians

The University of Minnesota reserves the right to change this schedule without notification.

Courses are held at the Center for Continuation Study or the Mayo Memorial Auditorium on the campus of the University of Minnesota. Usual tuition fees are $30 for a two-day course, $50 for a three-day course, and $75 for a one-week course. These are subject to change under certain circumstances.

Specific announcements are sent out for each course to all members of the Minnesota State Medical Association and to any physicians who request information for a specific course, about six weeks to two months before the date of the course. For further information write to:

DIRECTOR
DEPT. OF CONTINUATION MEDICAL EDUCATION
1342 MAYO MEMORIAL
UNIVERSITY OF MINNESOTA
MINNEAPOLIS 14, MINNESOTA
A Word About

Memorial Gifts

The Minnesota Medical Foundation welcomes your memorial contributions when an appropriate occasion arises. Memorial gifts serve the living and pay thoughtful tribute to the memory of a friend or relative.

The Foundation will promptly acknowledge your gifts to both the donor and the family of the deceased. The gift will help finance the Foundation's program for the advancement of medical education and research. The Medical School at the University of Minnesota will be the direct benefactor.

Gifts should be sent to the Minnesota Medical Foundation, 1342 Mayo Memorial, University of Minnesota, Minneapolis 14, Minn.