CALIFORNIA TUMOR TISSUE REGISTRY

FIFTY-FOUR SEMI-ANNUAL SLIDE SEMINAR

ON

ENDOCRINE TUMORS

DEDICATED
TO

ALINE G. BUTT, H. T. (ASCP)

SUPERVISOR, HISTOTECHNOLOGY LABORATORY
CALIFORNIA TUMOR TISSUE REGISTRY
1948 - 1971

MODERATOR:

NANCY E. WARNER, M. D.
DIRECTOR OF LABORATORIES AND PATHOLOGY
LAC-USC MEDICAL CENTER
AND
PROFESSOR AND CHAIRMAN OF PATHOLOGY
USC SCHOOL OF MEDICINE
LOS ANGELES, CALIFORNIA

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KAISER FOUNDATION HOSPITAL
SANTA CLARA, CALIFORNIA

SUNDAY, DECEMBER 10, 1972
9:00 A.M. 4:30 P.M.

SAN JOSE HYATT HOUSE
SAN JOSE, CALIFORNIA

Please bring your protocol, but do not bring slides or microscopes to the meeting.

A TRIBUTE

Aline G. Butt began with the California Tumor Tissue Registry in 1948 when E. M. Butt, M. D. started this organization to build a collection of oncological material for pathologists to have for study and their own continuing education. Aline was at that time with USC and started what is now the California Tumor Tissue Registry with two other part time technologists.

The early functions of the California Tumor Tissue Registry laboratory (then called California Tumor Registry) were to prepare histological slides for all cases submitted to the Registry by pathologists chiefly in the Los Angeles area. A study set was prepared each month for the local group of approximately 30 members.

The state conferences for which the Registry became responsible for the preparation and distribution of the slide sets began in 1950. Thus these conferences as now in effect were solely the Registry function, and the old way of everyone preparing a slide and sending it in was discontinued. This brought about a revolution in quality of histopathology slides which was in large part due to Aline.

As the Registry grew with providing monthly conferences and other services, more staff was added both in the technical and secretarial fields and she became the Supervisor in 1955, having also joined the Los Angeles County Hospital histopathology unit in Surgical Pathology. Not only did Aline supervise the technical end of the Registry, she prepared the budget, pinch hitted as secretary and coordinated the secretarial and technical activities.

Under Aline we can all attest to the superb quality of the histological preparations, her eagerness to aid all those who sought her help and to the many technologists she trained or gave refresher courses.

She was one of the founding members of the California Society of Histopathology Technologists in April 1969 and is still maintaining membership and interest in this outstanding organization whose primary purpose is to maintain a high order of technical knowledge in this important aspect of pathology.

Aline retired after serving the California Tumor Tissue Registry and LAC-USC Medical Center for 23 years and the Registry not only lost a strong right arm but a warm and generous friend. I am sure all of you join me in commemorating this Fifty-four Semi-annual Cancer Seminar to Aline Butt.

CALIFORNIA TUMOR TISSUE REGISTRY

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NAME: G. A. DECEMBER 10, 1972 - CASE NO. 1

AGE: 83 SEX: Female RACE: Caucasian ACCESSION NO. 19749

CONTRIBUTOR: Nancy E. Warner, M. D. Outside No. 71-13033
LAC-USC Medical Center
Los Angeles, California

TISSUE FROM: Thyroid gland

CLINICAL ABSTRACT:

History: Patient was a 83 year old Caucasian female, admitted to the hospital in July 1971. All records of this hospitalization have been lost.

GROSS PATHOLOGY:

The submitted specimen consisted of thyroid gland, measuring 6 x 4 x 3 cm. Section revealed a rim of compressed thyroid parenchyma, measuring up to 1 cm. in thickness, surrounding firm and hard tissue with variegated white to yellow to reddish tan surface. Focal areas showed soft papillary excrescences.

FOLLOW-UP:

Postoperatively she received I^{131} in October 1971. She was readmitted for progressive dysphagia of 1½ months duration with inability to swallow solids and only small amounts of liquid. On physical examination she appeared chronically ill with no specific abnormal physical findings. An I^{131} scan showed a mass in the mediastinum. Radiation therapy was begun and the patient died on October 17, 1971, three months postoperatively.

Autopsy findings: The tumor was found in the cervical lymph nodes, larynx, in the region of the resected right thyroid lobe, and infiltrating around the right common carotid artery. No distant metastases were found. The mediastinum was described as normal.

NAME: A. M. DECEMBER 10, 1972 - CASE NO. 2

AGE: 54 SEX: Male RACE: Caucasian ACCESSION NO. 19407

CONTRIBUTOR: E. R. Jennings, M. D. OUTSIDE NO. S-5176-71
Memorial Hospital of Long Beach
Long Beach, California

TISSUE FROM: Thyroid gland

CLINICAL ABSTRACT:

History: This 54 year old male patient was admitted to the hospital on July 27, 1971 complaining of a mass on the left side of the neck. The mass was first noted one month prior to admission and had been enlarging. There had been no associated pain, voice change, or dysphagia.

Past medical history: No previous significant illness or surgeries.

Physical examination was entirely within normal limits except for the presence of a 5 x 5 x 4 cm. firm, nontender mass in the lower pole of the left lobe of the thyroid gland. The mass moved with swallowing.

Laboratory data: Serum calcium 8.9 mg%. I^{131} scan showed a cold nodule in the left lobe of the thyroid gland. Further laboratory data were within normal limits.

SURGERY:

On July 28, 1971, a total thyroidectomy was performed. A mass was noted in the left lobe. Regional lymph nodes were unremarkable.

GROSS PATHOLOGY:

The left lobe weighed 42 grams and was almost totally replaced by an irregular, firm, 5 cm. nodule. The surface of the nodule was yellow-red, and tan. The right lobe weighed 8 grams and the surface was homogenous dark-red brown.

FOLLOW-UP.

The patient had some hypocalcemia problems following the operation but has remained free of recurrence.

NAME: J. H. DECEMBER 10, 1972 - CASE NO. 3

AGE: 43 SEX: Male RACE: Caucasian ACCESSION NO. 9613

CONTRIBUTOR: John J. Gilrane, M. D.
Santa Teresita Hospital
Duarte, California
OUTSIDE NO. ST744-57

TISSUE FROM: Lumbosacral vertebrae

CLINICAL ABSTRACT:

History: Patient is a 43 year old Caucasian male who entered the hospital on September 5, 1957 complaining of the insidious onset of low back pain over the lumbosacral area of one year's duration. During the two weeks prior to admission, the back pain localized over the left posterior iliac crest.

Past medical history: The patient had a history of pulmonary tuberculosis with two lobectomies prior to 1952. Sputums had been negative for the past 3 years, the last sputum was "doubtfully" positive. In 1950 in Dublin, Ireland, partial resection of a large substernal thyroid gland was performed. Pathological diagnosis was unknown but the patient thought that there was a questionable malignancy within the gland. In 1955, a transthoracic resection of residual substernal thyroid gland was performed. Pathological diagnosis was: "fetal adenoma, no evidence of malignancy."

Physical examination: Positive physical findings were limited to a fluctuant mass in Petit's triangle.

Radiographic studies. revealed extensive osteolytic destruction of the first sacral vertebra. The left iliac crest was also severely involved by a similar process.

SURGERY:

The patient was taken to surgery on September 9, 1957 with a pre-operative diagnosis of tuberculous abscess. The abscess was opened and drained and 17 grams of tissue fragments were removed.

GROSS PATHOLOGY:

The specimen consisted of 17 grams of fleshy red-tan tissue fragments in aggregate measuring 4.2 x 3.5 x 1.5 cm.

FOLLOW-UP:

The patient is lost to follow-up.

NAME: P. B. DECEMBER 10, 1972 - CASE NO. 4

AGE: 58 SEX: Female RACE: Caucasian ACCESSION NO. 19217

CONTRIBUTOR: Robert J. Rosser, M. D.
LAC-USC Medical Center
Los Angeles, California
OUTSIDE NO. 71-8310

TISSUE FROM: Thyroid

CLINICAL ABSTRACT:

History: A 62 year old Caucasian female was admitted to the hospital on March 25, 1971 with signs and symptoms of congestive heart failure. During that admission it was noted that she had a large thyroid gland, approximately 4-5 times normal size. She first noted the neck mass one year prior to admission and felt it was growing rapidly over the last six months. She denied nervousness, heat intolerance, weight loss, diarrhea or tremor. She did note easy fatigability, being unable to walk more than two blocks without resting. In 1933, she was told she had a heart murmur.

Physical examination: Blood pressure 100/70. Pulse 90 and regular. Respirations 20, afebrile. Positive physical findings included fine smooth skin, absent axillary hair, sparse pubic hair and a diffusely enlarged thyroid without bruits. Cardiac examination revealed the point of maximum impulse to be in the 6th intercostal space at the midclavicular line. A grade III/VI systolic ejection murmur was heard over the entire precordium but loudest in the second intercostal space to the right of the sternum. An intermittent S-4 gallop was heard at the apex.

Laboratory data: Hemoglobin 9.5; PCV 32%; WBC 9,500; PBI 6.4 mcgm% T3 uptake 12.7; T4 by column 1.9 mcgm%.

SURGERY:

On April 29, 1971, the entire left lobe and 95% of the right lobe of the diffusely enlarged thyroid was removed. No abnormal lymph nodes were apparent.

GROSS PATHOLOGY:

A 210 grams thyroid gland was submitted which on section showed multiple nodules varying in diameter from 0.2 - 3.5 cm. The nodules were yellow, white and pink; some were firm, others were soft and friable. The nodules closely approached the thyroid capsule. Also submitted were two lymph nodes measuring 2 x 1 cm. each.

FOLLOW-UP:

The lymph nodes were free of tumor and radiation therapy to the neck was begun; 4000 rads were completed on May 14, 1971. On September 7, 1971 the patient was re-admitted in congestive heart failure and died the same day. Autopsy findings revealed no evidence of tumor but severe aortic and mitral stenosis of rheumatic heart disease.

NAME: A. P. DECEMBER 10, 1972 - CASE NO. 5

AGE: 39 SEX: Female RACE: Caucasian ACCESSION NO. 15034

CONTRIBUTOR: Andrew J. McQueeney, M. D.
St. Francis Hospital
Santa Barbara, California
OUTSIDE NO. 66-1076

TISSUE FROM: Thyroid gland

CLINICAL ABSTRACT:

The patient was admitted to the hospital in June 1966 for evaluation of a recurrent nodule on the left side of the neck. The patient first presented in February 1959 for an enlarging nodule in the left lobe of the thyroid gland which was excised on March 10, 1959. Pathological diagnosis was "angioinvasive follicular carcinoma with amyloid deposition". The patient underwent uneventful post-operative recovery and had been asymptomatic until shortly before admission when noting a recurrent mass in the area of the previous surgery.

Physical examination: Revealed a small firm nodule in the left lobe of the thyroid gland and a suggestion of tracheal deviation.

Barium swallow revealed deviation of the trachea and esophagus to the right by a substernal soft tissue density.

I^{131} scan showed a normal right lobe of the thyroid and a 1.5 cm. in diameter area of functioning left lobe. No functioning thyroid tissue was noted in the sternal notch or anterior mediastinum.

SURGERY:

On June 19, 1966, a total thyroidectomy was performed.

GROSS PATHOLOGY:

The specimen included a 40 gram oval firm mass from the the left thyroid area which measured 7 x 4 x 3.7 cm. The main portion of the tumor was encapsulated, the surface being pale yellow-gray. A portion of the mass was attached to a vascular pedicle near the left superior thyroid artery and was adherent to the trachea. Also submitted were 11 grams of normal appearing right thyroid lobe and isthmus.

FOLLOW-UP:

A left radical neck dissection was performed on December 26, 1967. Seven of 22 lymph nodes contained metastatic tumor. Six of these positive lymph nodes were from the superior jugular area and one was from the mid jugular area. When last heard from in 1969 she was well, without evidence of recurrent tumor.

NAME: K. A. Z. DECEMBER 10, 1972 - CASE NO. 6

AGE: 14 SEX: Female RACE: Caucasian ACCESSION NO. 18670

CONTRIBUTOR: A. I. Rajala, M. D. Outside No. S70-941
Goleta Valley Community Hospital
Santa Barbara, California

TISSUE FROM: Thyroid gland

CLINICAL ABSTRACT:

This 14 year old female was treated by her physician for an URI and noted a nodule in the left lobe of the thyroid gland. She was admitted to the hospital in March 1970 for further evaluation and therapy of the mass.

On physical examination, a mass was noted in the left lobe of the thyroid gland. I^{131} scan showed a cold nodule in the left lobe of the thyroid. The patient received a 2 month course of Cytomel and repeat I^{131} scan showed no change. There was no history of radiation exposure.

SURGERY:

A 2 x 2 cm. firm mass was present in the left lobe of the thyroid gland. The right lobe was normal. No evidence of cervical adenopathy was present. Post-operative course was uneventful.

GROSS PATHOLOGY:

The specimen consisted of a 17 gram mass, measuring 3.5 cm. in greatest dimension. The mass was partially covered by a smooth capsule. On section a 1 cm. ill-defined hard nodule was present. It was most dense centrally, being hard, grayish, gritty and flecked with small yellowish areas. The edges were ill-defined.

FOLLOW-UP:

Patient living and well as of October 1972.

NAME: J. A. DECEMBER 10, 1972 - CASE NO. 7

AGE: 54 SEX: Male RACE: Caucasian ACCESSION NO. 19396

CONTRIBUTOR: Donald C. Gibson, M. D. OUTSIDE NO. 71-L-2779
South Coast Community Hospital
Laguna Beach, California

TISSUE FROM: Parathyroid

CLINICAL ABSTRACT:

The patient was admitted to the hospital in September, 1971, for evaluation of renal calculi. Numerous serum calcium determinations ranged from 14-16.5 mg%. A serum parathyroid hormone level was 2,360 units performed by Dr. Claud Arnaud of the Department of Endocrine Research, Mayo Clinic, where normal values are under 50.

SURGERY:

Adjacent to the right thyroid lobe, slightly below its midportion, a moderately firm, round, apparently grossly encapsulated tumor was removed. It weighed 11 grams and measured 3.7 x 3.5 x 3 cm.

GROSS PATHOLOGY:

On sectioning, a tan-yellow, slightly granular, somewhat fleshy tumor was noted. It was homogeneous throughout with no apparent foci of necrosis, hemorrhage, or cystic spaces.

FOLLOW-UP:

Post-operatively the patient has done extremely well. Numerous determinations of serum calcium and phosphorus have been within normal limits. In April 1972, serum PTH was determined by Dr. Arnaud and found to be normal.

The patient was last seen several days by his general physician. The patient was having mild symptoms of gastritis and was moderately depressed, a finding which had been present for a long time. However, there was no evidence of recurrence of the tumor nor of significant biochemical abnormality.

NAME: S. E. F. DECEMBER 10, 1972 - CASE NO. 3

AGE: 46 SEX: Female RACE: Caucasian ACCESSION NO. 19893

CONTRIBUTOR: S. K. Abul-Haj, M. D. Outside No. 71-2456
Ventura, California

TISSUE FROM: Adrenal gland

CLINICAL ABSTRACT:

History: This 46 year old Caucasian female, a known hypertensive since 1967, was admitted to the hospital on December 1, 1971 complaining of neck pain. She was being prepared for anterior cervical spine fusion when it was discovered that she had a persistent alkaline urine and a low serum potassium. Her medications at that time consisted of Reserpine and Diuril. A subsequent EKG also showed hypokalemia. This was attributed to Diuril therapy. Surgery was postponed because of the difficulty encountered in getting her serum potassium above 1.9 meq. inspite of oral and I.V. potassium administration and the withholding of Diuril. On December 7, 1971 anterior interbody cervical fusion was carried out with no complication.

Her present illness dated back to 1967 when she awoke with spontaneous severe epistaxis and was noted to have a highly elevated blood pressure. Antihypertensive therapy was initiated. No detailed workup or followup was available until this admission on December 1, 1970, other than the therapy for hypertension which consisted of Reserpine 0.25 mg. and Diuril 50 mg. daily since 1967.

Family history and past history were noncontributory. The system review showed that she had had the usual childhood diseases with no complications. She was gravida IV, para IV, ab. 0, with no pregnancy complications such as edema or hypertension. During the period of 1/53 - 12/64, she had six admissions to this hospital for the following: Breast biopsies, three times (all benign); hernia repair, two times; hysterectomy for descensus; and three episodes of bladder infection. No serious accidents; no allergies.

Physical examination: Blood pressure 160/100; pulse 72; rate 14; temperature 99° F. She was in no apparent distress. The remainder of the physical was entirely within normal limits, including eye grounds (fundi).

COURSE:

Following the cervical fusion she was discharged for outpatient evaluation of the hypertension. In view of the persistent hypokalemia, alkaline urine, and difficulty in maintaining a normal serum potassium level, an Aldosteronoma was suspected.

LABORATORY DATA:

Hemogram: Hemoglobin 15.2 gms; hematocrit 45; WBC 5,100 with normal differential. Urinalyses normal except for Ph of 7.5 - 7.8. Serum K varied between 1.9 - 2.4 meq. on many occasions. Electrocardiogram persistently showed flattened T-wave with prominent U-waves in leads I, II, III, AVF and anterior precordial leads secondary to hypokalemia. 24-hour urinary Aldosterone determinations showed 36 mcg/24 hrs (normal 2-26 mcg) on 6-22-71 and 44 mcg/24 hrs. on 9-27-71. Plasma renin on May 15, 1971 was at a low value of less than 30 NG/100 ml.

SURGERY:

On July 20, 1971, laparotomy was carried out. The left gland was explored first. It was found to be normal and was not removed. The right gland was then explored. A discrete tumor overlying the superior pole of this gland was found. The gland and tumor were removed.

