



Carcinoids

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I. CASE REPORTCARCINOID OF CECUM

By T. M. Berman

- Female - Age 63.

Entered 12/15/34.

Present Complaint

Abdominal disease 8 yrs.

Present Illness

Formerly suffered from attacks of right upper quadrant pain, suggestive of cholecystitis. Since 1926 has had attacks of vague epigastric distress with nausea, vomiting, and marked constipation increasing in past two years. These symptoms persist with remissions and exacerbations for 1-2 months followed by 6-12 months of comparative comfort. In 1933 lost 20 pounds during a siege of this nature. Since August 1934 symptoms have become aggravated.

Physical Examination

A moderately emaciated white female of 63. Head - negative. Chest - blood pressure 110/60. Heart negative. Lungs - negative. Abdomen - shows evidence of recent weight loss. A mass is palpable in right lower quadrant, medial and inferior to anterior superior spine. It is slightly movable, firm and painless.

Laboratory

Urine - negative. Blood - 66% hemoglobin. Erythrocytes 3,300,000; leucocytes 10,500.

X-ray

- 11/9/34 (Clinic) Gall-bladder - Pathological.
 11/12/34 (Clinic) Gastro-Intestinal - Negative.
 12/14/34 - Barium enema. Filling defect in cecum characteristic of carcinoma.
 12/17/34 - Gastro-Intestinal and follow-through - There is delay of the meal in the ileum with deformity of the cecum.

Diagnosis

Carcinoma of cecum.

Operation

12/29/34 - Mass found in cecum with metastatic regional nodes. Mikulicz resection performed.

Postoperative Course

Slow, but gradual improvement following a temporary urinary infection one week after operation.

Pathology

Gross: The specimen received consists of terminal ileum, cecum, ascending colon, appendix, and portions of their mesentery removed surgically. The cecum is contracted around a firm, sessile mass, 4x3x2.5 cm., projecting into the lumen and presenting superficial ulcerations. Cut section shows a granular yellow surface without necrosis. The mass infiltrates all the layers of the bowel. Small metastatic deposits of similar appearance are present in the mesentery. The cecal mass lies $1\frac{1}{2}$ cm. distal to the ileo-cecal valve and the terminal ileum is moderately dilated.

Microscopic: Nests of round and polygonal, uniform cells are seen showing vacuoles and fine granules in the cytoplasm. The nuclei are round and vascular. Mitoses are inconspicuous. The stroma is dense connective tissue.

The metastatic deposits present a similar picture.

Diagnosis:

Carcinoid of cecum with regional metastases.

II. ABSTRACTCARCINOID TUMORS

By T. M. Berman

Carcinoid tumors of the gastro-intestinal tract have been attracting increasing attention in recent years, particularly since their potential malignancy has received increasing emphasis. This disease has been recent-

nized at least since 1888. In 1907 Oberndorfer demonstrated the chromaffin nature of the cells and suggested the name "carcinoid" tumor. At various times they have been considered basal cell carcinomas, derivatives of pancreatic rests, and even true adenocarcinomas. Masson has shown that the cells of this tumor reduce ammoniacal silver and are, therefore, argentaffilic like the peculiar Kulchitzky cells found in the gastro-intestinal tract. These are cells of obscure function, found from cardia to anus, most numerous in the terminal ileum and appendix, and lying in the base of the crypts of Lieberkuhn. Through painstaking and convincing work Masson has traced budding of these cells in the submucosa of the appendix to form carcinoid tumors. His views are now generally accepted.

Location

The majority of these tumors occur in the appendix. Next in frequency is the lower ileum, followed by the upper ileum, jejunum, and rarely the colon, stomach, and even a Meckel's diverticulum. A recent survey of all the literature (Humphreys) enumerates 152 reported carcinoids of the small intestine and 8 of the colon. The Johns Hopkins Hospital's experience comprises 29 cases (Raiford): 60% in the appendix; 30% in the small intestine; and 7% in the colon. In this hospital since 1928 there have been only 2 cases, described above. Since most carcinoids are accidental findings the actual incidence cannot be determined. They are probably more than twice as frequent in the appendix as in the small intestine, occurring in .1 to .5% of surgically removed appendices.

