American Association of Endocrine Surgeons

Presidential address: The glands of Owen—A perspective on the history of hyperparathyroidism

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IT IS A DISTINCT AND CHERISHED HONOR to be the president of the American Association of Endocrine Surgeons and to address you in this capacity. Previous addresses have covered a myriad of subjects and have been witness to the erudition and catholicity of interests of our membership.

This presentation will relate to the glands of Owen, their discovery, their physiologic significance, and the consequences of their hyperfunction. Parathyroid has always seemed an unimaginative and vapid term for a gland the function of which is so critical to our well-being. Most endocrine glands were named for their configuration (pineal, thymus, thyroid), function (ovary, pituitary, testes), or composition (pancreas). Only the adrenal, distinguished by its relation to the kidney, was named because of its fortuitous location. For these glands to be named after their discoverer has a more romantic implication and is as explicit as to function as the term parathyroid. Unfortunately, eponyms have lost popularity, much to the detriment of our medical heritage.

Hyperfunction of the glands of Owen can be epitomized by the presentation of some early patients who provide a perspective on diagnosis, natural history, and management. Emphasis on patients seems appropriate since the patients rarely receive credit for their role in our understanding of normal and abnormal physiology. Although this may not be new information, I would remind you of a quote from George Santayana1, “That which is not too well understood is not too oft repeated.”

DISCOVERY OF THE PARATHYROID GLANDS

The glands of Owen can be traced to a few courageous amphibians that, some 100 million years ago, had sufficient hubris to crawl ashore. At that time endocrine control of their calcium and phosphate metabolism, requisite for their bony skeletons, was maintained through steroids, vitamin D metabolites, and the peptide hormone calcitonin. A more terrestrial environment constituted a stimulus for the production of a hormone adequate for maintenance of calcium and phosphate ion homeostasis. These glands were essentially the last to appear in the evolution of the vertebrate endocrine system.1

Despite their essentiality in millions of species for the
maintenance of the bony skeleton, the responsible endocrine glands were not discovered until 140 years ago.

"On the 24th of May, 1834, the Zoological Society of London acquired it's first specimen of the Great Indian Rhinoceros (*Rhinoceros unicornis*)." This animal, a male, arrived at the Society's menagerie on September 20, 1834; it reached an age of about 20 years on November 19, 1849. It was "anatomized" by Sir Richard Owen, Hunterian Professor and Conservator of the Museum in the Royal College of Surgeons of England (1827-1856) (Fig. 1). Owen welcomed the opportunity to dissect the anatomy of this rare species, which is evident in the following excerpt from a letter to one of his sisters:

"Amongst other matters time-devouring, and putting out of memory mundane relatives, sisters included, has been the decease of my ponderous and respectable old friend and client the rhinoceros. I call him 'client' because fifteen years ago I patronized him, and took it upon my skill, in discerning through a pretty thick hide the internal constitution, to aver that the beast would live to be a credit to the Zoological Gardens, and that he was worth the 1,000 guineas demanded for him. The Council had faith and bought him, and he has eaten their hay, oats, rice, carrots and bread in Brobdingnagian quantities daily ever since, and might have gone on digesting, had he not by some clumsy fall or otherwise inexplicable process, cracked a rib; said fracture injuring the adjacent lung and causing his demise. His anatomy will furnish forth an immortal Monograph, and so comfort comes to me in a shape in which it cannot be had by any of my brother Fellows."3

The deteriorating clinical course of the rhinoceros was succinctly recorded in the *Head-keepers Minute Book*4:

"1849, November 12th Rhinoceros vomited slimy mucus. 14th ditto ditto with blood 15th ditto ditto ditto 16th ditto ditto ditto, & from the nostril 17th ditto ditto ditto ditto 18th ditto ditto ditto ditto 19th ditto ditto ditto ditto"

Today, this would not be an acceptable record of a patient's illness or attending involvement.

The protracted and laborious dissection was carried out at the Conservator's resident quarters of the Royal College of Surgeons. Owen's wife recorded in her diary that "as a natural consequence" of this animal's death there is a quantity of the rhinoceros—approximately 2 tons—on the premises. Owen performed the dissection
during the winter months of 1849 to 1850 and indicated that the rhinoceros had passed into an "offensive state of decomposition." On Feb. 12, 1850, Owen presented the resulting monograph to a meeting of the Zoological Society.4

Owen's astuteness as an anatomist was evident from his discovery of "a small compact yellow glandular body attached to the thyroid at the point where the vein emerged." He had no prior knowledge of the presence of this small organ, which was in diameter and circumference no greater than a sixpenny piece. Owen's publication in March 1852, "On the Anatomy of the Indian Rhinoceros,"4 is recognized as the classic paper on the subject.