GROSS PATHOLOGY:

The specimen consisted of an adrenal gland which possessed the usual configuration and measured 6 cm. from pole to pole x 3 cm. in width and 0.5 cm. in average thickness. Attached to the surface was an olive-shaped smooth encapsulated tumefaction measuring 2 cm. from pole to pole x 1.5 cm. in average diameter. The cut surface of the tumefaction was canary yellow and homogeneous. The tumefactinn lay entirely within the capsule of the adrenal gland.

FOLLOW-UP:

The patient did well postoperatively. The serum potassium rose to normal level - 4.0 - 5.0 meq. and the urine alkalinity converted to an acid urine. Hypertension gradually subsided and she became normotensive.

NAME: J. L. S. DECEMBER 10, 1972 - CASE NO. 9

AGE: 10 SEX: Male RACE: Caucasian ACCESSION NO. 19892

CONTRIBUTOR: S. K. Abul-Haj, M. D. Outside No. A-60-220
Ventura, California

TISSUE FROM: Pineal recess

CLINICAL ABSTRACT:

History: This 10 year old Caucasian male student, was brought to attention by his parents because they felt he was "developing too fast" during the preceding four months. During this period, the child had attained a low-pitched voice; an "enormous" penis, larger than that of the father, with pubic hair; a masculine build with a weight gain from 72 to 93 lbs. Associated with these were other signs of pubescence such as acne, a full crop of axillary hair. There were no other systemic signs nor symptoms.

Past history, family history & system review were noncontributory, other than what was stated above. The child had apparently enjoyed good health and normal development until the onset of the present illness.

Physical examination revealed a body weight of 93 lbs., a height of 53½ inches. The body temperature, pulse, blood pressure, and respiration were normal. The child was obviously precocious with Hercules muscular body build, acne vulgaris, thick axillary and pubic hair, a low-pitched voice, and an 11.0 cm. long penis. Except for some bilateral testicular enlargement, the remainder of the physical, including neurologic examination, was within normal limits.

Laboratory data: Hemogram and urinalysis were within normal limits. Serum electrolytes were normal. Serum calcium was 10.1 mgm% and the phosphorus 5.6 mg%. Alkaline phosphatase was 23.8 units (normal up to 12 units - adults; 21 units for children).

Radiograph: Repeated chest films were interpreted as "clear" throughout his illness course. Bone survey showed advanced bone age.

COURSE:

Because of the apparent precocious puberty, it was felt there was excessive androgen production, the source of which was to be determined. An exploratory laparotomy revealed no abdominal masses and "normal" adrenal glands. Hormonal study revealed normal Keto and Ketogenic steroid (3.2 - 5.5 mg/24 hrs) repeatedly. They rose to 9.2 mg/24 hrs.; urinary 24-hr. Pregnandiol rose from a baseline of 1.6 mg to 5.2 mg. following the administration of ACTH. It then fell to 0 with the administration of Aristocort. This ruled out adrenogenital syndrome.

On the 14th hospital day, a testicular biopsy was obtained. It was interpreted as showing Leydig cell hyperplasia. The patient was then transferred to another hospital for further workup. In the referral hospital, the patient's general condition did not change. Review of the testicular biopsy showed the Leydig cell hyperplasia and adolescent tubules with proliferating primary and secondary spermatogonia, but no mature spermatogenesis, indicating a single-type gonadotrophic hormonal stimulus and suggesting an extra-pituitary chorionic-type gonadotrophic hormonal production such as seen with teratoma tumors of the tuber cinereum, roof of the third ventricle, and pinealoblastoma. Pregnancy test was performed and was strongly positive and 24-hr. urinary FSH levels were over 330 mouse units.

A pneumoencephalogram was then performed revealing a space occupying mass in the region of the pineal recess with spotty calcification.

Surgery: Circa June 27, 1960, craniotomy with ventriculocisternostomy was done. The tumor being judged as inoperable was not disturbed.

Postoperatively, the patient maintained a temperature of 102 - 103° F. Spinal fluid taps were sterile and xanthochromic. He was lethargic and withdrawn. On the 13th postoperative day he had a decerebrate seizure, lapsed into a deepening coma and expired two days later.

GROSS PATHOLOGY:

At autopsy, the salient findings were limited to the brain, lungs and genitalia.

The brain showed considerable edema and a bulging mass ballooning the floor of the third ventricle with bluish-purple change. On saggital sectioning a large 5.0 cm. round, soft, dark-brown-red mass was found. It was situated in midline within the pineal recess. It compressed the roof of the 3rd ventricle into its floor causing it to bulge between the optic tracts and attenuate the optic chiasm.

There were two discrete similar hemorrhagic nodules in the midportion of the left lower lung lobe, the largest measuring 1.4 cm.

The testes were somewhat large, each measuring 3.5 cm. from pole to pole. The prostate was also somewhat well developed.

NAME: L. S. DECEMBER 10, 1972 - CASE NO. 10

AGE: 73 SEX: Female RACE: Caucasian ACCESSION NO. 17724

CONTRIBUTOR: Leo Kaplan, M. D.
Cedars-Sinai Medical Center
Los Angeles, California

OUTSIDE NO. MS-13-59A

TISSUE FROM: Pancreas

CLINICAL ABSTRACT:

History: The patient was a 73 year old Caucasian female admitted to the hospital on March 5, 1959 with a 3 month history of abdominal swelling and generalized cramps. She had occasional semi-formed, nongreasy, hemorrhagic stools and loss of an unknown amount of weight. She had been on digitalis and a low salt diet for approximately 2 years prior to admission for arteriosclerotic heart disease and atrial fibrillation.

Physical examination disclosed a blood pressure 130/70, irregular pulse of 68 and temperature 98.6. There was a grade II-VI systolic murmur at the apex radiating to the axilla. There was marked abdominal distension with a suggestion of a mass about the size of an orange in the upper pelvis.

Laboratory data: included hemoglobin 11.2 gms%; WBC 4,1000, prothrombin time 40%. Stool was negative for occult blood. Urine was positive for 5-hydroxyindole acetic acid.

SURGERY:

On March 12, 1959, an exploratory laparotomy was performed. A large amount of dark yellow ascites was present. There was no pelvic mass. There was fullness and induration in the vicinity of the head of the pancreas that was clinically malignant and non resectable.

COURSE:

She died on March 18, 1959. An autopsy was performed, limited to the abdomen.

GROSS PATHOLOGY:

The liver weighed 1350 grams and showed numerous infarctions but no tumor. Severe atherosclerosis as well as thrombo-emboli was found in the branches of the hepatic artery. The spleen weighed 330 grams, contained numerous infarctions but no tumor. In the pancreas at the juncture of the neck and the head a large neoplasm was found. It arose from the anterior and superior portions of the neck to form a mass, measuring 9 x 8 x 8 cm. Its margins were ill-defined. It was soft in consistency and on section bulged and had a mottled, irregularly arranged lobulated grayish-yellow and tan moist surface. The mass compressed the portal and splenic veins. The lymph nodes were grossly free of tumor.

NAME: R. M. S. DECEMBER 10, 1972 - CASE NO. 11

AGE: 64 SEX: Male RACE: Caucasian ACCESSION NO. 13811

CONTRIBUTOR: James H. Cremin, M. D.
Los Angeles, California OUTSIDE NO. EA 147-64

TISSUE FROM: Pancreas

CLINICAL ABSTRACT:

History: The patient was admitted to the hospital for the final time in August 1964 complaining of abdominal pain. The patient first noted a mass in the neck one year prior to admission. After watching the mass grow for 7 months, he sought medical attention. A nodule, 3 cms. in diameter, was removed from the right posterior triangle of the neck. Pathological diagnosis was "undifferentiated" carcinoma. In search of a primary lesion, a thyroidectomy was performed, revealing a follicular adenoma. A biopsy of the tongue was next performed revealing nonspecific glossitis. The patient gave a history of "aches and pains" in the cervical and lumbar spines for many years.

Physical examination: The only abnormality noted was the absense of bowel sounds.

Laboratory data: Hemoglobin 13.9 grams %; WBC 7,100 with 84% neutrophils; 17% bands. Urinalysis revealed 2 plus proteinuria, 8-10 white cells/hpf; 5-6 red cells/hpf; 15-20 granular casts/lpf; BUN 59 mgs%; chlorides 87 meq/liter; CO_2 28 meq/liter; potassium 4.3 meq/liter; and sodium 133 meq/liter.

Radiograph: An upper gastro-intestinal series was performed revealing a duodenal ulcer. There were dilated loops of small bowel. Chest x-ray revealed free gas below the diaphragm. Diffuse osteoporosis was present.

COURSE:

The urine output decreased and the patient died on the 4th hospital day.

GROSS PATHOLOGY:

At autopsy 1000 cc. of cloudy yellow fluid was present in the peritoneal cavity. The liver weighed 4000 grams and was markedly enlarged by numerous firm, gray-white, centrally umbilicated nodules varying in size from 0.5 - 5 cm. The pancreas contained a firm, gray-white tumor, measuring 4.5 x 3 x 4 cm., located in the distal tail. Sectioning revealed a central firm yellow core and a somewhat trabecular appearance. Numerous smaller gray-white nodules were present in the pancreas. In the gastro-intestinal tract, a 0.5 cm. ulcer was present along the lesser curvature. The duodenum contained two ulcers just distal to the pylorus, measuring 2 cm. and 2.3 cm. in diameter. The more anterior of the latter two ulcers perforated the duodenal wall.

NAME: R. B.

DECEMBER 10, 1972 - CASE NO. 12

AGE: 34 SEX: Male RACE: Caucasian

ACCESSION NO. 19100

CONTRIBUTOR: J. R. Phillips, M. D.
St. Agnes Hospital
Fresno, California

OUTSIDE NO. S-71-1348

TISSUE FROM: Pancreas

CLINICAL ABSTRACT:

History: The patient was admitted to the hospital in March, 1971, following intermittent hypoglycemia since May 1970. Mutiple blood sugars were in the range of 30 mg%. He had frequent periods of confusion relieved by food.

Physical examination was unremarkable.

SURGERY:

On March 17, 1971, a distal pancreatectomy and splenectomy were performed.

GROSS PATHOLOGY:

The spleen weighed 220 grams and was unremarkable. The segment of pancreas weighed 25 grams and measured 5.5 x 2.5 x 2 cm. On mutiple section of the pancreas a 1.3 cm. well demarcated, somewhat lobulated, soft, glistening tan and gray nodule was noted.

FOLLOW-UP:

Follow-up not available.

NAME: D. K. DECEMBER 10, 1972 - CASE NO. 13

AGE: 67 SEX: Female RACE: Caucasian ACCESSION NO. 18737

CONTRIBUTOR: D. R. Dickson, M. D. Outside No. S69-3364
Santa Barbara Cottage Hospital
Santa Barbara, California

TISSUE FROM: Adrenal gland

CLINICAL ABSTRACT:

History: This 67 year old Caucasian female had no complaints other than pedal edema, but at her son's insistence she consulted a physician who recognized the classical signs and symptoms of Cushing syndrome. There had been a gradual weight gain with abnormal distribution of fat, edema of the lower extremities and gradually increasing hirsutism of the lower lip, chin and cheeks with deepening of the voice, all appearing in the past 6 to 8 weeks. She had mild hypertension for many years which increased markedly in the past 4-6 weeks.

Physical examination: Blood pressure 180/100 and the above described features of Cushing's syndrome.

Laboratory data: A perirenal gas study showed enlargement and loss of the normal contour of the right adrenal gland with a normal left adrenal gland. Urinalysis and hemogram were within normal limits. Urine 17-ketosteroids 11.4 mg/24 hr. (normal 1-6 mg); urine 17-ketogenic steroids 48 mg/24 hr. (normal 4-23 mg.); urine VMA normal. Plasma cortisol 21 mcg.% (normal 5-20); after one dose of Dexamethasone, plasma cortisol was 22 mcg.%, and after a 3-day period of Dexamethasone, plasma cortisol was 33 mcg.%.

SURGERY:

On June 18, 1969, the right adrenal mass was resected without difficulty. Its periphery was well defined and there was no invasion of surrounding tissues. Post-operative course was uneventful and she was discharged on June 28, 1965 on gradually tapering hydrocortisone.

GROSS PATHOLOGY:

The 7.9 x 6.5 x 2.8 cm. adrenal mass weighed 76 grams and maintained the general contour of the adrenal gland. The delicate capsular surface was intact. After removal of the loosely attached fat, the adrenal mass weighed 64 grams. Sectioned surfaces were composed of coarsely lobulated bulging golden yellow tissue with occasional islands having a more glistening tan hue. The individual lobules varied from 0.5 - 1.5 cm. in diameter and were well defined and lacked apparent intervening stromal framework inasmuch as they were easily dislodged.

FOLLOW-UP:

Four months later, the patient died, 48 hours after the sudden onset of coma. At autopsy, a ruptured congenital aneurysm of the terminal portion of the left internal carotid artery was found. There was no residual tumor found.

NAME: L. C. Y. DECEMBER 10, 1972 - CASE NO. 14

AGE: 39 SEX: Female RACE: Chinese ACCESSION NO. 19347

CONTRIBUTOR: Seth L. Haber, M. D. OUTSIDE NO. 71-5786
Kaiser-Permanente Medical Center
Santa Clara, California

TISSUE FROM: Adrenal gland

CLINICAL ABSTRACT:

History: The patient was a 39 year old Chinese female admitted to the hospital on July 1971. She was first noted to be hypertensive in 1967 in Toronto, Canada, where work-up revealed no specific findings. In 1969 marked increase in her hypertension was noted, associated with a pregnancy which was terminated by therapeutic abortion.

Radiograph: Aortogram and selective renal arteriograms showed no renal abnormalities.

Laboratory data: Urinary 17-hydroxysteroids were moderately elevated while 17-ketosteroids and Porter-Silber chromogens were normal. IVP was normal. Early in 1971, a diabetic curve was obtained on glucose tolerance test.

Physical examination: On admission was indicative of Cushing's syndrome.

SURGERY:

The left adrenal gland contained a 2 cm. tumor with the remainder of the left gland and entire right gland appearing markedly atrophic.

GROSS PATHOLOGY:

The specimen appeared as 8 grams of adrenal tissue consisting of up to 2.2 cm. golden-tan and brown nodules with attached atrophic adrenal. Approximately 10 grams of fat was adherent to the specimen. The tumor was slightly variegated on its cut surface with alternating golden-tan and dark brown areas.

FOLLOW-UP:

Post-operatively, the patient was treated with gradually tapering doses of hydrocortisone. Blood pressure in September 1971 was 165/110. In December, 1971, the patient's dosage was lowered to 10 mg hydrocortisone/day. Plasma cortisol was 2 mcg% in the morning specimen. Consequently the cortisone dosage was increased and diagnoses of hypothalamic cortisol releasing factor insufficiency and adrenal insufficiency were made. In January, 1972, urine aldosterone level was 13, which was normal. In August, 1972, she was "doing well with blood pressure 130/80, being treated with cortisol and Aldomet."

NAME: J. D. B. DECEMBER 10, 1972 - CASE NO. 15

AGE: 55 SEX: Male RACE: Caucasian ACCESSION NO. 18942

CONTRIBUTOR: Nelson J. Quigley, M. D.
Queen of Angels Hospital
Los Angeles, California
OUTSIDE NO. E 5036-70

TISSUE FROM: Adrenal gland

CLINICAL ABSTRACT:

History: The patient was a 55 year old Caucasian male who was admitted to the hospital in December, 1970, for surgery for removal of a medial meniscus. The evening after surgery the patient had a meal and experienced nausea, vomiting, dizziness, tachycardia and high blood pressure. The following morning he was again seen because of similar attack and his blood pressure was noted to be greater than 200/100. Further history revealed he had had similar attacks for the previous 8 years.

Laboratory data: Urine VMA 12.4 mg/24 hr. Histamine administration raised the blood pressure from 120/84 to 210/150. Regitine administration lowered the blood pressure from 150/90 to 120/68.

SURGERY:

The patient was taken to the operating room on December 29, 1970, where the left adrenal gland was removed.

GROSS PATHOLOGY:

The specimen consisted of left adrenal gland with surrounding adipose tissue. The gland contained a 2.5 cm. in diameter, soft and slightly rubbery nodule covered by glistening thin transparent capsule, beneath which could be seen variegated patches of bright yellow and gray-pink tissue. On section the parenchyma of the nodule was gray-pink which showed several foci of meaty red hemorrhagic tissue measuring up to 0.6 cm. in diameter. When portions were immersed in fresh Zenker's, the cut surface of the tumor took on a more brown appearance.

FOLLOW-UP:

Patient doing well as of October 1972.

NAME: A. R. DECEMBER 10, 1972 - CASE NO. 16

AGE: 34 SEX: Male RACE: Caucasian ACCESSION NO. 19682

CONTRIBUTOR: Vivian Gildenhorn, M. D. Outside No. 1387-72
Inter-Community Hospital
Covina, California

TISSUE FROM: Adrenal gland

CLINICAL ABSTRACT:

History: The patient was admitted to the hospital in late March 1972, suffering from severe hypertension. He was told in 1950 that his blood pressure was high and during cholecystectomy in 1964 hypertension was again noted. Several weeks prior to admission he was admitted to another hospital for hypertension and congestive heart failure with ankle edema, severe cough and dyspnea. He complained also of headaches and dizziness.

Physical examination disclosed blood pressure of 250/140, temperature 102 and marked diaphoresis. The fundi showed marked arterial narrowing.

Radiograph: Chest film showed borderline left ventricular enlargement. Electrocardiogram was within normal limits. A renogram showed delay in accumulation of radionuclide in the left kidney with an associated delay in excretion from the renal tubules. Aortogram demonstrated large vascular right adrenal tumor.

Laboratory report: Urinalysis and hemogram were normal. The 5 HIAA, 17-ketogenic steroids and 17-ketosteroids were normal. VMA was 23.4 mg/24 hrs.