Age

Carcinoid of the appendix affects chiefly young adults under 30. In the intestine it is largely a disease of the "cancer age". This discrepancy may be more apparent than real in that it is possible that all appear at the same age period but due to the small lumen in the appendix tumors here cause symptoms earlier.

Pathology

In the appendix the tumor appears in the submucosa and mucosa but may infiltrate all the layers. 60-80% are at the tip; the remainder at the base or in the midportion. They average from 5 to 10 mm. although some are much larger and others are microscopic. The lumen is usually obliterated at the site of the tumor. Grossly the mass causes a bulbous swelling of the organ, and is firm, rubbery, and on section presents a characteristic yellow color.

In the intestine the tumor also appears as a yellow submucosal nodule which projects into the lumen in sessile fashion, and may ulcerate, but does not present the piled up borders seen in a true malignant ulcer. The tumor is usually less than 3 cm. in diameter, grows slowly, and may cause intussusception or obstruction. There is a definite tendency to invade the muscularis and serosa and to metastasize to regional nodes, liver, peritoneum, and occasionally to the lungs. Cut section shows the characteristic yellow color and a marked absence of necrosis.

The following tables show frequency of malignancy as reported in the literature, cases being considered malignant which show metastases to regional nodes or beyond.

Humphreys' Series

<u>Location</u>	<u>Total Cases</u>	<u>Malignant Cases</u>	<u>PerCent Malignant</u>
Small intestine	152	37	25
Large intestine	8	3	38

Raiford's Series

Small intestine	9	2	22
Large "	2	2	100
Appendix	17	1	6

It is evident from these limited figures, and from the general impression in the literature, that appendiceal carcinoids are less malignant than intestinal.

Another peculiarity of intestinal carcinoids is their multiplicity. 30% showed multiple tumors varying from 2 to 10, and as many as thirty (30) have been reported.

The microscopic appearance is very characteristic and usually pathognomonic even with routine stains. The cells are remarkably uniform, and are arranged in columns and small masses. They are small, round, polygonal, columnar or cuboidal in shape, and the cytoplasm contains faintly acidophilic granules and lipid filled vacuoles. The nuclei are round or oval, and vesicular. Mitoses are rare. Occasionally rosettes are formed simulating gland tubules. The stroma is a fairly dense connective tissue containing smooth muscle fibers. Masses of cells are frequently seen invading the muscularis and serosa, and have been found in blood vessels. The metastatic deposits are similar in appearance. It should be emphasized that the microscopic appearance is very uniform and one cannot tell histologically which carcinoid is benign and which is malignant.

Clinical Picture

Most carcinoids of both appendix and intestine do not give symptoms and are therefore incidental findings. There is, however, a definite association between appendicular carcinoid and acute or recurrent appendicitis, especially if obstruction of the lumen occurs. In the intestine Humphreys finds that 24% of all cases showed some degree of obstruction. The clinical history, therefore, may often be that of recurrent attacks of right lower quadrant pain, or of constipation, nausea, vomiting, and cramping abdominal pain. A preoperative diagnosis may be suggested by recurrent partial intestinal obstruction without melena, anemia, or advanced cachexia. A bright, young house officer at Johns

Hopkins once made this exceedingly difficult diagnosis on the above findings.

Prognosis

The outlook is much better than in true carcinoma. Strictly local lesions are all cured by resection. Cases with metastases to the regional nodes are usually cured by resection of all involved tissue. Only those with widespread metastases are hopeless. The slow growth of the tumor and the usual paucity of symptoms makes an early diagnosis difficult. Mallory has seen a metastatic node 16 years after removal of an appendicular carcinoid, indicating how slow the evolution of the tumor may be even after metastasis has occurred.

Treatment

The treatment is surgical with removal of the involved areas. The procedure need not be as radical as in carcinoma. There is no adequate data on irradiation therapy.

Points of Particular Interest

1. 85% of carcinoids occur near the ileo-cecal valve.
2. Appendiceal carcinoids are much less malignant than intestinal.
3. 30% of intestinal carcinoids are multiple.
4. Benign and malignant carcinoids give the same microscopic picture.
5. Most carcinoids do not give symptoms.
6. There have been only eight previously reported cases of colon carcinoid.
7. The yellow cut surface seen in the gross examination is very characteristic.