Ivar Sandstrom celebrated his first birthday in March 1853. He matriculated at the University of Upsala in 1871, received his preclinical degree in 1878, and was appointed as "prosektor" in anatomy during 1879 to 1880 (Fig. 2). He obtained his diploma as a physician in 1887. His publication, "On a New Gland in Man and Several Mammals—Glandulae Parathyroideae,"5 was published in the Upsala Läkareföreningens Förhandlinger, 1880. This discovery was made in 1877 while Sandstrom was still a medical student.

"About three years ago (1877), I found on the thyroid gland of a dog a small organ, hardly as big as a hemp seed, which was enclosed in the same connective tissue capsule as a thyroid, but could be distinguished therefrom by a lighter color. A superficial examination revealed an organ of totally different structure from that of the thyroid, and with a very rich vascularity... even in the cat and the rabbit similar glands were found. However, time and material did not allow me to continue the investigations and it was not until this winter (1880) that I have been able to take the problem up again... Although the probability of finding something hitherto unrecognized seemed so small that it was exclusively with the purpose of completing the investigations, rather than with the hope of finding something new, that I began a careful examination of this region. So much the greater was my astonishment; therefore when, in the first individual examined, I found on both sides at the inferior border of the thyroid gland an organ of the size of a small pea, which, judging from its exterior, did not appear to be a lymph gland, nor an accessory thyroid gland, and upon histologic examination showed a rather peculiar structure.6

Sandstrom's description was so complete that little was to be added for several decades. He emphasized the frequency with which the gland was embedded in fat and might be overlooked unless the transparency of the fat lobule was examined against a strong light—analogous to ultrasound evaluation of today. He thought the glands should be looked on as embryonic thyroid glands that had been arrested at an early stage of development.

He emphasized the difference in these glands from accessory thyroid glands and suggested the name glandulae parathyroideae, which expressed the characteristic of being bye-glands to the thyroid. Sandstrom emphasized that although "an accessory thyroid gland is found in only one of ten cases, every individual has several glands of this kind."5 Sandstrom's excitement and reward must have been comparable to that of the surgeon who, after much searching, identifies an elusive parathyroid adenoma.

Sandstrom did not postulate any particular function but did speculate on clinical relevance.

"For the purpose of diagnosing a tumor of the parathyroid gland, I want to point out the proximity of the glands to the esophagus and the recurrent nerve, whereby in cases of a pathological growth process there may easily occur a compression of the former and a paralysis of the latter."6

Sandstrom's comments in a letter to his family on the presentation of his findings to a meeting of the prestigious natural scientists at Stockholm are prescient today.

"Everyone seemed to be there with the intention of showing what 'discoveries' he had made, and at the same time give the astonished world the opportunity to have a look at the fortunate discoverer. I cannot help the sad and discouraging impression that most of our scientists are more apt to work for their own reputation than for the sake of science itself, and that the latter is regarded as a kind of modern album, wherein a lot of gentlemen compete to get their names written. But for the discovery itself, for the revealed truth the interest was little or none."6

In searching the literature at that time, Sandstrom also cites two authors, namely, Remak (1855) and Rudolph Virchow (1863), who may have identified these glands earlier.6 Unfortunately, Sandstrom's academic career was terminated by his suicide in 1889.7

The glandulae parathyroideae at this time were basically structures in search of a function. A clue to their function was the development of tetany after thyroidectomy. Tetany was looked on as an acute form of "cachexia struma priva" or hypothyroidism.8 Glely9 demonstrated that removal of the parathyroid glands rather than the thyroid was the cause of death in the experimental animal after thyroidectomy. However, he still thought of the parathyroid glands as residual embryonic thyroid. Vassale and Generali10 were first to clearly document that thyroidectomy leads to myxedema and parathyroidectomy to tetany. They also confirmed that parathyroid tissue left in situ in the rabbit did not mature into normal thyroid.

A major advance was the establishment of the concept that tetany was caused by hypocalcemia and was not due
to a toxin that accumulated after parathyroidectomy.\textsuperscript{11} Hanson\textsuperscript{12} developed extracts of the parathyroid, which he believed enhanced the action of insulin. Collip\textsuperscript{13} demonstrated that such extracts consistently or uniformly prevented or relieved tetany in the experimental animal and that the probable manner of action of the hormone was through a direct effect on calcium metabolism.