SURGERY:

The patient was taken to the operating room on April 4, 1972 where the right adrenal gland was excised.

GROSS PATHOLOGY:

The tumor measured 6.5 cm. in diameter, was partly pigmented and chromaffin reaction was equivocal.

FOLLOW-UP:

The blood pressure day after surgery was 132/80 and have remained normal. The headaches have not recurred. A repeat VMA was normal.

Blood pressure gradually returned to normal and patient feeling well as of November 1972.

NAME: B. E. B. DECEMBER 10, 1972 - CASE NO. 17

AGE: 43 SEX: Female RACE: Caucasian ACCESSION NO. 18934

CONTRIBUTOR: Luis Quan, M. D. OUTSIDE NO. B 8289-70
Kaiser Foundation Hospital
Los Angeles, California

TISSUE FROM: Adrenal gland

CLINICAL ABSTRACT:

History: The Patient was a 43 year old Caucasian female admitted to the hospital in December, 1970. The only history available was that the patient was found to have signs and symptoms compatible with Cushing's syndrome.

Laboratory data: Plasma cortisol, 25 mg%, and following ACTH stimulation rose to 35.5 mg%.

Radiograph: Retroperitoneal air studies showed no abnormality of renal structures. The right adrenal gland was well outlined, normal in contour, and showed no enlargement. The left adrenal, although showing a normal contour, appeared enlarged.

SURGERY:

On December 21, 1970, patient was taken to the operating room for an exploratory laparotomy. A splenectomy and left adrenalectomy were performed.

GROSS PATHOLOGY:

A discrete and thinly encapsulated yellow tumor, measuring 3.6 x 3 x 2 cm, was described in the adrenal gland.

FOLLOW-UP:

Postoperative plasma cortisol (3-10-71) was 4 mg%. When last seen in October 1971, she appeared much thinner and 10 years younger than formerly.

Patient doing well as of February 16, 1972. Plasma cortisol level at that time was 14.5 mcg.%. The patient is on replacement therapy; weight 120 lbs.

NAME: G. K. DECEMBER 10, 1972 - CASE NO. 18

AGE: 52 SEX: Female RACE: Caucasian ACCESSION NO. 19245

CONTRIBUTOR: Richard Orselli, M. D. OUTSIDE NO. C-2330-71
Centinelli Valley Community Hospital
Inglewood, California

TISSUE FROM: Adrenal gland

CLINICAL ABSTRACT:

History: The patient was a 52 year old Caucasian female admitted to the hospital on May 13, 1971, for exploration of a retroperitoneal mass which was discovered during previous surgery. She had a history of uterine bleeding since 1970 and was treated with a total hysterectomy and bilateral salpingo-oophorectomy at another hospital in February 1971. At that time a retroperitoneal tumor was noted. The patient's general health was described as good.

Physical examination revealed a fullness of her left flank.

Laboratory data was within normal limits.

Radiograph: Because of iodine intolerance, an IVP could not be performed. Cystoscopy showed the presence of two orifices and interpreted as normal. Retrograde pyelogram and retroperitoneal CO_2 studies confirmed the impression of a large retroperitoneal mass believed to represent carcinoma of the kidney.

SURGERY:

By a transthoracic transabdominal approach, a left nephrectomy was performed. A 1000 gram yellow tumor was found attached to but not involving the upper pole of the kidney.

GROSS PATHOLOGY:

A large yellow tumor adjacent but not involving the upper pole of the kidney was circumscribed and lobulated. On section, solid and cystic areas with zones of necrosis and hemorrhage were noted. The adrenal gland could not be identified grossly and appeared to be replaced by the large tumor. No other organs were grossly involved.

FOLLOW-UP:

As of June 1972, the patient was in good health with no evidence of recurrent tumor.

NAME: M. K. DECEMBER 10, 1972 - CASE NO. 19

AGE: 54 SEX: Male RACE: Caucasian ACCESSION NO. 19891

CONTRIBUTOR: S. K. Abul-Haj, M. D. Outside No. 66-A-39
Ventura, California

TISSUE FROM: Pituitary

CLINICAL ABSTRACT:

History: This 54 year old Caucasian male, excarpenter, had been admitted to several mental institutions for psychiatric management during the several years preceding his demise. He was diagnosed eventually as presenile dementia (Alzheimer's disease). He was committed to a State Hospital in 1966. At the time of admission the patient showed extensive mental-motor retardation and was unable to give a history or account of his whereabouts. He was disoriented in time and space and responded only to simple commands.

Family history, past history and system review were uninformative.

Physical examination revealed a somewhat wasted Caucasian male appearing older than the stated age of 54. He was disoriented as to time and place but was in no apparent distress. The blood pressure was 128/84; pulse 64; rate 14; and temperature 98.2°F. The head was said to be unremarkable with no evidence of trauma. The eyes were externally unremarkable. No fundal examination was recorded. The ears and nose were within normal limits. The mouth showed poor dental repair with many missing and carious teeth. The neck was supple with no palpable masses. The chest and abdomen were unremarkable as were the genitalia and extremities. There was no external lymphadenopathy. The neurologic examination was not illuminating because of the mental state of the patient. There was, however, definite weakness of muscles, apathy, and disorientation. No localizing signs were detailed and no pathologic reflexes elicited.

HOSPITAL COURSE:

The patient was maintained on simple nursing case as he was not able to care for himself. At times he would sit for hours holding his head in his hands and talking incoherently. On the fifth hospital day, he was noted to be shocky with clammy cold skin and a blood pressure of 60/40. He was found to have soiled his bedding with tarry and brown-red semisolid stools. A N-G tube was placed in the stomach and returned bloody material. He was transfused with improved vital signs. On the eighth hospital day he underwent an upper G. I. series which showed a huge ulcer. On the ninth hospital day, laparotomy was performed and a huge gastric "ulcer" was resected with the pathologic diagnosis of lymphoma. A portion of the tumor was stuck to the liver and was not removed. He had an uneventful postoperative recovery.

The gastric lesion was interpreted as "Gastric Lymphoid Pseudo Tumor." The gross specimen showed an additional penetrating ulcer in the first portion of the duodenum and the gastric rugae away from the ulcer showed tremendous hypertrophy, suggesting a Z-E syndrome. The gastric mucus neck glands were obliterated by hyperplastic parietal cells.

Physical examination showed a distinct acromegaly with prognasthism, elongation of fingers and toes, a towering skull and marked muscular weakness. The eyes showed poor pupillary reflexes and marked papilledema. There was a nodular mass in the region of the thyroid gland.

Laboratory data: Hemograms: Hemoglobin, 17.5 gms. on admission - fell to 8.0 gms. with the upper G.I. hemorrhage, and was stable postoperatively at 14.6 gms. WBC was 7,600 with normal differential. Urinalysis normal.

On the 27th postoperative day, screening serum calcium was 14.6 mg%, the serum phosphorus was 1.3 mg%, and fasting blood sugar was 38 mg%.

Radiologic bone survey showed complete obliteration of the sella turcica and erosion of the sphenoid bone by a large space occupying mass. The lamina dura was absent with demineralization of bone. Similar "demineralization" involved the digits of all extremities. On the 29th postoperative day, the patient had a convulsive seizure, lapsed into coma and expired.

GROSS PATHOLOGY:

Cardiovascular system: Arteriosclerosis with calcinosis.

Lungs: Edema.

G. I. Tract: Well healed gastrectomy with no residual tumor.

G. U. Tract: Focal nephrocalcinosis of both kidneys.

R-E System: No pathologic diagnosis; no evidence of lymphoma.

Endocrine system: Pituitary: There was a 5.0 cm. ovoid discrete mass Its cut surface was gray-white and mushy. The mass eroded the sphenoid bone, compressed the optic chiasm and optic tract and invaginated the floor of the fourth ventricle. Thyroid gland: The thyroid gland contained a nonencapsulated nodular firm gray-tan 4.0 cm. mass. Parathyroids: Four glands were identified. The two inferior glands contained a 1.5 cm. discrete round tumor on the left, and a similar 2.1 cm. tumor on the right. The cut section was greenish-tan to orange and glistening. Pancreas: The pancreas contained a 2.6 cm. round nonencapsulated tumor in the tail and within the hilus of the spleen. Its cut surface was orange-brown.

The body as a whole showed visceromegaly.

The brain showed edema, dilation of the lateral ventricles, uncal and cerebellar tonsillar herniation.

NAME: J. Y. DECEMBER 10, 1972 - CASE NO. 20

AGE: 61 SEX: Male RACE: Caucasian ACCESSION NO. 11611

CONTRIBUTOR: Donald L. Alcott, M. D. Outside No. S60-292
Santa Clara County Hospital
San Jose, California

TISSUE FROM: Left lung

CLINICAL ABSTRACT:

History: This patient underwent a left thoracotomy on February 17, 1960, because of an abnormal chest x-ray. A tumor was found in the left lower lobe and a left pneumonectomy was performed. No metastases were found at the time of operation.

GROSS PATHOLOGY:

In the left lower lobe bronchus was an elevated 2 x 1.3 cm. tumor which had destroyed the bronchial mucosal markings and had extended into the prehilar lymph nodes. The lung tissue distal to the tumor was engorged with blood, and the bronchi were dilated with thick yellow purulent material. There was a gross margin of 1 cm. between the visible tumor and the bronchial resection line, and frozen section of the surgical bronchial margin revealed no tumor. There was no gross or microscopic involvement of the separately submitted hilar lymph nodes.

COURSE:

He did well until August 1960, when he began to complain of shortness of breath. On September 24, 1960, he was admitted to the hospital because of generalized body swelling and shortness of breath.

Physical examination: There was moderate swelling of the face and arms. The neck veins were flat. There were a few soft lymph nodes in the left supraclavicular area. There was a well healed thoracotomy scar. The left chest was uniformly dull and there were no breath sounds. The liver was enlarged to 3 cm. below the right costal margin. There were healing herpetic lesions on the left leg. In the hospital the patient presented a problem in the differential diagnosis of edema. There was no history of physical evidence of renal or heart disease. Although there was swelling of the face, the absence of venous distention ruled out the possibility of superior vena caval syndrome. Venous pressure was 6 cm. measured in the right antecubital vein with the patient lying flat and arm held up to chest level. The patient's blood pressure was 90/56; pulse 102; respiration 25; and normal temperature.

Laboratory report: On October 8, 1960, serum sodium was 153 meq/L; serum potassium was 2.7 meq/L. He was treated with 1000 mg. sodium diet and potassium triplex. By November 1, 1960, his serum sodium had improved to 146 meq/L and the potassium to 3.1 meq/L. When he was presented to Grand Rounds, the concensus of opinion was that the edema was due to excessive adrenocortical steroids. Further studies done at Stanford showed 17-hydroxysteroids averaged 135 mg/24 hr; 17-ketosteroids averaged 50 mg/24 hr. Retroperitoneal air studies revealed enlarged adrenal glands bilaterally.

A transphenoid hypophysectomy was performed on December 7, 1960, following which the patient gradually deteriorated, contracted pneumonia, and expired on December 22, 1960.

AUTOPSY:

There were metastases to the supraclavicular, hilar, and periaortic lymph nodes, both adrenals, liver, spleen, right kidney, gastrocolic ligament, and the right frontal lobe of the brain. The right adrenal weighed 105 gm. and measured 10 x 7 x 6 cm. The cortex was hemorrhagic, tumorous, and 3 cm. thick. The medulla was soft, homogeneous, firm, and yellow-gray. The left adrenal weighed 35 gm. and measured 8 x 5 x 4 cm. The section was similar to that of the right adrenal.

BIO-ASSAY:

"Lyophilized plasma was assayed for corticotropic activity in hypophysectomized rats by the method of Lipscomb and Nelson; decidedly elevated levels of 4.5 milliunits per 100 ml. of plasma were found....Assays of tumor revealed corticotropic activity of 23 milliunits per gram of tissue. The concentration of corticotropin in the pituitary was unusually low at 0.7 milliunits per mg. of tissue. Corticotropic activity was not found in other tissues. It was postulated that the carcinoma was autonomously secreting large quantities of corticotropic substance."

Note: Thanks are extended to Drs. John Nuckton and Grant Little for the bio-assay of the tumor.

NAME: S. J. G.

DECEMBER 10, 1972 - CASE NO. 21, 22 & 23

AGE: 20 SEX: Female RACE: Negro

ACCESSION NO. 19755

CONTRIBUTOR: Robert M. Silton, M. D.
LAC-USC Medical Center
Los Angeles, California

OUTSIDE NO. A 80662

TISSUE FROM: Kidney (Case 21)
Parathyroid (Case 22)
Bone (Case 23)

CLINICAL ABSTRACT:

History: Patient was a 20 year old Negro female who was admitted to the hospital on April 16, 1968, because of abdominal pain of 5 years duration. There was no nausea, vomiting, or diarrhea. She admitted to polyuria and nocturia. Her menstrual period had been irregular for the past year. She was gravida II, para II, Ab 0. In 1963 she had toxemia of pregnancy with secondary renal failure. Since that time renal function was poor. Kidney biopsy in 1963 revealed "discrete intracapillary fibrinoid deposits interpreted as chronic pyelonephritis." In 1965, a second episode of toxemia occurred. In 1968, peritoneal dialysis was performed at UCLA. Later in 1968 the patient was hospitalized for abdominal pain, diagnosed as gastroenteritis. At that time BUN was 165 mg%.

Physical examination: Blood pressure 140/70. Pulse 110. Respirations 40. Temperature 94. She was described as cachetic with multiple subcutaneous nodules. There were bilateral rales and a grade II - VI apical systolic murmur. Abdominal tenderness was diffuse but maximal in the right lower quadrant.

Laboratory data: Hemoglobin 4.9; WBC 18,600. Blood sugar 110 mg%. BUN 177 mg%. Sodium 141 meq/liter. Potassium 4.1 meq/liter. CO_2 11 meq/liter. Calcium 9.3 mg%. Phosphate 9.6 mg%. Creatinine 20.7 mg%. Amylase 1,065 units.

COURSE:

The abdomen remained tender and the patient had tetanic seizures. She gradually lapsed into a coma and died on April 26, 1968, the 10th hospital day.

GROSS PATHOLOGY: (AUTOPSY)

In the abdomen, the liver extended 6 cm. below the right costal margin. The spleen was subcostal. The peritoneal surfaces were dull. The cavity contained 1500 cc. of gray-pink fluid. Beginning 2 cm. distal to the ligament of Treitz, the bowel and its mesentery was rotated 1½ times. The ascending colon was free floating with the appendix lying in the left upper quadrant. The small bowel had a purple serosa, dark red mucosa and a very thin wall with areas of fibrinous adhesions. The pancreas was normal.

(Case No. 21) The right kidney weighed 25 grams and the left kidney 18 grams. Cortical surfaces were coarsely granular and the capsule stripped with difficulty. On sectioning, the cortex was pale and poorly demarcated from a pale medulla. The calyces and pelves were normal in number. The ureters were normal. The bladder was the usual size and the wall was thin. The renal arteries and renal veins were normal.

(Case No. 22) Four firm, gray-brown parathyroid glands were found, not further described.

(Case No. 23) The vertebrae showed increased density and a pale marrow. Just lateral to the costochondral junction of the 5th rib was a 1.5 cm. round, smooth cystic structure. At the midaxillary line in the 6th rib was a 2 cm. round nodule. The ribs, clavicle and sternum were soft.

NAME: R. S. DECEMBER 10, 1972 - CASE NO. 24

AGE: 24 SEX: Male RACE: Caucasian ACCESSION NO. 17674

CONTRIBUTOR: Raid Chappell, M. D.
Modesto, California OUTSIDE NO. 68 JM 3954

TISSUE FROM: Testis

CLINICAL ABSTRACT:

History: The patient was a 43 year old Caucasian male, admitted to the hospital in September, 1968. On a routine annual physical examination at the Modesto State Hospital for the mentally disturbed, the patient was found to have bilateral asymptomatic testicular enlargement. The right testicle was twice normal size and nodular; the left was questionably enlarged. There was no gynecomastia.

SURGERY:

At surgery only the right organ was removed. "A number of days post-operatively, out of curiosity as to whether there really was or wasn't a left testicular tumor, I examined the patient and palpated his scrotum. At that time, the patient was heard to mutter, 'the doctors around here are crazy. You're the fourteenth one to feel my balls'".

GROSS PATHOLOGY:

The specimen consisted of testicle with attached cord. The testicular portion measured 6 x 4 x 3.5 cm. The tunica was smooth and glistening. The testes was largely replaced by a firm, tan and nodular lobulated tumor, measuring 4 x 3 x 3 cm. and was variegated in color from gray to tan to brownish-yellow. The periphery of the tumor was partially demarcated, almost encapsulated, with an abrupt line of transition between the tumor and adjacent compressed testicular parenchyma.

NAME: C. R. DECEMBER 10, 1972 - CASE NO. 25

AGE: 17 months SEX: Male RACE: Cauc. ACCESSION NO. 19894

CONTRIBUTOR: John Tsai, M. D. Outside No. 72-19802
LAC-USC Medical Center
Los Angeles, California

TISSUE FROM: Liver

CLINICAL ABSTRACT:

History: The patient was admitted to the hospital in October 1972 with history of increasing abdominal distension for 8 days prior to admission and intermittent fever. There was no vomiting or diarrhea. One bowel movement with blood streaks was noted four days before admission.

Physical examination: Temperature 101°. The abdomen was distended with firm mass felt in the right upper quadrant. No rectal or abnormal scrotal mass

Radiographs: Abdominal series, IVP, and aortic angiography all showed tumor in the right upper quadrant with tumor vessels seen in the right dome of the liver. Liver scan showed a large intrahepatic or "retrohepatic" mass.

Laboratory data: Hemoglobin 7.5 gm%; hematocrit 26%; WBC 23,400 with 47% neutrophils (2% bands), 45% lymphcytes, IgG 975, IgA 216, IgM135. Screening test for fetaglobulin was positive.