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III. STAFF MEETINGDate: Jan. 17, 1935Place: Recreation Room,
Nurses' HallTime: 12:15 - 1:25Attendance: 92Program: EndometriosisDiscussion: L. A. Lang
J. C. Litzenberg
I. J. Pass

Theme: L.A.L.: Literature for the past 15 to 20 years is full of the subject. Our experience has not been very complete. We found considerable difficulty in freeing this cyst and they often rupture. Some areas did not have endometrial lining characteristic of endometrial cysts. Only few areas where we could make positive diag-

nosis. From now on I have idea we are going to find many more. We had patient this week who had tender mass developing in laparotomy scar. We feel rather confident we are going to find endometriosis in this particular case. Dr. Urner and I saw patient together, with diagnosis of endometriosis, operated upon her and confirmed the diagnosis.

J.C.L.: Endometriosis is definitely established, but it is only since work of Sampson in 1921 that there was a revival of discussion of the condition. History dates back to before I was born. The two interesting things to me about endometriosis are its confusion with other things. As Dr. Lang has pointed out trouble depends upon the location. For a very great many years ovary was removed when chocolate cyst was found. I cannot see any logic in removing the other ovary if Sampson theory is correct.

The thing that interests me is the theory of etiology. Sampson and Novak talk endometriosis. They are very close friends. Both were trained by Kelly at Johns Hopkins, and exceedingly well trained. Both are superior type of gentlemen who never call each other liars, but they do not agree on origin. In theory of Sampson, it must be assumed that the endometrium is sloughed off and that it is expelled through the tube into the peritoneal cavity. I want to relate why I lean more to Novak's ideas than to Sampson's. According to Sampson, structure is in women only during menstrual life. The blood can be seen escaping from the tube during the menstrual period. Early lesions are found near the ends of the tube. The tubes are usually patent. Lesions observed in the abdominal scar do not necessarily prove this theory. Endometriosis likely to occur in abdominal scars after section. Uterus is open as the baby is dragged out and endometrium may be implanted in the wound. Contrarywise Novak does not agree with any of these ideas. He never saw regurgitated blood, as normal peristalsis of the tube is toward the uterus. To prove peristalsis in the opposite direction is a difficult job.

When we recall the anatomy of the fallopian tube, particularly, the interstitial tube, it is very hard for me to believe that the endometrium (i.e. endometrium sloughed off during menstruation) can go through the cavity of the uterus out of the tube into the abdominal cavity. The caliber of the interstitial tube is exceedingly small. It does not go in a straight line through the uterus. It goes in an angular way. From the cornu of the uterus it goes upward, outward, and backward. I think Sampson has some support to his theory, but it does not appeal to me. Where does it come from? I have heard Sampson deliver most of his papers. One of his demonstrations is most beautiful proof that these tumors are endometrium. Operated upon a woman who was in early pregnancy. Found endometriosis of the ovary. On sections of the endometriosis sections showed perfectly normal typical decidua. She proved to be pregnant and later normally delivered. There is one point that Dr. Lang brought out in the review, the form which takes place when the endometriosis becomes far advanced. We see this in endometriosis which occurs in the culdesac and grows down into the posterior vaginal septum. Brought out in earlier work that they are anomalous rests and by the stimulation of hormones we get solid endometrial tumor in the rectovaginal septum.

Treatment is simple. They should be removed as a rule by surgery. Growth can be stopped by x-ray or ovaries. We do not want to do that in young women if we can help it. Sometimes when we get this vaginal septal endometriosis we have a thing just as bad as cancer. It means rectal removal. It is impossible to remove this mass without invading the rectum. They should be treated with x-ray. In cysts in women near the menopause radium can be used. Case here 10 years ago, finally succeeded in curing the woman. Implanted with radium which held it down for long time.

Slides shown.

I.J.P.: I have seen case which would bear out Sampson's contention that endometriosis is transplantation. Saw case in General Hospital. Young woman

about 30, who had lesions in the laparotomy scar. She had some pelvic operation exact nature of which was not understood. Regularly at every period had menstrual flow through sinuses in this scar. At operation one of the tubes found embedded in scar. Actual endometrium in the scar found in microscopic section from operation.

Gertrude Gunn,
Record Librarian.

IV. STAFF MEETING

Date: Jan. 24, 1935

Place: Recreation Room,
Nurses' Hall.