\textbf{EARLY CLINICAL OBSERVATIONS}

The association between bone disease and parathyroid enlargement was again one of observation and speculation, and this association was finally determined by studies in the patient. The earliest clinical reports on hyperparathyroidism have been culled from the literature by Selwyn Taylor\textsuperscript{14} who cited (1) "the boney changes of osteitis fibrosa" in a prehistoric North American Indian; (2) a 42-year-old man who had bones that softened like leather and who was a patient of the French surgeon Courtial (1705); (3) Bevan’s report in 1743 of a 40-year-old woman with severe hypotonia, polyuria, and pliable soft bones who at autopsy had soft bones consisting of a fibrous shell; and (4) a 13-year-old girl described by Davies-Colley in 1884 with typical changes in her mandible and long bones in association with multiple renal calculi.

\textbf{Osteitis fibrosa cystica.} The predominant manifestation of primary hyperparathyroidism was described by Friederick Daniel von Recklinghausen\textsuperscript{15} (1833-1910). In 1891 he described the case of Herr Bleich, the seventh of 16 cases in a festschrift (volume of writings by different authors presented as a tribute) in honor of the seventy-first birthday of Rudolph Virchow. Herr Bleich illustrated all the findings now included in the term \textit{osteitis fibrosa cystica of von Recklinghausen}. Von Recklinghausen, in describing this patient, used the term \textit{fibrosa ostitis, multiple osteosarcoma}. The clinical picture was described by Albright.\textsuperscript{16}

"Herr Bleich was a 40 year old married man who had undergone a mercury cure for syphilis. In April, 1888, he fell from a three meter high ladder and eight days later he was hospitalized because of severe pain in his hip. It was clear whether a fracture of the neck of the femur or a coxitis was present. He was treated with extension until August when improvement was so far advanced that he began to walk with a stick. In October the patient slipped, fell against a bench, and fractured his clavicle. He was readmitted to the Surgical Clinic where he underwent a transverse fracture of the diaphysis of the right femur while lying in bed because the bedpan was clumsily maneuvered. Continued pain and unsatisfactory union made it necessary to transfer him to a non-clinical division of the City Hospital. In the course of the summer of 1889, he not only showed the most extensive bending of several long bones, but complained of excruciating pain in many bones and appeared very emaciated. Although the fracture seemed to heal, the patient was unable to raise the leg, marasmus increased and he died on October 4, 1889. Von Recklinghausen made a detailed description of Herr Bleich’s skeleton, and emphasized three of the chief pathological characteristics of the bone disease which so often accompanies hyperparathyroidism: widespread fibrosis, cysts, and brown (or giant-cell) tumors.”

Jung,\textsuperscript{17} in 1933, reviewed the original autopsy report at the Pathological Institute of Strassburg and noted the following statement: "Above the left thyroid gland, a lymph gland, red-brown in color is present." Even today some of our most astute surgeons have difficulty in differentiating a lymph gland from a parathyroid gland. It was evident that von Recklinghausen had failed to make a relation between the small tumor in the neck and the advanced bone disease of his patient.

In 1904 Askanazy\textsuperscript{18} described a patient with osteitis fibrosa cystica and commented on the presence of a parathyroid tumor. He was the first to make the association between the two entities. However, because of the stature and the highly respected opinions of Professor Jacob Erdheim,\textsuperscript{19} an eminent Viennese pathologist (1906),
the enlarged parathyroid gland found in this type of bone disease was generally regarded as a secondary phenomenon. The relation between calcium metabolism, bone disease, and the parathyroid glands was a career interest of Erdheim. From his studies on rats and observations in man, he concluded that the enlargement of the parathyroid glands in bone disease was a compensatory phenomenon.

A few skeptics, however, including Schlagenhaufer (1915), pointed out that in von Recklinghausen's disease of bone the parathyroid enlargement involved only one gland, which would be difficult to explain if the hypertrophy were secondary or compensatory. However, another decade passed before Schlagenhaufer's recommendation that the parathyroid "tumor" be removed was implemented.