SURGERY:

Partial resection of liver was performed. There was extensive necrotic tumor originating from and replacing medial segment of the left lobe of liver with involvement and replacement of part of the right lobe. The tumor was partially fixed to the right diaphragm and transverse colon.

GROSS PATHOLOGY:

The specimen consisted of a 360 gm. mass of tissue, including the lateral portion of the right lobe of the liver with attached 14 x 13 x 6 cm. tumor on the anterior-superior surface. Included with the specimen was another 350 gm. mass of partially necrotic, hemorrhagic, friable, irregularly mottled tan, red, brown and gray tissue, measuring up to 13 cm. in greatest dimension. A 7 cm. segment transverse colon with adherent tumor tissue was also included.

A D D E N D A

CALIFORNIA TUMOR TISSUE REGISTRY

FIFTY-FOURTH SEMI-ANNUAL SLIDE SEMINAR

ON

ENDOCRINE TUMORS

MODERATOR:

NANCY E. WARNER, M. D.
DIRECTOR OF LABORATORIES AND PATHOLOGY
LAC-USC MEDICAL CENTER
AND
PROFESSOR AND CHAIRMAN OF PATHOLOGY
USC SCHOOL OF MEDICINE
LOS ANGELES, CALIFORNIA

SUNDAY, DECEMBER 10, 1972

SAN JOSE HYATT HOUSE
SAN JOSE, CALIFORNIA

APOLOGIES

THIS LATE ADDENDUM OF THE SEMI-ANNUAL SEMINAR MODERATED BY NANCY WARNER, M.D., WAS PREPARED BY JOHN R. CRAIG, M.D., REGISTRAR OF THE CALIFORNIA TUMOR TISSUE REGISTRY WITH HER COLLABORATION. HE BROUGHT THE LITERATURE UP TO DATE THRU 1975.

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THYROID TUMORS

INTRODUCTION

The main purpose of a classification is to promote better understanding of etiology, course, prognosis and therapy. The classification of thyroid cancer remains similar in the two AFIP Fascicles on the thyroid. But, finding a name for a particular tumor is complicated by the frequent finding of variable histologic features in one tumor. For example, papillary adenocarcinoma frequently contains follicular elements, and a follicular carcinoma may show a small focus of oxyphilic cells. Mixed papillary and follicular tumors behave as papillary tumors and are best classifed as such (Franssila). However, the two pure tumors (papillary and follicular) differ in etiology, course and survival.[1]

TABLE I

CLASSIFICATION OF PRIMARY THYROID CANCER

Epithelial:	(1)	Papillary Adenocarcinoma
	(2)	Follicular Carcinoma
		(a) Clear Cell Carcinoma
		(b) Oxyphil Carcinoma
	(3)	Medullary Carcinoma
	(4)	Undifferentiated Carcinoma
		(a) Small Cell Carcinoma
		(b) Giant Cell Carcinoma
		(c) Spindle Cell Carcinoma
	(5)	Epidermoid Carcinoma
Nonepithelial:	(1)	Malignant Lymphoma
	(2)	Sarcoma
	(3)	Malignant Teratoma

The relative frequency of the epithelial tumors is noted in the review of 885 cases seen at the Mayo Clinic.[2]

	%	M : F
Papillary	61%	1 : 2.4
Follicular	18%	1 : 2.6
Medullary	6.5%	1 : 1.3
Undifferentiated	15%	1 : 1.3

The main clinicopathologic features are tabulated below:

	Rate of Growth (5 yr.Survival)	Age	Encapsulated	Metastasis
Papillary	Slow (73-93%)	Any; children	Rare	Lymphatic spread
Follicular	Slow (57-85%)	Slightly older	Yes - mixed	Infiltrative; vascular spread; distant metastasis (72%)
Medullary	Slow	Older	Yes	Lymphatic spread
Undifferentiated	Rapid	Older		Distant metastasis

PAPILLARY CARCINOMA

Papillary carcinoma of the thyroid is usually easily recognized by a mixture of papillary and follicular elements, invasion of adjacent thyroid tissue and psammoma bodies. Some tumors may be predominantely follicular (24% of cases), but local invasion, lack of capsule and presence of psammoma bodies indicate the tumor is best classified as papillary. A true papilla is differentiated from a pseudopapilla (seen in the follicular type) by the presence of a thin connective tissue core. Vascular invasion is unusual, but found in about 7-10%. Approximately 40-50% of papillary cancer will have psammoma bodies which are laminated, basophilic calcium deposits (5-100 micrometer dia). The tumor cells are cuboidal with amphophilic cytoplasm surrounding a central "ground-glass" nucleus. Mitoses are rare. Franssila classified solid tumors as papillary if ground-glass nuclei were present.[1] The ground-

glass effect has been shown by electronmicroscopy to be cytoplasmic enfolding.[4] A small number of papillary tumors are grossly cystic. The cyst fluid is clear or dark brown and papillary fronds are attached to a thick capsule. Other tumors may be solid and measure up to 10 cm. diameter.

A variety of histologic variations may be seen. Sometimes a fibrous scar is seen and the tumor is small (occult or sclerosing type). Squamous metaplasia is reported in 45% and oxyphilic cell nests may be seen in one third. Lymphatic spread is found in approximately 60-75% of patients at the time of initial diagnosis. Papillary hyperplasia is the major histologic problem. The best evidence of cancer is invasion of the stroma, capsule, vessels or lymphatics and the presence of psammoma bodies. Papillary carcinoma originates from normal thyroid, but follicular carcinoma is associated with non-neoplastic goiter. Also, papillary, but not follicular carcinoma has been reported to occur more frequently after irradiation.[1]

FOLLICULAR CARCINOMA

These tumors also have a variable histologic pattern, but invasion is required for the diagnosis. The follicles may be large, normal, small, or absent and the tumor may be solid and entirely oxyphilic. The tumor cells are relatively uniform and mitoses are rare. Invasion of capsule, vessels or lymphatics is essential in order to distinguish this from a follicular adenoma.[1,3] However, Woolner et al classified some tumors as non-invasive follicular carcinoma if severe epithelial changes were present.[2]

HURTHLE-CELL CARCINOMA

Frazel and Duffy reviewed 40 cases of this tumor, but it is not clear if all tumors were composed solely of Hurthle Cells.[5] Historically, it seems that Askanazy was the first to describe this cell in thyroid disorders, although Ewing referred to the cancer cells as Hurthle cells. However, the parafollicular cell (C-cell) was actually the cell described by Hurthle.[6] The origin of Hurthle cells in the thyroid remains a mystery as similar appearing cells are noted in the respiratory tract, pancreas, esophagus, pituitary and salivary glands.

Hurthle cells frequently are seen in many types of thyroid conditions, (hypothyroidism, follicular, and papillary carcinoma).[6] In the review by Horn of 75 cases of Hurthle cell lesions in the thyroid, 14 were involutional nodules, 27 were benign adenomas, and 34 were carcinoma.[6] Of the malignant forms of Hurthle cell tumors, the predominant histological pattern was follicular (5), papillary (4), adenocarcinoma (4), or giant and spindle cell (4). The incidence of this cancer is very low. In the series from Memorial, Hurthle cell carcinoma constituted 10% of thyroid cancer 1930-1949. The age range was 21-72 years.[5]

The Hurthle Cell Carcinoma is usually encapsulated and resembles a benign adenoma. Horn subclassified the malignant tumors into frank carcinoma (metastatic lesions) and malignant adenomas (histologically malignant).[6] Microscopically, the cells are large, opaque, and have finely granular acidophilic cytoplasm. Pleomorphism is variable and Horn emphasized it was of no particular significance. The tumor may form sheets of alveolar groupings and follicle forms. Vein invasion does not indicate a rapid course or metastasis. Metastases usually are skeletal (12/40), cervical nodes (10/40), lung (6/40), and remote distant metastases are noted (pancreas, dura, eye, nasal cavity, liver). In the series by Frazell & Duffy, 12 of 40 died of the cancer.

Electron microscopy shows that the cytoplasm is filled with mitochondria. This finding supports the follicular origin of Hurthle cells.[7] Some investigators suggest that the term "oncocytoid-like" be used for Hurthle cells unless electronmicroscopy demonstrates abundant mitochondria. The Hurthle cell was considered a degenerative and non-functioning cell yet recent histochemical evidence indicate that oncocytes are highly active cells. However, tissue from oxyphil adenomas was tested for thyroglobulin and thyroxine biosynthetic capacity and no activity was found.[8,9]

MEDULLARY CARCINOMA

This distinct clinical and pathologic form of thyroid carcinoma became widley recognized after the description by Hazard,et al in 1959.[10] Some reports were noted before and many after 1959, but a large series (82 cases) from the MD Anderson Hospital was reviewed by Ibanez,[11] and another large series of 139 cases was reviewed by Chong and Woolner etal.[12] This tumor is 5-10% of all thyroid carcinoma and 10% of these are familial. The sex ratio is generally found to be 1:1, but in familial cases, females predominate. The age of recognition is childhood to 80 years or older (2-80 yrs).[11,12] The median age of all tumors was 51 years, but was 29 years in the familial cases.[3]

The clinical symptoms are highly variable. Diarrhea was found in 32% (36 of 111) in the Mayo Clinic Series. A few patients have the carcinoid syndrome. In the Mayo Clinic Series, 50% noted a thyroid lump.[12] Only 54% of the patients were aware of a neck mass in the MD Anderson series whereas at Memorial, 90% of the patients had a neck mass or thyroid nodule.[17] The tumor was found incidentally in 27% (MD Anderson).

The tumor is bilateral in approximately one half and if unilateral, the distribution between right and left is equal. Of the familial cases, 7 of 9 had separate primary tumors in each lobe.[11] Grossly, the tumor may be 1 to 9.5 cm. diameter.[17] The cut surface is firm, gray-white to yellow. There may be some necrosis, hemorrhage or calcification. Microscopically a variety of patterns is seen and reflects the reason this variant was frequently placed in the anaplastic category. The patterns include: solid-alveolar (our case), streaming (spindle cells), ribbon (trabecular), rosette and some tumors had papillary structures.[15] The amount of amyloid stroma is variable (none to much). Amyloid is not required for the diagnosis whereas several authors claim cal-

citonin content is necessary.[18] A medullary carcinoma of the lung was described and immunoperoxidase staining indicated that the tumor did contain calcitonin.[13] On the other hand, amyloid is found in myeloma, renal cell carcinoma, and islet cell tumors. The medullary epithelial tumor cells varied from spindle, to plasmacytoid, to polyhedral to round in configuration. The cytoplasm was waterclear to eosinophilic. By silver stain, dendritic tumor cells may frequently be seen.[15] Also, argyrophil granules were seen to correlate directly with the amount of amyloid stroma.[15] This suggests that amyloid forms from polymerization of polypeptide hormones.

Furthermore, the presence of argyrophil granules is more specific for medullary carcinoma than the presence of amyloid.[15] Some reported cases of thyroid cancer associated with Cushing's Syndrome or bilateral pheochromocytoma may be medullary carcinoma with papillary differentiation. Ibanez quotes that amyloid was found in cultured cells although there were no secretory granules.[11]

The histogenesis of this tumor is from the parafollicular cell. These parafollicular cells arise from the ultimobranchial body which contain cells from the neural crest.[22] In aged bulls, 30% have ultimobranchial tumors and another 15-20% have hyperplasia of remnants.[21] Also, multiple endocrine tumors were found in the bulls available for autopsy. Biologic assay also indicated thyrocalcitonin activity in these thyroid tumors. The association of medullary carcinoma, and bilateral pheochromocytoma, suggested a defect in chromaffin system.[16] Pearse postulated that the APUD system accounted for this unusual relationship; namely that an error in development of the neural crest may result in widespread neoplastic changes in many endocrine organs.

In the Mayo Series, 34% developed recurrent tumors. In 90% of these patients, the tumor was recognized within 8 years of the primary diagnosis. Interestingly, recurrence was less common in patients with bilateral tumors.[12] Presence of cervical nodal metastases at actual surgery was associated with recurrence.[12] Metastases of medullary carcinoma were found in the following: Neck (80%), Mediastinum (30%), Lung (24%), and Liver (17%).[11]

Medullary carcinoma is associated with a variety of hormonal substances including thyrocalcitonin, prostaglandin, and serotonin.[13] Radioimmunoassay of calcitonin has proven of value in localizing medullary carcinoma.[14] Others have used serum histaminase as a marker for metastatic disease. Another unusual association is that of multiple endocrine adenomatosis type 2, with medullary carcinoma of the thyroid, bilateral adrenal cortical hyperplasia, pheochromocytoma, or parathyroid disease.[13] It has been estimated that 2-4% of patients with medullary carcinoma have a combination of endocrine tumors. Medullary carcinoma has been associated with Cushing's Syndrome due to production of an ACTH-like substance by the thyroid tumor.[20] Recently, medullary carcinoma of the mediastinum was described.[23,24] A confusing situation is that reported to be a metastatic nonchromaffin paragangliomatosis to the thyroid.[19] The histologic pattern is nearly identical to a medullary carcinoma, but with proper analysis, the calcitonin content should be zero in true paragangliomas.

Because the prognosis is better for medullary carcinoma than for anaplastic carcinoma, they should be separated. The 5-year survival is 71-80%; 10-year survival is 58-67% (Memorial-Mayo).[13,16] Total thyroidectomy with removal of lymph nodes is the recommended treatment.

ANAPLASTIC TUMORS

The anaplastic thyroid tumors have a far graver prognosis than the well-differentiated carcinomas from which they probably are derived.[24] The age at diagnosis is considerably older than the usual thyroid carcinoma (range 39-93; average 64 years). In a review of 53 cases (1932-1969) at University of Michigan Medical Center, each patient had a goiter of long duration.[24]

The histologic patterns seen are: spindle cell, giant cell (multinucleated), and a medullary pattern. Of the 53 cases in the Michigan series, 42 had well differentiated components usually follicular carcinoma. Thus suggesting that the anaplastic tumor derives from a well differentiated one. Upon careful review, many believe that spindle cell sarcomas (fibrosarcoma and leiomyosarcoma) are in fact spindle carcinoma.[24] Survival was poor and in the University of Michigan series, 52 of 53 died within 1 year of diagnosis.[24]

Small cell tumors include the malignant lymphoma of the thyroid, reticulum cell sarcoma and small cell carcinoma.[25] Rayfield et al reviewed 14 cases and concluded that there was no useful purpose in classifying them as carcinoma. They found no examples of primary carcinoma.

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DECEMBER 10, 1972 - CASE NO. 1

ACCESSION NO. 19749

MODERATOR'S DIAGNOSIS: Papillary Carcinoma with Transformation to Anaplastic Carcinoma, Thyroid

CLINICAL ABSTRACT:

The patient was an 83 year old woman with a cerebral vascular accident 1½ years prior to hospitalization for subtotal thyroidectomy. She also had diabetes mellitus and hypertension. She was treated with I-131. Eight months after surgery she had progessive dysphagia and inability to swallow any solids. An I-131 scan showed a mediastinal mass. She died 10 months after surgery and an autopsy showed a large intrathoracic tumor that displaced the esophagus and larynx.

MICROSCOPIC:

The tumor has a papillary component and invasive solid spindle cell component. In the area of transition between the two, squamous neoplastic elements are present, with well developed epithelial pearls. This region merges with anaplastic spindle cells. The papillary area is about 1 cm. diameter and there is a moderate amount of nuclear anaplasia with moderate hyperchromaticity and enlargement of nuclei. The spindle cell tumor extends without an apparent capsule into adjacent vessels and nerves.

DISCUSSION:

Transformation of long standing differentiated carcinoma of thyroid into rapidly fatal anaplastic carcinoma is a relatively rare event. Nevertheless, the occurrence of this transformation militates in favor of complete excision of papillary carcinoma if surgery is feasible. In this case, the physical condition of the patient was precarious at the time of the initial surgery.

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DECEMBER 10, 1972 - CASE NO. 2

ACCESSION NO. 19407

MODERATOR'S DIAGNOSIS: Medullary Carcinoma, Thyroid

CLINICAL ABSTRACT:

A 54 year old male was admitted because of a left neck mass. An I-131 scan showed a cold nodule. The serum calcium was 8.9 mgm%. A total thyroidectomy was done. The left lobe was nearly replaced by a 5 cm. nodule.

FOLLOW-UP:

The patient was clinically free of tumor as of July 28, 1971.

MICROSCOPIC:

The tumor is composed of fusiform and spindle-shaped neoplastic cells, disposed in sheets with fibrovascular trabeculae interspersed. The nuclei are round, elongated, pleomorphic and hyperchromatic. Mitotic figures are not prominent. Throughout the tumor are masses of pale pink structureless material resembling amyloid. Congo red stain is positive. This is an aggressive tumor which is infiltrating its capsule and it appears to be pentrating endothelial-lined spaces at the periphery.

DECEMBER 10, 1972 - CASE NO. 3

ACCESSION NO. 9613

MODERATOR'S DIAGNOSIS: Hurthle Cell Carcinoma, Thyroid, Metastatic to Vertebrae

CLINICAL ABSTRACT:

A 48 year old male was hospitalized for low back pain. Seven years previously (1950) a partial resection of a large substernal "thyroid gland" was performed. In 1955, an operation was performed from the lumbosacral spine which yielded the tissue for this case.

FOLLOW-UP:

Lost to further care.

MICROSCOPIC:

The tumor is composed of solid sheets and cords of cells with acidophilic cytoplasm and centrally placed nuclei. The cells are rather pleomorphic and the nuclei are hyperchromatic with prominent nucleoli. A distinct lack of cohesiveness of the cells is evident. The spicule of bone which is present undoubtedly represents residual vertebral tissue. This neoplasm in my opinion is a malignant Hurthle cell tumor.