Time: 12:10-1:15

Attendance: 104

Program: December Autopsies

Discussion: C. D. Creevy
K. W. Stenstrom
L. G. Rigler
Richard Johnson
I. McQuarrie
R. Koucky
O. H. Wangenstein
J. R. Paine
Alex Blumstein

Theme:

1st Case:

C.D.C.: This patient admitted in uremia after much delay. Resection for relief and radiation. Good deal of relief from pain from irradiation.

2nd Case:

K.W.S.: We give x-ray treatments after colostomy before resection in carcinoma of rectum. Wait about 6 weeks between colostomy and resection. Surgery by far the better method. Radiation shows less than 20% cures. Some patients who are radiated either refuse operation or cannot be operated upon for some other reason. Usually treat them with heavy series of rays. We used to implant

them first and then use x-rays.

3rd Case:

L.G.R.: In 1933 she had marked enlargement of the heart, almost all the chambers being involved, particularly left ventricle. Conus pulmonalis, and left atrium suggestive of mitral lesion plus some generalized enlargement of the heart as might occur from long standing decompensation or involvement of other valves.

R.J.: Ordinarily we use subtotal thyroidectomy. We have not performed total thyroidectomy in cardiacs who have not had hyperthyroidism. Girl had been in bed 2 years before she came to us. Had operation on her thyroid and was not controlled by the use of ordinary medication. Total thyroidectomy done. Able to be up and around for a time. When she came in the picture looked like pyelitis, i.e. pyuria, chills, fever, and renal pain. Temperature came down. She responded pretty well to medication, then suddenly had stroke or some sort of vascular accident. We thought of subacute bacterial endocarditis but did not give it sufficient consideration. At necropsy the unusual thing in a heart as large as that was the finding of involvement almost an inch from the free margin of the mitral valve in one solid lesion with only a few small vegetations. One wonders that it could have given rise to difficulty. Thyroid must have been an added factor.

I.McQ.: Wome men I have talked to are quite enthusiastic about thyroidectomy. Used only in hopeless patients.

12th Case:

R.K.: In fat embolism the lungs may be very characteristic. In the ordinary sections do not see fat but hemorrhage into the lungs. The brain hemorrhages are due to fat. Surprising thing is enormous amount of fat globules in the brain. Condition is combination of pulmonary, heart, and brain lesions. Delirium, high fever, mental symptoms undoubtedly come from brain. Fall of blood pressure, shock-like state attributed to brain injury or change in blood vessels of the heart. In mild cases fat droplets are not so numerous, and are

apparently filtered out through lung.

14th Case:

O.H.W.: My own impression is that something closed the cardiac sphincter. Pressure probably great enough to rupture esophagus. Ordinarily one would not think the esophagus would do that. The thoracic duct being in juxtaposition to the esophagus tore as the esophagus was stretched. All viscera have certain breaking point. Working on this now from experimental side.

J.R.P.: He probably had ruptured lung as he had air in his chest cavity. At the time of autopsy saw several tears in the lung, but we were not sure that he had rupture. It is difficult for me to visualize what happened. Since then Dr. Wangenstein had me measure pressure of esophagus in patients during coughing and breathing. We found in coughing, esophageal pressure raised very high. Only after injection of methylene blue did we orientate ourselves. At the time we first aspirated the fluid was like milk. Later it looked like thin soup, a little blood tinged. Under microscope it was pure emulsion of fat droplets. On that basis we made diagnosis of ruptured duct. Thereafter material became purulent, no doubt from contamination from esophagus. Not having found it at the time of autopsy, it might be possible he didn't have rupture, and it was milk going into the chest cavity. Dr. McQuarrie ran analysis of this fluid and it was his opinion that he probably was chyle.

17th Case:

K.W.S.: Chest tumor in a young man is embryonic type. Expected it to respond fairly well to irradiation, particularly if it contains much lymphoid structures. More inclined to believe tumor of lung as it did not respond. Might be teratoma of resistant type?

32nd Case:

C.D.C.: Came in for treatment of infection. I think the prostatic hypertrophy and bladder obstruction incidental as it had nothing to do with death.

34th Case:

A.B.: Only in long standing jaundice may the central nervous system be stained, then only the meninges. Exceptions have been mentioned: (1) jaundiced brain which occurs occasionally in children with brain outstanding thing. The other exception central nervous system disease with possible infection.