Felix Mandl, a Viennese surgeon, established the etiologic relationship between a parathyroid tumor and von Recklinghausen's osteitis fibrosa cystica (Fig. 3). At 34 years of age, Albert Jahne, a streetcar conductor, experienced initial symptoms of pain and a sense of tiredness in his legs. Within 4 years the diagnosis of von Recklinghausen's disease was established, culminating in pathologic fractures of his leg. Jahne had received parathyroid extract from animals without benefit and failed to improve after transplantation of four parathyroid glands from a moribund patient. On July 30, 1925, under local anesthesia, a parathyroid tumor measuring $25 \times 15 \times 12$ mm was removed from the left inferior area behind the thyroid gland. Within a few days the patient's condition improved, the calcium content of the urine and blood was considerably lower, and he felt better. At 4 months the bones were seen by roentgenography to be more dense; the bone pain had subsided, and for the first time in years he was able to sit up in bed and walk with the aid of crutches.

Mandl's observations were presented to the Medical Society in Vienna, Dec. 4, 1925. Present were Professor Eiselsberg, a student of endocrine glands, and a number of well-known Viennese surgeons and physicians. Apparently they expressed little reaction to this remarkable achievement.

After 6 years of improvement, Jahne's condition worsened. By September 1932, he once more had a renal calculus, hypercalcemia, hypophosphatemia, and his bones became decalcified. The patient was incapacitated and underwent surgery again on Oct. 18, 1933; no tumor was found in the entire neck region or in the mediastinum. A large portion of the thyroid gland was removed, which by microscopy included two parathyroid glands. The patient showed no improvement and died in February 1936. Autopsy did not reveal parathy-
Table I. Patients with primary hyperparathyroidism treated by parathyroidectomy, 1925 to 1930

<table>
<thead>
<tr>
<th>Author</th>
<th>Surgeon</th>
<th>Date</th>
<th>Age (yr)/Sex</th>
<th>Serum calcium level (mg/dl)</th>
<th>Operative findings</th>
<th>Immediate postoperative course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mandl21</td>
<td>Mandl</td>
<td>7/30/25</td>
<td>30/female</td>
<td></td>
<td>Adenoma, 25 × 15 × 12 mm</td>
<td></td>
</tr>
<tr>
<td>Beck24</td>
<td>Beck</td>
<td>1927</td>
<td>41/female</td>
<td></td>
<td>2 “adenoma,” size of almond, coffee bean</td>
<td>Tetany</td>
</tr>
<tr>
<td>Gold25</td>
<td>Gold</td>
<td>1927</td>
<td>56/female</td>
<td>13.1</td>
<td>Adenoma, 3 cm, “walnut sized”</td>
<td>Severe tetany</td>
</tr>
<tr>
<td>Olch</td>
<td>Och</td>
<td>8/1/28</td>
<td>56/female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barr et al.26</td>
<td>Rankin</td>
<td>12/17/28</td>
<td>35/female</td>
<td>12.8</td>
<td>Carcinoma, 5 × 3.5 × 3 cm</td>
<td>Paresthesias</td>
</tr>
<tr>
<td>Lanz</td>
<td>2/28/29</td>
<td>56/male</td>
<td>19-23</td>
<td>Adenoma, 2.4 × 1.4 cm</td>
<td>Disoriented, impending tetany</td>
<td></td>
</tr>
<tr>
<td>Boyd et al.31</td>
<td>Peterson</td>
<td>4/12/29</td>
<td>19/male</td>
<td>17.6</td>
<td>3.5 × 2.5 cm</td>
<td>Paresthesias, mild tetany (serum calcium, 5 mg/dl)</td>
</tr>
<tr>
<td>Barr and Bulger27</td>
<td>Brown</td>
<td>6/18/29</td>
<td>38/male</td>
<td>13.3-16.7</td>
<td>2.5 cm palpable mass</td>
<td>Paresthesias</td>
</tr>
<tr>
<td>Compere32</td>
<td>Phemister</td>
<td>6/24/29</td>
<td>59/female</td>
<td></td>
<td>1 × 1.5 cm</td>
<td>Paresthesias</td>
</tr>
<tr>
<td>Hunter33</td>
<td>Walton</td>
<td>11/29/29</td>
<td>44/female</td>
<td>12-16.7</td>
<td>3 × 3 × 3.7 cm</td>
<td>Paresthesias</td>
</tr>
</tbody>
</table>

Mandl’s observations were significant since they clearly demonstrated that, in his patient, the bone disease, von Recklinghausen’s osteitis fibrosa cystica, was secondary to a small tumor of the parathyroid. The patient had a remarkable recovery, but after 6 years his disease recurred.

INITIAL RESULTS OF SURGICAL TREATMENT

A review of the initial patients who were successfully operated on between 1925 and 1930 for von Recklinghausen’s disease provides a striking picture of the natural history of hyperparathyroidism as influenced by surgical treatment. Although the immediate results of parathyroidectomy were dramatic, serious problems of tetany, renal failure, and recurrent disease remained. Including Mandl’s patients, 10 well-documented reports are cited chronologically (Table I).