DISCUSSION:

The tumor is named after the pathologist Hurthle, but actually the pink cells in the thyroid were described first by Askanazy, who initially observed them in the thyroid of a patient with Basedow's disease. Askanazy's cells are polygonal, cuboidal or columnar with an eosinophilic finely granular cytoplasm. Hamperl calls these same cells oncocytes.

In retrospect, it seems clear that the cells described originally by Hurthle were not acidophilic follicular cells, but rather were interfollicular cells. Most likely these interfollicular cells were the same elements described by Baber and by Nonidey, which today are known as the C-cells, associated with calcitonin production.

DECEMBER 10, 1972 - CASE NO. 4

ACCESSION NO. 19217

MODERATOR'S DIAGNOSIS: Anaplastic Carcinoma, arising from Follicular Carcinoma, Thyroid

CLINICAL ABSTRACT:

A 62 year old female was admitted with congestive heart failure and noted to have a large thyroid gland. Thyroid tests indicated euthyroid state. A subtotal thyroidectomy revealed 210 grams of thyroid tissue and local lymph nodes were free of tumor.

FOLLOW-UP:

She died 4 months later of heart failure and no tumor was found at autopsy.

MICROSCOPIC:

Broad bands of fibrous tissue separate this small cell anaplastic tumor into distinct nodules. Within the fibrous tissue, prominent intravascular penetration of tumor is seen. At the edges of the bands, small thyroid follicles are fading into the basophilic tumor. Small irregular follicles interspersed throughout appear to show transitions from follicular epithelium to the anaplastic type of cell which makes up the tumor. The tumor cells are deeply basophilic, extremely pleomorphic with scanty cytoplasm, and very dense hyperchromatic nuclei that are predominantely round. Mitotic figures are present. Many areas show necrosis and acute inflammation.

DECEMBER 10, 1972 - CASE NO. 5

ACCESSION NO. 15034

MODERATOR'S DIAGNOSIS: Medullary Carcinoma, Thyroid

CLINICAL ABSTRACT:

A 30 year old female was admitted for recurrent nodule in the left neck. Seven years earlier, a thyroid nodule was removed and called "angio-invasive follicular carcinoma with amyloid deposition." At the current admission, the total thyroidectomy specimen weighed 40 grams.

FOLLOW-UP:

A left radical neck dissection showed 7 of 22 lymph nodes contained metastatic tumor. Three years later she was well without evidence of recurrent tumor.

MICROSCOPIC:

There is a thin fibrous hyalinized capsule around this tumor which is divided into lobules by thin extensions of the capsule. Approximately 30% of the tumor is hyalinized pink stroma in clumps and strands. The intervening tumor cells are arranged in small masses and sheets. These cells are elongated and polygonal with small dark nuclei and pale cytoplasm. There is abundant vascularity and tumor is growing within spaces some of which appear to be lined by endothelium. This neoplasm is composed of small masses & strands of elongated and polygonal cells with small dark nuclei and pale cytoplasm. Separating the cells are numerous anastomosing fibrovascular septa. Interspersed are masses of pink hyaline material resembling amyloid, which proves to be Congo red positive.

DISCUSSION:

Medullary carcinoma has a poorer prognosis than the other forms of differentiated carcinoma of thyroid, i.e. papillary and follicular tumors. The cell of origin of this tumor is the C-cell or parafollicular cell which is the source of calcitonin. These cells in the human migrate in embryonic life from the last bronchial pouches to colonize the developing thyroid, parathyroid and thymus glands.

Recently Pearse has clarified the status of certain of the polypeptide-secreting endocrine cells, which he refers to as APUD cells. This designation is based upon the cytochemical characteristics of the cells as noted in the tables on p. 14 Pearse showed that the APUD cells arise from the neural crest early in embryonic development to colonize the primitive foregut and its derivatives. This brilliant research has clarified a great many puzzling and obscure relationships.

SIGNIFICANCE OF THE A-P-U-D CONCEPT

(Pearse)

"..THE REAL SIGNIFICANCE OF THE A-P-U-D CELL CONCEPT ... IS THAT IT PROVIDES A SATISFACTORY EXPLANATION FOR THE PECULIAR AND HITHERTO OBSCURE RELATIONSHIPS OF A NUMBER OF ENDOCRINE DISORDERS AND SYNDROMES. IT SUGGESTS, FURTHERMORE, THAT A NUMBER OF UNDESCRIBED SYNDROMES MAY BE AWAITING RECOGNITION..."

Pearse, A.G.E.
J. Histochem. Cytochem. 17:303-313, 1969.

PEARSE'S A-P-U-D CONCEPT

1. A group of apparently unrelated endocrine cells, some in endocrine glands and some in other organs, share a number of cytochemical and ultrastructural characteristics.

2. These characteristics (from which the term A-P-U-D is derived) indicate a common metabolic pattern and common mechanisms of synthesis, storage and secretion.

3. A-P-U-D cells produce low molecular weight polypeptide hormones and their characteristics reflect production and storage of precursors.

4. A-P-U-D cells have a common ancestor, the neural crest cell.

5. Progenitor cells from the neural crest colonize the primitive foregut and its derivatives (organs in which A-P-U-D cells are located).

6. Tumors of A-P-U-D cells may arise in any of these organs, and may secrete polypeptide hormones.

CYTOCHEMISTRY OF POLYPEPTIDE HORMONE-SECRETING CELLS OF THE A-P-U-D SERIES

(A) 1. Fluorogenic amine content (catecholamine, 5-HT or other)

(P) (U) 2. Amine precursor uptake (5-HTP, DOPA)

(D) 3. Amino Acid decarboxylase

4. High side chain carboxyl or carboxyamide (masked metachromasia)

5. High nonspecific esterase or cholinesterase

6. High phosphoglycerate dehydrogenase

7. Specific immunofluorescence

Pearse, A.G.E.
The cytochemistry and ultrastructure of polypeptide hormone-producing cells of the APUD series and the embryologic, physiologic and pathologic implications of the concept.
J. Histochem. Cytochem. 17:303-313, 1969.

NEURAL CREST ORIGIN OF THE A-P-U-D CELLS OF THE GI TRACT AND PANCREAS

Methods of tracing neural crest cells from their origin to their final destination:

(1) AUTORADIOGRAPHY ——————→ NEUROECTODERMAL CONTRIBUTION TO VISCERAL ARCH CARTILAGES

(2) HETEROSPECIFIC TRANSPLANT→ NEUROECTODERMAL ORIGIN OF C-CELLS IN THE ULTIMOBRANCHIAL BODY

(3) AMINE UPTAKE & FLUORESCENCE→ NEUROECTODERMAL ORIGIN OF C-CELLS IN THYROID GLAND

Using method #3, Pearse demonstrated that A-P-U-D cells in the mouse arise from neural crest, and are the precursors of all endocrine polypeptide-secreting cells of the adult pancreas, stomach, duodenum and small and large intestine.

Pearse, A.G.E. and Polak, J.M.
Neural crest origin of polypeptides (APUD) cells of the gastrointestinal tract and pancreas. Gut 12:783-788, 1971.

POLYPEPTIDE SECRETING ENDOCRINE CELLS
(Pearse's A-P-U-D Series)

PRODUCT HYPOTHETICAL, OR NOT CONFIRMED:

A-P-U-D CELL	HORMONE POSTULATED
STOMACH D	ENTEROGASTRONE
STOMACH EC	INCRETIN
STOMACH EC - LIKE	FUNDIN
INTESTINAL EC	VASOACTIVE INTEST. PEPTIDE
INTESTINAL I	MOTILIN
CAROTID BODY TYPE I	GLOMIN
MELANOBLAST	NIGRIN
ADRENAL A	MEDULLARIN
ADRENAL NA	NEURALEISTIN
LUNG P (FEYRTER)	PNEUMOKININ
UROGENITAL TRACT U	UROGASTRONE

Pearse, A.G.E.

The APUD cell concept and its implications in pathology. Pathology Annual, 1974, pp. 27-41, S.C. Sommers, Ed. Appleton-Century-Crofts, New York.

POLYPEPTIDE SECRETING ENDOCRINE CELLS
(Pearse's A-P-U-D Series)

PRODUCT CONFIRMED:

A-P-U-D CELL	HORMONE PRODUCED
PIPUITARY CORTICOTROPH	ACTH
PITUITARY MELANOTROPH	MSH
PANCREATIC ISLET BETA (B)	INSULIN
PANCREATIC ISLET ALPHA (A_2)	GLUCAGON
PANCREATIC ISLET DELTA (A_1)	GASTRIN
THYROID & EXTRATHYROID C	CALCITONIN
STOMACH G	GASTRIN
DUODENUM S	SECRETIN
DUODENUM D_1	GASTRIC INHIB. POLYPEPTIDE
INTESTINE EG (L)	ENTEROGLUCAGON

Pearse, A.G.E.

The APUD cell concept and its implications in pathology. Pathology Annual, 1974, pp. 27-41. S.C. Sommers, Ed. Appleton-Century-Crofts, New York.

DECEMBER 10, 1972 - CASE NO. 6

ACCESSION NO. 18670

MODERATOR'S DIAGNOSIS: Psammomatous Papillary Carcinoma, Thyroid

CLINICAL ABSTRACT:

This 14 year old female was noted to have a cold nodule in the thyroid. A 1 cm. hard nodule was found in the thyroid gland (1970).

FOLLOW-UP:

She was living and well as of October, 1972.

MICRCSCOPIC:

This thyroid gland appears to be the seat of a chronic thyroiditis characterized by small follicles, scanty cells, desquamated cells in some follicular lumens and abundant lymphocytic infiltration with formation of germinal centers. The unremarkable features of this thyroid are the widely dilated lymphatic spaces which contain tufts of papillary neoplasm in which there are numerous psammoma bodies. This case is unique and I am unaware of a similar case in the literature.

PARATHYROID

INTRODUCTION

NORMAL ANATOMY:

Prior to 1925, enlargement of the parathyroid glands was considered a compensatory mechanism in patients with osteitis fibrosa cystica. Removal of the glands would aggravate the bone disease so believed, the early researchers! A Viennese surgeon, Felix Mandl, removed a parathyroid adenoma from Albert, who was crippled by bone disease. Extracts of parathyroid failed to help his bone condition. In 1924, Mandl attempted successfully to transplant four parathyroid glands into Albert. Finally in desperation, Mandl resumed the adenoma and within one week Albert's white urine became clear!

The parathyroid glands were first described in 1852 after dissection of a rhinoceros (p. 56 Paloyan). There are usually four glands. Heinback, reported the number of normal glands in a large series of human dissections, and found five glands in 8% and six glands in another 8%.[2] Up to 10% are located inferior to the thyroid and some parathyroid glands have been found behind the esophagus. Minute clusters of parathyroid cells may be found in soft tissue and lymph node of the neck area. Other types of pharyngeal pouch cell differentiation has been noted. Occasionally squamous cells or salivary gland elements are seen within or adjacent to parathyroid tissue.

The parathyroid gland changes in size and content with age. The normal adult weight is 117.6 mgm (males) and 131.3 mgm (females).[3] In a child, the parathyroid gland is fairly uniform sheets of chief cells and there is little fat. In older adults, fat cells may compose 60-70% of the volume. Oxyphil cells are seen first during puberty.

PARATHYROID GLAND DISORDERS:

The widespread application of screening laboratory tests including serum calcium has resulted in earlier diagnosis and more frequent diagnosis of parathyroid gland dysfunction. Latimer found 62% of patients with hyperparathyroidism had unrelated symptoms and most were 51-70 years old.[4] The frequency of the mechanism of hyperfunction is apparently changing. In the past, parathyroid adenoma was most common (possibly 90% of tumors), but as of 1974, hyperplasia is catching up as a recognized cause of hyperparathyroidism. The best report is that by Esselstyn et al because only patients with four glands examined are tabulated.[5] Twenty percent of their patients had histologically abnormal parathyroid tissue in an abnormal location.

	Woolner (1952)	Cope (1966)	Black (1968)	Leedham (1970)
Adenoma	90%	30.6%	(22) 76%	(40) 46%
Primary hyperplasia	8.5%	15.1%	(7) 24%	(48) 54%
Secondary hyperplasia	-	-	- -	- -
Carcinoma	1.5%	4.3%	0 0	0 0

	Latimer (1972)	Kay (1973)	Esselstyn (1974)
Adenoma	(27) 90%	(73) 76%	(51) 47%
Primary hyperplasia	(3) 10%	(18) 18%	(49) 45%
Secondary hyperplasia	- -	- -	(7) 65%
Carcinoma	0 0	0 0	0 0

The histological criteria for separating parathyroid gland tumors was outlined by Roth.[11] Hyperparathyroidism may be caused by one or two benign tumors in separate glands (adenoma), a carcinoma, or hyperplasia of all four glands. Amyloid deposition has been documented in medullary carcinoma of thyroid, islet cell tumors, and also parathyroid tumors (hyperplasia and adenoma) (Leedham).[9] Of the nine patients with parathyroid tumors with amyloid, seven had a pluriglandular syndrome. The amyloid was intrafollicular.

ADENOMA

The parathyroid adenoma is tan, rather than yellow because of the lack of fat. Interestingly, the other glands are not atrophic. Histologically, the adenoma may be sheets and cords or nodules of packed cells. The cells may be dark or light chief cells, oxyphil cells, or transitional oxyphil cells, or water clear cells. Water clear adenomas are larger.[6] There are no mitotic figures, but some adenomas show giant nuclei.[6] A thin fibrous capsule may be seen, but adjacent normal or "atrophic" parathyroid tissue must be identified in adenomas (Roth). Kay noted that without the capsule, hyperplasia and adenoma may be histologically identical. Some adenomas will have hemorrhage and rarely calcification.[6] Some cystic glands have been reported as hyperfunctioning. Kay reported three cases of multiple adenomas of which there were three adenomas in one patient (with medullary carcinoma of the thyroid). An oxyphil adenoma with hyperparathyroidism was of interest because many believe the oxyphil cell is resting.[12] Sometimes hyperplasia may be a nodule within one gland

and this may confuse the unwary histologist.[3] The distribution of cell types in 115 adenomas reviewed by Woolner et al is:[6]

Chief Cell	43%
Transitional Water Clear	22%
Water Clear	4%
Oxyphil	3%
Mixed	29%

HYPERPLASIA

A single hyperplastic gland may be indistinguishable from an adenoma (Roth). Primary chief cell hyperplasia, first described in 1958 by Cope et al, was divided into three categories by Black and Haff.[12] The groups were: (1) Classic (all four glands diffusely enlarged), (2) "pseudoadenoma" (large nodular glands with smaller hyperplastic ones) and, (3) "occult" (microscopic diagnosis of hyperplasia). Of 39 cases of primary chief cell hyperplasia at Barnes Hospital, division into the three groups was about equal (13, 12, 14 each). Roth points out that patients in category three may have adenomas in unexamined parathyroid glands. The gland sizes may be symmetrical or extremely asymmetrical. Cyst formation is common.[6]

Primary water clear cell hyperplasia produces large glands (smallest total weight was 2.85 gm.)[11] The uniform, multivacuolated cells with basally oriented nuclei are found in sheets, cords or acini, Secondary hyperplasia due to renal failure usually is recognized by a mixture of cells.[5]

CARCINOMA

Parathyroid carcinoma can be recognized grossly by the aggressive growth into adjacent tissues and by metastasis. The tumor may be tough because of fibrosis. The cell type may be chief cells or oxyphil cells. Mitotic figures are usually found.

At Massachusetts General Hospital, parathyroid carcinoma was 4% of primary hyperparathyroidism. Castleman & Schrantz reviewed 20 cases (since 1930) and added consultation cases for a total of 70 cases.[14] The average age at diagnosis was 44.3 years (age range 13-84 years, 84% were 3-6th decade). The sex ratio was equal. Clinical symptoms and signs were:

Bone Disease	62%
Neck Mass	31%
Urolithiasis	30%
Renal Disease	21%

The tumor size was 3.3 cm. average diameter (range 1.3 - 6.2 cm.) and weight was 12.0 gram (0.8 - 42.4 grams). The histologic criteria were of malignancy.

Fibrous Trabeculae	90%
Mitotic Figures	81%
Capsular Invasion	67%
Blood Vessel Invasion	12%

Cellular atypia and variation was in fact a criterion in favor of adenoma.[14]

PROGNOSIS:

Many reports in older literature emphasize that multiple surgeries may be necessary to eradicate all parathyroid disease. Therefore, identification of four glands at the initial surgery was recommended.[15] If carcinoma is found, there is reason to resect the primary site and local nodal metastasis. Of the patients with parathyroid carcinoma reported by Castleman and Schrantz, 31% died within five years and more than 29% were alive without disease at five years.

Hypercalcemia may be a clinical problem in the patient with metastases of parathyroid carcinoma. Death occurs secondary to hypercalcemia usually rather than widespread tumor.[3] Surgical excision is recommended for the functioning metastases and persistent tumor because control of hypercalcemia may be achieved.[16] Sometimes metastases are surgically inaccessible and medical therapy is the sole treatment. Hill, et al reported that long term administration of salmon calcitonin failed to control hypercalcemia due to persistent parathyroid carcinoma.[17]

NON-PARATHYROID TUMORS PRODUCING HYPERPARATHYROIDISM

A review of this subject and nine unpublished cases were reported by Omenn, Roth and Baker.[18] Seventy-three cases were tabulated. The cell types were:

Renal Cell Carcinoma
Transitional Cell Carcinoma, Renal Pelvis
Squamous Cell Carcinoma, Lung
Squamous Cell Carcinoma, Vulva
Squamous Cell Carcinoma, Cervix
Squamous Cell Carcinoma, Penis
Unspecified Carcinoma, Lung
Adenocarcinoma, Pancreas
Dysgerminoma, Ovary
Leiomyosarcoma, Uterus

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DECEMBER 10, 1972 - CASE NO. 7

ACCESSION NO. 19396

MODERATOR'S DIAGNOSIS: Carcinoma, Parathyroid

CLINICAL ABSTRACT:

This is a 54 year old man with renal calculi. The serum calcium was 14 - 16.5 mg.% and a serum parathyroid hormone level was markedly elevated. An 11 gram parathyroid nodule was removed.