I. McQ.: In India and China they have cirrhosis frequently in children. I have seen one such case. Infection in the large intestine, i.e. dysentery had developed in a patient 2 years old. Had marked cirrhosis of liver. See it in all different ages. In Banti's disease occasionally. Have had two of them here. Type occurs in Wilson's disease. This looks like a case of portal cirrhosis.

A.B.: We have had no cases of Wilson's disease. One suspected case. He describes progressive lenticular degeneration more often in males. Many of his cases showed jaundice. Neurological picture one of extrapyramidal disease. Patient has tendency to spasticity. Differential diagnosis is from chronic encephalitis (marked spasticity). One of the men down south reported case which he thought Wilson's disease in Negro male with jaundice and some changes in the lenticular nuclei.

Gertrude Gunn,
Record Librarian

V. STAFF MEETING

Date: Jan. 31, 1935

Place: Recreation Room,
Nurses' Hall

Time: 12:15 to 1:30

Attendance: 103

Program: Intracranial Meningioma

Discussion: L.G. Rigler
A. W. Adson
W. T. Peyton

G. Kamman
E. J. Engberg
J. C. McKinley

Theme: L.G.R.: Made encephalogram, i.e. air injected through the spinal cord instead of thru ventricular puncture. Striking picture. Air got through ventricles in spite of this method of introduction. Note very excellent picture. Both ventricles shown. Note displacement of left ventricle to the left, with marked deformity. Same shown in lateral view. There was a tumor in the frontoparietal region, on right side, pressing and displacing the right ventricle. No bony changes made out. Displacement of ventricle is typical of tumor.

A.W.A.: Mayo Clinic, In attempting to present subject like meningiomas we are dealing with large subject. Abstract Dr. O'Brien read relative to history, character of pathology sums it up accurately. In the 15 minutes allotted to me it might be worth while to discuss operability of these tumors.

Only short time ago that medical profession realized there are brain tumors that can be removed. I can remember as a student we looked upon subject of neurology as interesting, but after localizing lesion, nothing was done. That is not true today. There are many things that can be done not only relative to symptoms but also as to cure or to lengthen life and usefulness of patients suffering with brain tumors. We used to think incidence of meningiomas was rather small, as we dared not look into the brain recesses for these tumors. It was through the introduction of electric coagulation by Cushing that it was possible to elevate the brain and remove tumors piece meal.

First meningioma I ever operated upon was in 1916. Dr. Judd and I did it together. When we uncovered the tumor we saw fibrous mass. Tied these vessels and cut the tumor out. We have learned quite a little about taking them out since. Meningiomas occur in about 15% of brain tumors. This new number is due to the fact that we are looking for them in the various recesses and are

able to remove them better piece meal by electrosurgical methods.

There are various locations of meningiomas. It is true largest percentages are rather intimately associated with large sinuses (longitudinal and lateral). Next common location of meningiomata is on ridges on either side of the tentorium, petrous ridge, etc. Next, along lower margin of falx, formerly thought inaccessible. Today, not all of them are operable, but large percentages are.

Most of them are benign but they will recur if you leave tumor tissue behind. The fact that they do recur does not mean that we should call them hopeless. We used to think the way to remove a tumor was to hurriedly turn bone flap, stick your finger in, shell it out, and put the flap back. If meningioma comes to the surface, invariably find spicule of bone attached to bas. If bone flap is turned back have recurrence at the point. I much prefer to deliberately rongeur away part involved and do graft of boil bone. Be sure to remove every portion of bone invaded by meningioma cells. In second place, in tumor along longitudinal sinus, there are two factors: bone and hemorrhage. If you deliver tremendous tumor, blood pressure drops. If you attempt to deliver tumor suddenly you have drop in blood pressure because of thalamic changes. Patients do have cures, but you must get ample exposure. If you find not enough bone go across to the other side. We like to do it in one stage. You must not injure brain to get cure, but get ample exposure, and control bleeding. Slides were then shown to illustrate points.

In brief summary, I emphasize 3 points: (1) There are many more meningiomas than we usually think exist. (2) The removal of the meningioma has to be done by piece meal to avoid excessive hemorrhages and sudden release of pressure that may cause death. (3) Many tumors situated in various depressions on ridges of the bone are now successfully removed by the electrosurgical method whereas formerly they were inoperable. Bound to have certain surgical risk, but by proceeding cautiously, surgical risk is lowered,

and results exceedingly worth while.