FOLLOW-UP:

One year later the patient was well and the serum calcium was normal for several months following surgery. Approximately one year later, the serum calcium was elevated.

MICROSCOPIC:

The low power shows a tumor with a fibrous capsule that is infiltrated by the fairly uniform, pale neoplastic cells. In some areas, these cells infiltrate adjacent fat and skeletal muscle. The tumor is separated into lobules by broad fibrous trabeculae. The cells are fairly uniform with pale cytoplasm, but a few are larger and have prominent nucleoli. Occasional mitotic figures are seen. Many small blood vessels are present within the tumor and a few areas are suggestive of vascular invasion. On one slide in the contributor's set, there are tumor cells within the perineural sheath.

DISCUSSION:

Although histological proof of malignancy in parathyroid tumors may be difficult, the features that suggest malignancy are (1) large size, (2) p. - o. elevation in serum calcium, (3) infiltration of tumor into capsule and adjacent tissue and (4) tumor within vessels and/or perineural lymphatics.

DECEMBER 10, 1972 - CASE NO. 19

ACCESSION NO. 19891

MODERATOR'S DIAGNOSIS: Acidophilic Adenoma, Pituitary

CLINICAL ABSTRACT:

This 54 year old man was committed to a state hospital because of mental changes. He was noted to have acromegalic changes. During hospitalization, a large gastric ulcer was found and removed. The gastric mucosa showed hyperplastic parietal cells. The serum calcium was 14.6 and a blood sugar was 36 mg.%. He died and the autopsy findings were: (1) Pituitary tumor = 5.0 cm. diameter, (2) thyroid nodule - 4 cm. diameter, (3) parathyroid glands - 3 adenomas, (4) pancreatic islet cell tumor 2.6 cm. diameter.

MICROSCOPIC:

The remaining pituitary gland is compressed by a tumor composed of sheets of eosinophilic polygonal cells. The nuclei are relatively uniform and mitotic figures are lacking.

DISCUSSION:

An H & E stain is the best way to demonstrate acidophils because these cells contain a protein hormone that stains well with eosin. The many hormones of the anterior pituitary include: ACTH, TSH, FSH and prolactin. Of the several stains available, the PAS-Orange G, and performic acid Alcian Blue-Orange G are useful. The mucopolysaccharides stain well with the Alcian Blue after performic acid and the PAS stains the carbohydrate. Cells elaborating growth hormone stain with Orange G and the pituitary tumor in this case takes the stain.

The parathyroid glands in this case are difficult to classify. According to one authority, if one or two glands are large, then the diagnosis is adenoma. Four enlarged glands are diagnosed hyperplasia and three large glands are "impossible"! The microscopic appearance of the parathyroid glands shows a mixture of water clear cells and chief cells forming sheets and trabeculae. Unfortunately for the histopathologist, sometimes an enlarged parathyroid gland is divided so that part is analyzed by researchers. It is always possible that the gland which is sent to the research lab is the part that has the remnant of gland which would allow the distinction between adenoma and hyperplasia.

The pancreatic tumor is a typical islet cell tumor with ribbons of cells with hyalinized stroma. Sometimes the stroma contains amyloid.

The thyroid nodule shows a follicular pattern with nuclear crowding, papillary formation and ground glass nuclei. On this basis, the diagnosis is follicular carcinoma.

In the presence of the multiple endocrine tumors in this patient, we may call this multiple endocrine adenomatosis.

DECEMBER 10, 1972 - CASE NO. 21,
22 and 23

ACCESSION NO. 19755

MODERATOR'S DIAGNOSIS: End Stage Disease, Kidney (Case 21)
Hyperplasia, Parathyroid (Case 22)
Osteitis Fibrosa Cystica, Vertebrae (Case 23)

CLINICAL ABSTRACT:

This 20 year old female had chronic renal disease and dialysis. A biopsy showed chronic pyelonephritis, and two episodes of toxemia. She died on the 10th hospital day with renal failure and the serum calcium was 9.3. At autopsy, the kidneys weighed 25 and 18 grams. The cortical surfaces were coarsely granular. The number of calyces was said to be normal.

MICROSCOPIC: (Case 21)

The low power of the kidney shows widespread interstitial scarring, fibrotic glomeruli, periglomerular fibrosis, residual tubules which are hypertrophied, other areas of atrophic tubules, and a few relatively normal glomeruli. Many foci of lymphocytes, foci of calcification and some acute inflammation can be seen. Clearly this is some form of "end stage" kidney disease, consistent with chronic pyelonephritis though not diagnostic.

All four parathyroid glands were enlarged and were creamy-yellow rather in contrast to the chocolate color of adenomas.

MICROSCOPIC: (Case 22)

The patterns of the enlarged glands are variable, with masses and clusters of chief cells, water clear cells and some foci of oxyphil cells. Adipose cells are virtually absent. No residual uninvolved parathyroid tissue is evident at the periphery.

MICRCSCOPIC: (Case 23)

Under the influence of excess parathyroid hormone, there is widespread resorption of bone, with enlargement of haversian canals and surfaces of trabeculae. At the same time new bone is laid down. The vertebrae show remodeling with thickened trabeculae having extensive and fibrous replacement typical of osteitis fibrosa cystica (von Recklinghausen's disease of bone). The marrow also is widely replaced by fibrous tissue. The polarized light shows woven bone characteristic of remodeling and an appearance suggestive of extensive osteoid deposition.

DISCUSSION:

Chronic renal disease is well known to produce parathyroid hyperplasia. In this situation, all four glands are functioning and enlarged. If the hyperplastic tissue becomes autonomous, the condition is known as tertiary hyperplasia and the serum calcium is elevated. In this case, the calcium was normal. The chronic excess in secretion of parathormone which is stimulated by the loss of calcium due to renal failure and retention of phosphate leads to bone resorption and osteitis fibrosa cystica, with formation of brown tumors. The brown tumor may become large and may simulate giant cell tumor of bone.

ISLET CELL TUMORS

INTRODUCTION

The true incidence of pancreatic islet cell tumors is unknown, although 1.5% of autopsies may reveal an islet cell adenoma.[1] Most of these tumors are clinically inapparent, yet there are five distinctive clinical syndromes related to them. It is generally believed that each tumor is derived from a single islet cell type. However, some tumors produce several hormones. For example, in the series of 17 gastrinomas reported by Creutzfeldt, 6 of 10 produced insulin.[2] The clinical syndromes and the cell of origin are listed below.

Clinical Syndrome	Islet Cell
Hyperglycemia (glucagon)	alpha
Hypoglycemia (insulinoma)	beta
Carcinoid	non-beta
Zollinger-Ellison (gastrinoma)	non-beta or delta or alpha I
Water Diarrhea, Hypokalemia	non-beta

INSULINOMA

The commonest clinical syndrome associated with an islet cell tumor is due to insulin release. The patient will have hypoglycemic (glucose 40 mgm%) episodes with tremor, hunger and sweating. Unfortunately for diagnostic purposes, up to 50% of patients have normal insulin levels. Recently, it has been shown that proinsulin may be increased in such patients.[3] Islet cell carcinomas may present as obstructive jaundice in about 15% of cases. Single adenomas account for 80% of insulinomas. Approximately 10% have metastases at the time of diagnosis and 10% of patients have multiple adenomas or diffuse hyperplasia. Although, there are more islet present in the tail of the pancreas, islet cell adenomas are evenly distributed in body, head and tail.[1]

ZOLLINGER-ELLISON SYNDROME

The second commonest clinical syndrome associated with islet cell tumor is the Zollinger-Ellison Syndrome. Some suggest that gastrinoma is preferred term.[4] These tumors may be found in the pancreas, duodenum or stomach.[4] Recently, a case of multifocal hyperplasia of gastric antral argyrophilic cells was found to account for a Zollinger-Ellison Syndrome.[5] Abdominal pain is the main clinical problem and is typically present more than one year. Diarrhea is seen in about 1/3 to 3/4 of patients.[4] The atypical location of an ulcer is

a clue to the diagnosis, but in 60-75% of cases a single gastric or duodenal ulcer is found.[6] If plasma gastrin levels cannot be measured, a 12 hour overnight gastric secretion of 1000 ml. or more suggests the diagnosis (85% positive).[1] Calcium infusion over three hours results in marked increase in serum gastrin.[4] Also, "resting" serum gastrin is usually elevated.

Other endocrine tumors are found in 10-40% of patients with Zollinger-Ellison Syndrome (Multiple Endocrine Adenomatosis). The islet cell tumors producing Zollinger-Ellison Syndrome are commonly malignant (60%), but 20% of patients have diffuse hyperplasia or multiple adenomas.[1,7] Less than 25% of tumors are accessible by surgery. Therefore, total gastrectomy is frequently performed for treatment.[8] However, the recently described antral gastrin producing hyperplasia may be treated with less surgery. To provide long term study of Zollinger-Ellison Syndrome, we recommend reporting documented cases to Dr. Stuart D. Wilson, Zollinger-Ellison Tumor Registry, Division of Surgery, Medical College of Wisconsin, Milwaukee, Wisconsin 53226.

GLUCAGON

The rarest of the functioning islet cell tumors is the glucagon secreting tumor which results in hyperglycemia. Several other hormones have been reported associated with islet cell tumors including Cushing's Syndrome (ACTH-like secretion).

CARCINOID

Carcinoid tumors of the pancreas are rare. These tumors are rapidly fatal (mean survival 15 months) and thereby differ from other intestinal carcinoid tumors. Morphologically, the carcinoid tumor is typical and special stains show argyrophilia, but the usual histochemical stains for islet cells are not positive.[9]

MORPHOLOGY OF ISLET CELL TUMORS

By light microscopy and H & E stains, islet cell tumors cannot be recognized by cell type. Special histochemical stains may separate some tumors into cell type, but many tumors fail to take the stains possibly due to loss of specific secretory product during fixation. Specific morphologic patterns were correlated with several cell types.[10] If a gyriform pattern was seen, then the tumor was alpha or beta cell in origin. Glandular formations were associated with Zollinger-Ellison Syndrome or diarrhea syndrome. There were no distinctive features in the series by Greider, Rosai and McGuigan that indicated metastatic potential.

Ultrastructural studies have been useful in separating some cell types because the secretory granules may be distinctive.[10,11] There was a vague cor-

relation between the absence of granules and the severity of the clinical syndrome.[4] Some investigators have subdivided the gastrinomas and insulinomas into several categories based on types of granules.[2]

ISLET CELL CARCINOMA

Islet cell carcinomas are usually nonfunctional(60%).[12] In a review of 30 cases from Memorial, the clinical syndromes were: Hypoglycemia - 4, Hyperglycemia - 5, Zollinger-Ellison - 3 and the remaining 18 cases had no apparent clinical syndrome. The age range (all cancer) was 8-76 years. The tumors were 2-12 cm. diameter and the soft tumors had hemorrhage and necrosis. Histologically there was a pseudocapsule in most and splenic and portal vein invasion was noted in four cases. Three main patterns were reported: solid, trabecular and mixed.[12]

An exhaustive review of the familial MEA Syndrome was presented by Ballard, Frame and Hartsock and a simplified scheme is shown below:[13]

MULTIPLE ENDOCRINE ADENOMATOSIS (MEA)

TYPE I	TYPE II
1. Parathyroid Adenoma or Hyperplasia	1. Parathyroid Adenoma or Hyperplasia
2. Islet Cell Adenoma or Carcinoma	2. Pheochromocytoma
3. Pituitary Adenoma	3. Medullary Thyroid Carcinoma
4. Other Tumors	4. Other Tumors

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DECEMBER 10, 1972 - CASE NO. 10

ACCESSION NO. 17724

MODERATOR'S DIAGNOSIS: Carcinoid-Islet Tumor, Pancreas

CLINICAL ABSTRACT:

This 73 year old female with chronic heart disease, ascites, anemia and urine test positive for 5-hydroxyindole acetic acid. A laporotomy indicated an unresectable tumor in the head of the pancreas.

FOLLOW-UP:

An autopsy performed 6 days after surgery showed a large tumor in the head of the pancreas. The mass compressed the portal and splenic veins. No metastatic tumor was found..

MICROSCOPIC:

The low power shows many fibrous strands dividing the tumor into lobules and separating the adjacent normal pancreatic acinar and ductular elements. The tumor cells found within the lobular patterns are small, moderately pleomorphic with eosinophilic cytoplasm and moderately small nuclei. There is little mitotic activity. The tumor cells within the lobules are arranged in ribbons, acini, and in some places as irregular masses. This looks like an ordinary islet cell tumor. The argentaffin stain shows no granules.

DISCUSSION:

This islet cell tumor was found in the duodenal-pancreatic area of a patient with carcinoid syndrome. These tumors are called carcinoid-islet cell tumors.

DECEMBER 10, 1972 - CASE NO. 11

ACCESSION NO. 13811

MODERATOR'S DIAGNOSIS: Islet Cell Carcinoma, Metastatic to Liver; Probable Zollinger-Ellison Syndrome

CLINICAL ABSTRACT:

This 64 year old man had abdominal pain. One year earlier he had a neck mass removed which was called "undifferentiated carcinoma". In search of a primary, a thyroidectomy showed a follicular adenoma. A duodenal ulcer was found by radiograph.

FOLLOW-UP:

He died on the 4th hospital day. At autopsy, the liver had multiple gray-white umbilicated tumor nodules. A 4.5 cm. diameter tumor was noted in the distal tail of the pancreas. The stomach had a 0.5 cm. ulcer on the lesser curvature and there were two duodenal ulcers, one of which perforated anteriorly.

MICROSCOPIC:

At low power, most of the tumor is composed of dense, fibrous hyalinized stroma with interspersed nests of small eosinophilic fairly uniform cells. Some areas are quite cellular and here the cells form an organoid pattern resembling islet tissue. The adjacent liver is compressed by this large tumor nodule.

DISCUSSION:

Sections of the pancreatic tumor are similar to the hepatic metastasis. Also, there is perineural invasion by tumor. It is very difficult to evaluate the malignancy of islet cell tumors, but we know the present case is malignant because of the presence of metastasis. In the Zollinger-Ellison Syndrome, it is helpful to have clinical evidence for unrelenting gastric hypersecretion. The pancreatic tumor may be solitary or multiple and some patients have diffuse islet hyperplasia. Surgical resection of the pancreas may cure some patients of the syndrome. Metastasis of these islet cell tumors is proof of their malignancy and apparently the metastatic lesions can also function. The metastasis in a lymph node may look very benign. It is impossible to tell by H & E that these cells contain alpha granules.

The stomach is altered in the Zollinger-Ellison Syndrome. The gastric mucosa is thickened and the rugae are thickened. The gastric glands, usually include mucous secreting cells in the upper 2/3, but in the Zollinger-Ellison Syndrome the glands are entirely enzyme secreting cells. In the conference case, there are no mucus secreting cells and therefore this patient probably had a functioning islet cell tumor and the Zollinger-Ellison Syndrome.

DECEMBER 10, 1972 - CASE NO. 12

ACCESSION NO. 19100

MODERATOR'S DIAGNOSIS: Islet Cell Tumor (beta cell type), Pancreas

CLINICAL ABSTRACT:

This is a 34 year old man with intermittent hypoglycemia. A distal pancreatectomy was done and a 1.3 cm. diameter gray nodule was found within the pancreas.

MICROSCOPIC:

The low power shows a tumor which resembles an overgrown islet subdivided by a few thin hyalinized fibrous bands. Adjacent pancreas is compressed. The tumor is composed of uniform polyhedral cells with abundant granular cytoplasm and small nuclei with prominent nucleoli. Trabecular or winding ribbon pattern is a prominent feature.

DISCUSSION:

The fingers of tumor cells interdigitating with adjacent pancreas are not indicative of malignancy. By morphological criteria, this is an islet cell tumor, but the cell type is not demonstrated by H & E staining. The clinical story clearly indicates this must be a beta cell tumor secreting insulin. The Gomori aldehyde fuchsin stain when properly done may differentiate some of the islet cell types; the beta cells have purple granules in the cytoplasm. Autopsy tissue, poorly fixed tissue and other technical problems frequently preclude adequate staining. Electron microscopy is the best way to distinguish the islet cell types, but promptly fixed fresh material is essential. The alpha cells have large dense granules and beta cells have distinctive crystals. The delta cells have small pale granules. Therefore, the electron microscopist can tell what type of cell is present in the islet cell tumor.

What is the origin of pancreatic islet cell tumors? Some appear to have originated as an islet which enlarged to form the tumor. Other islet cell tumors appear to originate from the pancreatic ducts. That this can occur is not surprising, since the pancreas originates from a diverticulum of the GI tube. In humans, I have observed groups of islet cells in close relation to pancreatic ductal structures. At times, one can see islet cells interspersed with columnar duct cells. In lower animals (e.g. the mouse) the islet may bud from the ducts. In the present case, the islet cell tumor lies close to large ducts. In passing, other tumors which may cause hypoglycemia include retroperitoneal mesenchymal tumors (CTTR Conference 1956, Case 26) and hepatomas.

ADRENAL CORTICAL TUMORS

INTRODUCTION

The diagnosis of adrenal tumors usually begins with clinical suspicion because of hormonal changes. However, non-functioning adrenal tumors are recognized in two forms: (1) Incidental findings at autopsy as small to very large nodules, or (2) clinically evident abdominal masses that frequently are described as malignant.[1] The exact frequency of these functioning and non-functioning tumors (adenoma vs. carcinoma) is difficult to assess. In a review of 62 patients studied at the Peter Brent Brigham Hospital between 1930 and 1970, the following tumors were found by surgical removal:[2]

Adrenal Cortical Adenoma (Conn's Syndrome)	23%
Adrenal Cortical Adenoma (Cushings Syndrome)	24%
Adrenal Cortical Carcinoma	29%
Adrenal Medulla-Pheochromocytoma	16%
Adrenal Cyst	8%

The clinical and pathologic features of each syndrome are interesting, but the histopathologist will not be able to predict which tumors are functioning. Adenomas consisting of clear and compact cells may cause Cushing's Syndrome or be non-functioning. Also, an adenoma of compact cells, the cell capable of producing all three cortical hormones (corticosteroids, androgens and estrogens), may produce virilism or occasionally Cushing's Syndrome or appear as an adenoma associated with stress (Symington p. 159)! Probably the most reliable criterion of adrenal tumor function is to witness atrophy of the contralateral adrenal gland. Interestingly, some adrenal tumors arise in ectopic adrenal tissue.[3]

NON-FUNCTIONING ADRENAL CORTICAL TUMORS

If the adrenal cortical tumor is non-functioning, and detected in life, then it is usually greater than 12 cm. diameter.[3] One patient with a large apparently non-functioning adenoma was considered a renal cell carcinoma by clinical examination.[3] However, adrenal insufficiency was found post-operatively and the authors recommended suspecting adrenal insufficiency in patients with shock following removal of a tumor from the upper pole of the kidney.

FUNCTIONING ADRENAL CORTICAL TUMORS

I. CUSHING'S SYNDROME: This is the commonest example of adrenal hypercorticalism. In a review of 81 patients with Cushing's Syndrome, the following distribution of tumors was noted:[4]

A.	Bilateral adrenal cortical hyperplasia (69/81)		85%
	(1) Simple hyperplasia	62%	
	(2) Adenomatous or nodular hyperplasia	12%	
	(3) Hyperplasia associated with non-endocrine tumor	11%	
B.	Benign tumors of adrenal cortex		6.2%
C.	Malignant tumors of adrenal cortex		8.6%
			99.8%

The distinction between the different types of tumors is suggested by the weights: Simple hyperplasia - 95% weight less than 12 grams each; Adenoma - (5/8) weight more than 12 grams. In 59/69 patients with bilateral adrenal cortical hyperplasia, the adrenal weights were within 2 grams of each other.

Simple bilateral hyperplasia: The cortex is thicker than normal and shows an outer yellow layer with an inner brown layer is removed surgically, but in glands removed at necropsy, only a uniform brown color is seen. The inner brown layer are compact cells that are the zona reticularis and the outer yellow layer are wide clear cells of the zona fasciculata. The post-mortem gland usually shows compact cells extending medulla to capsule or to the zona glomerulosa. After treatment with op'DDD in two patients, the adrenal cortical layers presented a confusing histological picture with clear and compact cells scattered and no demarcation was noted.[4]

Bilateral "adenomatous" or nodular hyperplasia: One or more cortical nodules in one or both adrenal glands are the hallmark of this lesion. Usually the yellow nodule is more than 2.5 cm. in diameter. Microscopically, clear lipid containing cells like those of the zona fasciculata are the main cell in the nodule. The adjacent adrenal cortex is always hyperplastic. At post mortem, glands with adenomatous hyperplasia show compact cells in the nodules.

Bilateral hyperplasia and non-endocrine tumors: The cortex is uniform, brown and compact cells fill the cortex. Some foci of clear cells are found and frequently metastatic tumor is seen. In the series of Neville and Symington, 8/9 were males and there were 8 bronchial carcinomas and 1 argentaffin stomach tumor.

Benign tumors of adrenal cortex: There were four females and one male in the five cases of Neville and Symington.[4] The tumors weighed less than 40 grams, had a capsule, and were attached to an atrophic adrenal gland. Clear cells of the zona fasciculata type were the major cell and the few foci of compact cells (microscopically).

Cushing's Syndrome: Less commonly this syndrome is due to adenoma. Bilateral hyperplasia is discussed above. The ultrastructure of an adenoma producing Cushing's Syndrome showed cytoplasmic inclusion.[9]

II. ALDOSTERONISM: Neville and Symington reported 18 cases of primary aldosteronism.[7] The tumors were usually small (usually less than 6 grams and occurred at 31-50 years, slightly more frequent in female - 14/18). In females, the left gland is more frequently involved, but in males each side is equal in frequency. One tumor was 2032 grams (a carcinoma). The microscopic pattern was variable. Clear cells were the most common pattern, but the compact cells were also seen in some. All the benign tumors had a fibrous capsule, but one case was a malignant tumor. In the series reviewed, 91% were single, and if multiple tumors they were limited to one gland. Examination of the remaining adrenal cortex shows focal or diffuse hyperplasia of the zona glomerulosa and this feature was missed by earlier reporters.[7] There are more than ten cases of adrenal cortical carcinoma producing aldosteronism reported.[8]

III. VIRILIZATION: The ultrastructure of an androgen producing adenoma showed cytoplasmic inclusions similar to the spironolactone bodies.[10] The patient was an 18 year old girl with virilization and a large partly calcifed mass in the right adrenal region. The tumor weighed 730 grams and was circumscribed, encapsulated and no residual adrenal tissue was seen. The tumor cells were closely packed polygonal compact cells. Most of the cells had round or irregular lipofuschin granules. Whereas spironolactone bodies have been noted by light microscopy in patients treated with aldactone, and none were seen in the reported case.

IV. FEMINIZING ADRENAL TUMORS (ADENOMAS & CARCINOMAS): Fifty-two patients with this syndrome were reported.[11] Bilateral gynecomastia was the most common symptom and was noted in males 25-50 years of age. Testicular atrophy and decreased libido was reported in about one-half. The tumors were usually large and palpable in 50%. Most of these tumors were malignant, but some were adenomas.[11]

BLACK ADENOMAS

This rare tumor probably arises from cells of the zona reticularis and/or cells at the interface of the reticularis and fasiculata.[12] A dark mass in the adrenal is more likely a myelolipoma, melanoma, hemangioma, or hematoma. The tumor described by Macadam was not encapsulated and by light microscopy there were numerous dark cytoplasmic granules. The cells resembled only vaguely the compact cells of the reticularis. The dark granules were thought to be lysosomal in origin.

ADRENAL CORTICAL CARCINOMA

In the review by Neville and Symington of Cushing's Syndrome there were seven patient (six females) with carcinoma.[4] All tumors were palpated or seen radiographically. All tumors had a thin compressed fibrous capsule that had projections within the tumor that formed smaller nodules. Many nodules were friable, soft, hemorrhagic, necrotic and there were cystic areas. Microscopically, all the functioning tumors reported by Neville were composed of compact cells with eosinophilic cytoplasm and prominent nucleoli. Huvos, et al found the same correlation, but one functioning tumor was composed of clear cells. Some tumors were sarcomatoid. There was considerable nuclear and cellular pleomorphism with giant cell formation. Lewinsky, et al correlated degree of pleomorphism with prognosis.[14] Although no blood vessel invasion was seen, there were tumor cells within vessels. In 4/9 cases the criteria of malignancy were: large vesicular nuclei, extensive necrosis and large size. Mitotic activity was also uniformly increased in the review of cases by Huvos.[13]

In the series of 62 adrenal tumors at Peter Brent Brigham Hospital, there were 18 adrenal cortical carcinomas.[2,15] The Memorial Hospital series of 34 patients was described in 1970 by Huvos, Hujdi, Brasfield and Foote.[13] Adrenal hyperfunction was present in (18/34) 53% as noted by symptoms or lab studies.

In the Memorial group, all but one patient with clinical symptoms of function had elevated urinary 17 Ketosteroid and 17-hydroxycorticosteroid excretion. The patients with non-functioning carcinomas were older (average 18 years greater) and more likely male. The average time of onset of symptoms and death was 2.6 years (male) and 3.3 years (females) whereas the time of diagnosis was 0.7 - 0.9 years after the onset of symptoms.

Syndromes of Adrenal Cortical Carcinoma (1930-1970)

	PBB		MEMORIAL	
Cushing Syndrome and Virilization	(11)	61%	(6)	33%
Virilization	(4)	22%	(9)	50%
Feminization	(2)	11%	(1)	6%
Aldosteronism with Carcinoma	(1)	5%	-	-
Precocious Sexual Development	-	-	(2)	11%

The tumor was palpated in 12/18 and lab studies are tabulated.

Lab Values in Adrenal Cortical Carcinoma

Elevated Urinary 17-OH CS & 17-KS	(8/18)	45%
Elevated Urinary 17-KS only	(3/18)	17%
Elevated Urinary 17-OH CS	(1/18)	6%
Response to ACTH	(2/13)	15%
Dexamethasone Suppression	(1/6)	17%

Therefore screening urine studies were indicative of adrenal tumor in about 2/3 and suppression and stimulation studies usually indicated an autonomous tumor.

The primary tumor was more frequently on the left in the largest series reported (Huvos).[13]

Gross Features of Adrenal Cortical Carcinoma

		Neville et al	Huvos et al	Bennet et al
Side	Left	3	22	10
	Right	4	12	8
Size	Range	Not stated	4-40 cm.	2.5 - 21 cm. (10.1 cm. ave.)
Weight	Range	139-4040	Not stated	Not stated

Prognosis of adrenal cortical carcinoma is poor. Only 3 of 34 patients in the Memorial series were alive at the time of publication. One of the three patients had widespread metastases for more than 6 years. Of the 20 patients reported by Lewinsky et al, 14 had metastases at death.

Metastases

	Neville et al		Huvos et al		Lewinsky	
Lung	(6/9)	67%	(10/25)	40%	(5/14)	35%
Lymph Node	(4/9)	45%	(10/25)	40%	(2/14)	14%
Liver	(3/9)	33%	(15/25)	60%	(6/14)	42%
Brain	(2/9)	22%	0	0	0	0
Bones					(6/14)	42%
None	(1/9)	11%	0	0	(6/14)	42%

ADRENAL CORTICAL CARCINOMA WITH UNUSUAL FEATURES

A virilizing adrenal cortical carcinoma in a 4 year old female was treated with op'DDD.[5] She improved, but the tumor recurred and metastases were found and the tumor became a feminizing one.

Feminizing adrenal cortical carcinoma in men are unusual. Nine cases were summarized by Gabrilove et al.[6] Usually this syndrome is found in an adenoma rather than a carcinoma.

The "non-hormonal" adrenal cortical carcinomas were reviewed by Symington and Neville.[14] These tumors were noted in an older group (5-7th decades), twice as often in males as females and the authors presented 20 new cases (11 males, 9 females; age 2½ years to 66 years) and reviewed reports of 168 in the literature. The left side was the primary site in 55 of 89. The clinical symptoms most often noted were anorexia, weight loss and fever. Strangely, some very large tumors were associated with long survival.

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DECEMBER 10, 1972 - CASE NO. 8

ACCESSION NO. 19893

MODERATOR'S DIAGNOSIS: Adenoma, Adrenal Cortex; Secreting Aldosterone

CLINICAL ABSTRACT:

This 46 year old woman had hypertension for 4 years, a low serum potassium, and an alkaline urine. Urinary aldosterone was elevated and the plasma renin was low. An adrenal cortical tumor was found on the left side.

FOLLOW-UP:

The patient recovered well and the hypertension disappeared.

MICROSCOPIC:

The low power shows a discrete tumor nodule composed predominantly of clear cells. The adjacent adrenal cortex is atrophic. Histologically, it is not possible to decide what hormone is being made by this tumor. High power shows large pale foamy cells and few compact cells. A fat stain shows abundant fat.

DISCUSSION:

Aldosteronomas are bright yellow tumors and are usually small. Some tumors have the cells arranged in clusters and cords whereas the conference case has a somewhat haphazard pattern.

DECEMBER 10, 1972 - CASE NO. 13

ACCESSION NO. 18737

MODERATOR'S DIAGNOSIS: Carcinoma, Adrenal Cortex

CLINICAL ABSTRACT:

This 67 year old Caucasian female had Cushing's Syndrome. The urinary 17-Ketosteroids were elevated and the plasma cortisol was not suppressible. A 76 gram adrenal tumor was found.

FOLLOW-UP:

The patient died 4 months post-op from ruptured arterial aneurysm and no tumor was found.

MICROSCOPIC:

At the periphery, a capsule is present with some residual adrenal cortical elements adjacent. Many of the tumor cells are large and pleomorphic with large prominent nucleoli. Occasional multinucleated cells may be found. In comparison with the adenoma (Case 14) the cells in the carcinoma are larger and more pleomorphic. No calcification is observed. In some fields there appears to be vascular permeation.

DISCUSSION:

Morphological distinction of adrenal adenomas and carcinoma depends upon several factors. These include: (1) Size - the usual carcinoma is a bulky tumor, (2) calcification - present in carcinoma, (3) vascular invasion - if tumor is within endothelial lined spaces (vascular channels), it is more likely a carcinoma.

Adrenal cortical carcinomas do not have to look bad histologically. A case was illustrated at this conference of a Japanese man with gynecomastia that was surgically corrected. A testicular biopsy showed atrophy with maturation arrest. The search for the source of estrogens led to an adrenal tumor that was removed. Five years later he died at LAC/USC Medical Center and an astute medical student recognized the patient as one described in J. Clin. Endo. Metab. This man died of cerebral metastases and he also had pulmonary metastases. The testes at autopsy showed atrophy so the metastases were probably functioning. Histologically the original tumor was originally thought to be benign.

The laboratory studies indicated that this tumor was autonomous. The urinary 17 Ketosteroids were elevated and the plasma cortisol remained elevated following oral dexomethasone. Adenomas and bilateral adrenal hyperplasia will suppress with dexomethasone, but carcinoma will not.

DECEMBER 10, 1972 - CASE NO. 14

ACCESSION NO. 19347

MODERATOR'S DIAGNOSIS: Adenoma, Adrenal Cortex

CLINICAL ABSTRACT:

A 39 year old chinese female had hypertension for four years, elevated urinary 17 Ketosteroids and a diabetic glucose tolerance test. A 2 cm. tumor was found in the left adrenal gland and the right gland was atrophic.

FOLLOW-UP:

The patient was doing well one year later.

MICROSCOPIC:

The adrenal cortex adjacent to the nodule is atrophic. The tumor is well encapsulated and composed of a mixture of compact and clear cells with uniform nuclei.

DISCUSSION:

The presence of atrophy in the uninvolved cortex adjacent to the tumor indicates that the nodule was functioning. The patient was maintained on hydrocortisone following surgery. When the adrenal gland is removed in a patient with a functioning tumor, the pituitary-adrenal axis may be slow to respond, and steroid therapy may be needed for some time until the pituitary "wakes-up". In this patient both adrenals were removed.

DECEMBER 10, 1972 - CASE NO. 17

ACCESSION NO. 18934

MODERATOR'S DIAGNOSIS: Adrenal Cortical Adenoma, Left, with Cushing's Syndrome

CLINICAL ABSTRACT:

A 43 year old female admitted with suspected Cushing's Syndrome. An adrenal tumor was removed and the patient is doing well.

MICROSCOPIC:

A thin rim of compressed adrenal cortex forms the capsule. The tumor is a mixture of cells with pale foamy cytoplasm intermingled with groups of cells with darker, more compact cytoplasm. The nuclei are uniform and show little atypia. No necrosis or calcification is evident.

DISCUSSION:

The normal adrenal gland has foamy cells in the outer 2/3 of the cortex (the glomerulosa and fasciculata) which are considered the site of production of glucocorticoids, whereas compact cells from the inner 1/3 of the cortex, the zona reticularis, which is the site of androgen production. The normal ratio of glomerulosa, fascicularis, and reticularis is about 1:3:2.

Normal adrenal glands weigh 4 to 4.5 grams each if removed surgically, whereas at autopsy, they weigh about 6 grams. The glands of a patient with Cushing's Syndrome due to hyperplasia may weigh 15 grams or more each. Microscopically, the fasciculata may be 9:1 relative to the reticularis.

Cushing's Syndrome is due to adrenal cortical hyperplasia whereas Cushing's disease (the disease described by Harvey Cushing in 1932) is due to a pituitary tumor.

Both adenomas and carcinomas of the adrenal cortex may produce the same clinical syndromes: Cushing's Syndrome, virilization, and Conn's Syndrome. However, feminizing adenoma remains to be reported, although feminizing carcinomas are well known though not common.

DECEMBER 10, 1972 - CASE NO. 18

ACCESSION NO. 19245

MODERATOR'S DIAGNOSIS: Granulosa - Theca Tumor, Adrenal

CLINICAL ABSTRACT:

During a total abdominal hysterectomy, bilateral salpingo-oophorectomy, this 52 year old woman was found to have a large retroperioneal tumor. The pelvic organs removed were normal. A few months later a left nephrectomy and adrenalectomy was performed. The tumor was 1000 grams,yellow and separate from the kidney.

FOLLOW-UP:

The patient was doing well several months later.

MICROSCOPIC:

In several submitted sections, a narrow rim of compressed adrenal cortical tissue can be found just inside the fibrous capsule of the tumor. Several different histologic patterns are evident within the tumor. A conspicous feature is the presence of structures resembling follicles which are lined by elements resembling granulosa cells, the so-called macrofollicles of von Kahlden, complete with a hyaline membrane. The stroma between resembles ovarian theca. In other fields, the pattern is that of granulosa cell tumor with numerous Call-Exner bodies. In still other areas a sarcomatoid pattern merges with foci of trabecular or frankly tubular differentiation. The resemblance to an ovarian theca granulosa tumor is overwhelming and consultants were unanimous in affirming this diagnosis.

DISCUSSION:

The gross photograph shows the large bulky tumor attached to the upper pole of the kidney. The tumor is honeycombed with cystic areas containing gelatinous material and old blood; the intervening tissue is yellow-gray. No vestige of adrenal gland could be identified grossly.