W.T.P.: Presents patient. Noticed about $1\frac{1}{2}$ years ago, she was getting swelling and eye beginning to protrude. She came here about a year ago and we gave her some x-ray therapy at that time. No change. 5 weeks ago had headache. We think it is sphenoidal meningioma.

L.G.R.: This is same type of thing Dr. Adson showed. Tumor in sphenoidal region anterior to sella. Note hyperostosis with trabeculated, needle-like points. Radiations are projecting out and there is increased density. Quite typical of meningioma. With picture like this one can be sure about the diagnosis.

A.W.A.: I suspect tumor is on the outer $2/3$ of the sphenoid. Probably hyperplasia of lateral inferior surface of the orbital plate rather than coming back into the sella. Another interesting thing -- venous marking in the skull is always greater in the vicinity of the meningioma than on the opposite side. Just a simple little diagnostic hint.

G.K.: What result have you had from deep x-ray therapy in tumor one cannot reach? We wonder if you are having better results than formerly.

A.W.A.: Ordinarily benign meningiomas do not respond to x-ray treatment. We are getting bolder about going underneath brain for them. Dura over the clinoid is almost inaccessible. You need not hesitate to resect one lateral sinus. You can lift up the cerebellum. Sessile tumors frequently produce larger osteoma, and are frequently called malignant. I operated upon a fellow that I saw 3 years who had seen every one in the country. We did biopsy which proved to be meningioma. I was elected to take off his head. Cut longitudinal sinus down to orbital ridge. Attended World Fair and he came up to see me. He has gone since 1925. Not so malignant as one thought. They may be bigger than my fist, depends upon how much room they have. Parasagittal ones the largest.

E.J.E.: When you do not have characteristic x-ray findings do you rely on encephalogram or ventriculogram?

A.W.A.: We recently studied our cases. During period of 15 or 16 years, we were not always accurate in recording psychiatric examination. At one time we had six frontal lobe tumors in the hospital. Guessed 4 rights and 2 lefts, and clicked. Interesting thing in a right hand person with a left frontal lobe tumor. Patient changes from normal existence to moroseness and depression. Whereas the tumor on the right frontal lobe invariably changes patients from normal existence to one of euphoria. Some relationship? Must never resect left frontal lobe in right-handed people. You can not dissect right frontal lobe without producing changes. Headaches, choked discs, vomiting, indicate ventriculogram? Patient came in with that picture the other day, ventriculogram advised.

Did not cut hair. Did ventriculogram, and saw big left frontal lobe tumor.

J.C.McK.: About how many of these patients will get well? We do not have enough experience with it here.

A.W.A.: I think a lot depends upon how much damage has been done and location of tumor. In longitudinal sinus tumors can get absolute cure. Can not give percentage as to how many of these will develop epilepsy. Some will develop epilepsy probably due to impairment of circulation, others due to cicatricial change. Some meningiomata invariably produce changes such as involvement of the 7th, 8th, 5th, and may produce cerebellar changes. Should not say they are capable of getting perfectly well. Tumors that arise around lateral sinus cannot be resected as with the longitudinal sinus, etc.

Note: An excellent meeting due to Dr. Adson's presentation.

VI. CORRECTION

It was not Max Cutler, Chicago, but Elliott C. Cutler Moseley, Professor of Surgery, Harvard University Medical School, who will deliver the Judd Lecture in the Chemistry Auditorium February 19th, at 8:15 P.M. on "Total Thyroidectomy for Heart Disease." The error was ours, and we are sorry.

VII. NOTICE

A sectional meeting of the American College of Surgeons, embracing Minnesota, North Dakota, South Dakota, Wisconsin and Manitoba is to be held in St. Paul, March 15th, 16th, and 17th. A special invitation is extended to all physicians to attend the program. Men of national reputation will come to St. Paul to participate in the meeting. All physicians, whether of the College or not, are urged to reserve these dates. Dr. Wallace H. Cole is chairman and Dr. E. M. Jones, secretary.

VIII. MOVIES

Title:

Seed Dispersal.

Prepared by the Electrical Research Products Co.

Gertrude Gunn,
Record Librarian.