This tumor is unique so far as I am aware. The question of its histogenesis is an interesting one. Both the ovary and the adrenal arise from the so-called genitourinary ridges which are paired bilateral structures on the posterior body wall. Whereas it is not particularly uncommon to find ectopic adrenal cortical tissue incorporated in the hilus of the ovary or testis, and the ovarian or testicular adnexae, the finding of gonadal tissue within the adrenal rare. In 1971 Dr. Wong and I reported the finding of tissue resembling microscopic foci of ovarian stroma within the adrenal cortex. Sub-

sequently we and our colleagues have found more than 30 additional cases. Thus far thecal metaplasia of the adrenal, as we have elected to call the lesion, has been found only in women.

I believe that this neoplasm is a theca-granulosa tumor arising in such metaplastic adrenal tissue. This tumor is unique in my experience and I know of no reports of similar cases. A report of this case by Drs. Orselli and Bassler has been published.

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ADRENAL MEDULLA TUMORS

INTRODUCTION

Tumor of the adrenal medulla may be classified as (1) hyperplasia, (2) benign pheochromocytoma and (3) malignant pheochromocytoma.

ADRENAL MEDULLARY HYPERPLASIA

Adrenal medullary hyperplasia is relatively unknown to pathologists. In 1962, Montalbano et al reported a 23 year old woman with clinical findings of a pheochromocytoma. Both adrenal glands were removed and the left gland (8 gms) showed a prominent medulla. Histologically, the medullary tissue interdigitated with the adjacent cortex and the cells were vacuolated. Following surgery, the clinical findings reverted to normal.

BENIGN PHEOCHROMOCYTOMAS

Benign pheochromocytomas are encapsulated and well demarcated when large.[2] The size is 1-25 cm. diameter, and the average weight of a surgical specimen is less than 100 grams.

A lobulated pattern is seen grossly due to fibrous trabeculae. The cut surface is gray or light brown. Occasionally cysts are seen as well as hemorrhage and necrosis. Calcification of the capsule and cyst wall is common. Viable tumor should be collected for catecholamine assay.

Microscopic.

Microscopically, the tumors resemble normal adrenal medulla. There seems to be no relationship between different morphologic patterns and clinical behavior. Consequently, histological subtypes are not important. However, the various patterns include tumor cells in sheets, alveoli, or anastomosing cords. The tumor cells may be large polyhedral cells or a smaller cell with less granular cytoplasm. Large nucleated forms and even ganglion-like cells may be seen. The chromaffin reaction is useful, but not necessary. Most important is the biochemical assay for catecholamines.

The fat cells surrounding the pheochromocytoma usually are multivesicular.

MALIGNANT PHEOCHROMOCYTOMAS

Malignant pheochromocytomas cannot be recognized histologically and metastases are the only adequate proof.[2]

Benign tumors may violate the capsule, invade adrenal vein and even inferior vena cava and not disseminate. Also, many pheochromocytomas are multicentric and the definition of a metastasis must be examined. In a review by Symington et al of 280 pheochromocytomas, 31 were reported as malignant. Yet only 1 case actually was proven to be malignant![3] In 1961, Kennedy, Symington, and Woodger reported a case of a 56 year old woman with a 383 gram left adrenal pheochromocytoma.[4] The liver contained numerous tumor nodules that histologically were identical to the benign appearing left adrenal tumor. Chemical analysis confirmed the presence of catecholamines in primary and metastatic tumor.

EXTRAMEDULLARY PHEOCHROMOCYTOMAS

Extramedullary pheochromocytomas (better called paragangliomas) are rare and interesting. Microscopically, they are identical to the adrenal types. By electron microscopy, some differences in type of granules are reported.[5] In children, extra-adrenal pheochromocytomas constitute 31% of all pheochromocytomas and multiple tumors are found in 32% of patients.[6] In a review of 205 cases up to 1968, the distribution of paragangliomas was:[7] Neck - 5, Intrathoracic - 24, Superior para-aortic - 88, Inferior para-aortic - 58, Urinary bladder - 20, Other sites - 10.

Nonfunctional, nonchromaffin paragangliomas are called chemodectomas and usually occur in the head and neck area. However, recently they have been noted in the retroperitoneum.[8] These recently described cases, and those reviewed (total of 21), indicate that the retroperitoneal nonchromaffin paragangliomas are more likely to be malignant (28%), infiltrate locally and look malignant histologically.[8] Up to 1974, there were five cases of pheochromocytoma and chemodectoma reported.[9]

The importance of biochemical assay was illustrated by the two cases of Sato et al. A retroperitoneal tumor was a chemodectoma histologically and contained noradrenalin and was classified as a pheochromocytoma.[9]

After widespread metastases occur, death may result from cardiovascular problems rather than the mass of tumor. Therefore, treatment is best aimed at blocking the hormonal effects of the catecholamines.[10]

Clinical Features of Pheochromocytomas:

The excessive catecholamine release accounts for most of the signs and symptoms. Hypertension, (paroxysmal or persistent) is noted in 95%; Headache in 80%; Sweating in 70%; Palpitations in 60%. Upon palpation of a prominent tumor, a paroxysmal hypertensive attack may occur. Urination is known to cause such an attack if the tumor is within the bladder.

Laboratory Studies for Rheochromocytomas

The VMA is most important.[11] A urine collected following a hypertension attack may be diagnostic. Recently, catheterization and measurement of venous catecholamine allowed localization of the tumor.

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DECEMBER 10, 1972 - CASE NO. 15

ACCESSION NO. 18942

MODERATOR'S DIAGNOSIS: Pheochromocytoma, Adrenal Medulla

CLINICAL ABSTRACT:

A 55 year old male had surgery for a torn medial meniscus. Following anesthesis and surgery he had nausea, vomiting, tachycardia and hypertension. He had similar attacks the previous eight years. The left adrenal was removed which contained a 2.5 cm. diameter gray-pink tumor.

FOLLOW-UP:

He was doing well 2 years later.

MICROSCOPIC:

The overlying adrenal cortex is thin and attenuated. The tumor is composed of cells resembling normal adrenal medulla, arranged in trabeculae and acini,with abundant vascularity. The cells are polygonal or occasionally fusiform and the cytoplasm is abundant, glassy and slightly granular. The nuclei are small and usually eccentrically located. No mitotic activity is evident.

DISCUSSION:

The chromaffin cell is derived from the sympathicoblast which arises from the neural crest. The neural crest cell has many capabilities, including differentiation as bipolar neuroblasts, unipolar ganglion cells, symphathicoblasts, cells that turn into pial and arachnoid cells, cells in the visceral arches, and cells that form bone, mesenchyme and pigment. Thus, the neural crest cells are multipotent, but not totipotent. The cells of the adrenal medulla arise from the neural crest, and often the cells resemble fusiform ganglion cells or epithelial elements.

The adrenal medullary cells synthesize and secrete epinephrine and norepinephrine which are derived from tyrosine. These compounds are called catechols which have two hydroxyl groups on the benzene ring. The metabolic products, metanephrine, nor-metanephrine and 3-methoxy 4-hydroxymandelic acid (VMA) may be excreted in excess in patients with tumors of the chromaffin system.

The chromaffin test requires placing the tissue into 3% potassium dichromate. One may add 40% formalin (10:1 chromate: formalin) overnight to allow fixation as well as the chromaffin reaction. Unstained slides should be examined for intracellular granules.

In a positive reaction the tissue turns black grossly and granules are found within the cytoplasm microscopically.

The catecholamines are fluorescent and pheochromocytomas show fluorescence.

Some of the tumors are large (15 cm. dia.) and the center may be necrotic with fibrous tissue. Grossly this tumor may appear fleshy and neural.

DECEMBER 10, 1972 - CASE NO. 16

ACCESSION NO. 19682

MODERATOR'S DIAGNOSIS: Pheochromocytoma, Adrenal Medulla

CLINICAL ABSTRACT:

This 34 year old man had hypertension for more than 20 years and recently was noted to have congestive heart failure. The urinary VMA was elevated. The right adrenal gland was removed and contained a 6.5 cm. pigmented tumor.

FOLLOW-UP:

The VMA was normal and the blood pressure became normal after surgery.

MICROSCOPIC:

A thick fibromuscular capsule surrounds the tumor; some adrenal cortical elements are intermixed in the capsule. Most of the tumor cells are fusiform with less cytoplasm than those in the previous case. The cytoplasm is granular or foamy and the nuclei are round and uniform. There is prominent vascularity, but mitotic figures are lacking. The adjacent adipose tissue shows focal moruloid change.

DISCUSSION:

The decision of benign vs. malignant can only be ascertained by finding metastases. The adjacent fat surrounding pheochromocytomas often shows embryonal changes. In this condition the lipid is finely dispersed in the cytoplasm, so that the cell has multiple small vacuoles rather than one large vacuole.

Pheochromocytomas occur outside the adrenal medulla. These places include the retroperitoneum, thorax, liver and urinary bladder. In 1956 at Dr. Nathan Friedman's CTTR conference, a case of a urinary bladder pheochromocytoma was presented. This condition was misdiagnosed for a time. The urinary bladder contained the tumor within the muscle.

DECEMBER 10, 1972 - CASE NO. 9

ACCESSION NO. 19892

MODERATOR'S DIAGNOSIS: Choriocarcinoma, Pineal

CLINICAL ABSTRACT:

The patient, a 10 year old male was evaluated for precocious puberty because of low pitched voice, pubic hair, enlarged penis and bilateral testicular enlargement. Adrenal genital syndrome was excluded by laboratory studies.

FOLLOW-UP:

A testicular biopsy showed Leydig cell hyperplasia, adolescent tubules and secondary spermatogonia. Pregnancy tests were positive. A pneumoencephalogram showed a mass in the region of the pineal. The tumor was found to be inoperable at surgery and the patient died on the 13th post-operative day. At autopsy, the testes were large and measured 3.5 cm. in length.

MICROSCOPIC:

Brain: Compressed cerebral tissue is present at the periphery of the tumor. There is extensive old and fresh hemorrhage with focal hematoidin pigment. The tumor cells are arranged in sheets of anastomosing cords of generally uniform polyhedral cells with a few larger syncytial cellular masses having multiple large pleomorphic hyperchromatic nuclei. This is a typical pattern of choriocarcinoma.

Testis: The testicular tubules are mature because they are lined by germinal epithelium with mitotic activity and incomplete spermatogenesis. There are only occasional spermatid. The interstitial cells of Leydig are numerous.

DISCUSSION:

The histogenesis of the extragonadal germ cell tumor is puzzling. I believe that the choriocarcinoma arises from a totipotent germ cell as stated by Friedman.[1] How the germ cell reached the pineal is debated. Witschi reviewed the events in the migration of germ cells from their first location in the yolk sac to their definitive location in the gonads. The gonads, adrenals and kidneys are derived from nests on the genitourinary ridge. Germ cells are not segregated very early in the development of the zygote, but after a dozen divisions they are segregated. They migrate up the body wall and into the gonads. Presumably they get lost in other areas because we know there are germinal tumors in the mediastinum, liver, head, and neck and in the sacroccygeal area. It remains conjectural how a germ cell might reach such an ectopic location as the pineal, but it is conceivable that such an ectopic germ cell might become neoplastic.

The evaluation of sexual precocity may be summarized as follows. (See table one.) Seckel[2] has defined the lower age limit of normal puberty at 10 years in boys and 8 years in girls. Sexual precocity then should be recognized before those ages and has 3 major causes: cerebral, adrenal and gonadal.[3] The cerebral type has two forms: functional and organic. The functional form is also known as constitutional precocious puberty, usually is familial and has no demonstrable organic basis. The organic forms are due to a variety of lesions including: pineal tumors or tumors near the pineal, hydrocephalus, tuberous sclerosis, hamartoma of the tuber cinereum, encephalitis and craniopharyngioma. The cerebral form in the male is easily differentiated from the gonadal and adrenal types because the testes grow to adult size only in the cerebral type. Also, the 17 Ketosteroids are normal. In the adrenal form, due to adrenal hyperplasia or neoplasm, the 17 Ketosteroids are elevated above the normal adult level, but the testes are infantile. The gonadal form of precocious puberty in the male is usually due to an interstitial cell tumor of the testis and there should be unilateral enlargement of the testis. Of particular interest, however, are the reports of unilateral or bilateral interstitial cell tumors associated with adrenogenital syndrome.

In passing, it is worth noting that there are other morphologic forms of germ cell tumors of the pineal. Johnson[4] etal reported 19 cases of extragonadal malignant germ cell tumors and 2 were in the pineal. There were a seminoma and a malignant teratoma.

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DECEMBER 10, 1972 - CASE NO. 25

ACCESSION NO. 19894

MODERATOR'S DIAGNOSIS: Yolk Sac Carcinoma arising in Liver

CLINICAL ABSTRACT:

A 17 month old boy was admitted because of abdominal distention. A partial resection of liver was performed to remove a large necrotic tumor originating from the medial part of the left lobe.

FOLLOW-UP:

The boy died and no autopsy was done. Careful examination during life by Urology Staff failed to note any enlargement of gonadal tissues.

MICROSCOPIC:

The tumor consists of communicating channels and cavities lined by epithelium; interspersed are fields with a meshwork pattern. Among the communicating spaces is an occasional small blood vessel surrounded by stroma which in turn is covered by a layer of neoplastic epithelium. These blood vessels with their epithelial covering resemble endodermal sinuses of Duval in the placenta of the rat and expand and dissect around the vessels of the extra-embryonic membranes. Because of the striking resemblance Teilum originated the term endodermal sinus tumor for this neoplasm. The meshwork pattern has trabeculae containing hyaline globules which are PAS positive and diastase resistant.

DISCUSSION:

The present case was the subject of a case report by William R. Hart, M.D. This is the first documented case of an endodermal sinus tumor that originated in the liver. Several examples of endodermal sinus tumors arising in extragondal sites are reported.[2] Usually, these tumors are found in the testes of infants and prepubertal boys. Careful clinical examination and surgical exploration indicated that the present case originated in the liver and not in a testis. Alpha-fetoprotein was present and is associated with other germ cell tumors arising in the testis, ovary, retroperitoneum and presacrum. The patient died with recurrent tumor and no autopsy was performed. Alpha-fetoprotein has been found in yolk sac tumor.[3] It has been suggested that the yolk sac was the origin of the alpha-fetoprotein.[3]

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ENDODERMAL SINUS (YOLK SAC) TUMOR

("MESONEPHROMA OVARII")

TEILUM: A GERMINAL TUMOR OF TESTIS AND OVARY, ARISING IN EXTRA-EMBRYONIC MESOBLASTIC ELEMENTS REPRODUCES STRUCTURES COMPATIBLE WITH ENDODERMAL SINUSES OF DUVAL (YOLK SAC ENDODERM AND ALLANTOIC MESODERM OF RAT'S PLACENTA)

SCHILLER: A MALIGNANT CYSTIC OVARIAN TUMOR ARISING FROM REMNANTS OF MESONEPHROS INCLUDED IN THE OVARY, AND CONTAINING ELEMENTS INTERPRETED AS ABORTIVE MESONEPHRIC GLOMERULI.

DECEMBER 10, 1972 - CASE NO. 20

ACCESSION NO. 11611

MODERATOR'S DIAGNOSIS: Oat Cell Carcinoma, Lung;
Secreting ACTH like substance.

CLINICAL ABSTRACT:

A 61 year old man had a lung tumor detected by chest radiograph. The left lower lobe had a 2 x 1.3 cm. tumor which had spread to perihilar lymph nodes. Seven months later he had facial swelling, low blood pressure, a serum potassinum of 2.7 mEq/L. Urinary 17 Ketosteroids were elevated. A retroperitoneal air study indicated both adrenal glands were enlarged. He died following brain surgery to remove the hypophysis.

FOLLOW-UP:

The lung tumor had metastasized to many lymph nodes, both adrenal glands, liver, spleen, brain and other areas. Bio-assay of the tumor indicated it had ACTH-like activity.

MICROSCOPIC:

The low power shows a pleomorphic, spindle and fusiform small cell tumor growing through lymph nodes, soft tissue and eroding mucosa. The lymph node contains anthracotic pigment and by polarized light there are a few birefringent spots that may be silica. The cells have scanty cytoplasm and the nuclei are varied and hyperchromatic.

DISCUSSION:

The adrenal glands contained metastatic tumor and the cortex was thickened. The individual adrenal cortical cells are enlarged. Thus we have an oat cell carcinoma secreting an ACTH-like substance causing Cushing's Syndrome.

DECEMBER 10, 1972 - CASE NO. 24

ACCESSION NO. 17674

MODERATOR'S DIAGNOSIS: Interstitial Cell Tumor, Testis

CLINICAL ABSTRACT:

This 43 year old man with mental disease was noted to have an enlarged right testicle. The testis was surgically removed. There was an encapsulated firm, tan, nodular lobulated tumor replacing the testis.

FOLLOW-UP:

Not available.

MICROSCOPIC:

Just under the tunica albuginea, a compressed rim of testicular parenchyma containing tubules with atrophic germinal epithelium is present between the tunica and the tumor. The neoplasm is an interstitial cell tumor made up of Leydig cells disposed in sheets. The polygonal neoplastic cells are rather uniform, with abundant granular pink cytoplasm and nuclei which are usually eccentric and contain a single nucleolus. I was unable to identify a crystalloid of Reinke in any of the cells, though these are not required for diagnosis. An interesting feature of this tumor is the presence of mature adipose tissue within the neoplasm.

DISCUSSION:

Interstitial cell tumors fall into the category of non-germinal tumors of the testis. Teilum groups Sertoli and Leydig tumors together under the generic designation of androblastoma, a classification which I support. These gonadal stromal tumors are quite rare in man. The cut surface of such tumors is gray, pale, yellow or tan and firm. In contrast to the rarity of the tumor in humans, the neoplasm is relatively common in the dog. Since the Sertoli elements may secrete estrogen, such dogs may excrete estrogen in the urine and become attractive to other male dogs.

Rarely, interstitial cell tumors of the testis may be malignant and produce generalized metastases.