In 1927 Beck24 removed two parathyroid tumors (one was the size of an almond, and the other was the size of a coffee bean) from a 41-year-old woman. Three years earlier she had undergone amputation of her right leg for a sarcoma. Her elevated serum calcium level returned to normal by postoperative day 3. Tetany followed on postoperative day 5; the patient died of tetany on postoperative day 21. In the same year, Gold25
readmitted 1 year later because of a fracture of the left humerus, a tumor of the mandible, and a benign giant cell sarcoma of the left ulna (Fig. 4). Elva Dawkins' course is summarized in a letter from her surgeon, Dr. I. Y. Olch (Fig. 5) to Dr. Walter Ballinger (1972).

"I remember her vividly because of the way the diagnosis was made and the postoperative course, which was very stormy. . . . we were struck by the marked hypotonia of most of the voluntary muscle and the formation of the tumors and fractures that followed rather minor trauma. On her second admission the hypotonia and the calcium depletion of her bones had increased greatly and these along with kidney stones had made her a good subject for ward rounds, conferences and clinics. This was where Henry Dixon first saw her. He was a senior student who was doing some extra work with Ransom, Professor of Neurology at Northwestern. They had been working with frog muscle nerve preparations studying the changes in tonicity as affected by the relative concentration of calcium versus phosphorus in suspending solutions. With higher calcium concentration, the muscle tone decreased. Dixon wondered whether this had any relation to Mrs. Dawkins and so the next morning he drew blood and found her serum calcium was nearly 17 mg%. He called this to Bulger's attention and we had the patient transferred to his ward rounds, conferences and clinics. She enabled Bulger and Dixon to carry out extensive metabolic studies both before and after surgery. She went to surgery on August 1, 1928 and a tumor about 3 cm. in diameter was found behind the lower pole of the right thyroid lobe. Her hypercalcemia immediately began to drop and the next morning she began to show signs of severe tetany. It was necessary to give her large doses of calcium chloride intravenously to control the tetany (Fig. 6). She had to be maintained on calcium lactate as long as she lived and eventually died of renal insufficiency."

Barr, Bulger, and Dixon published a report of Elva Dawkins in the *Journal of the American Medical Association* on March 23, 1929, "Hyperparathyroidism," after having presented the paper before the Central So-

<table>
<thead>
<tr>
<th>Medication</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate improvement, recurrence at 8 yr, 2 normal parathyroids removed at 9 yr without improvement; death at 11 years—no tumor at autopsy</td>
<td>Died in tetany 21 days postoperatively</td>
</tr>
<tr>
<td>Calcium lactate, parathyromone, intravenous calcium chloride</td>
<td>Improved, died of renal insufficiency 14 mo postoperatively</td>
</tr>
<tr>
<td>Relief of bone pain, increased bone density, disappearance of maxillary tumor at 18 mo; no recurrence at 12 yr</td>
<td>Marked improvement at 6 mo</td>
</tr>
<tr>
<td>Calcium lactate, parathyroid extract, intravenous calcium compound</td>
<td>At 10 years, &quot;walks, with one stick, able to lead a normal life&quot;</td>
</tr>
<tr>
<td>Improved; progressive bone repair at 3 mo, recurrence at 3 yr, reoperation at 14 yr with improvement; death from renal failure at 17 yr</td>
<td>Well at 7 yr; transplanted tumor not palpable</td>
</tr>
<tr>
<td>Calcium lactate</td>
<td>Calcium 12.6 mg/dl and phosphorus 5.7 mg 9 mo postoperatively</td>
</tr>
<tr>
<td>Good recovery with improvement in all symptoms, 10 days</td>
<td></td>
</tr>
</tbody>
</table>

*She died 14 months after surgery [written communication, P. M. Weeks, MD, 1990].*
ciety for Clinical Research, Nov. 23, 1928. The following year they cited the current thinking regarding the association of osteomalacia, parathyroid tumors or parathyroid hyperplasia, high serum calcium level, and the physiologic changes that occurred when an excess of parathyroid secretion was present. The concept of hyperparathyroidism was introduced and is an excellent example of inductive reasoning. The clinical features of this new entity were defined as follows: (1) rarefaction of bone; (2) the occurrence of multiple cystic bone tumors, several of which, on pathologic examination, have been found to be giant cell sarcoma; (3) muscular weakness and hypotonia; (4) abnormal excretion of calcium in the urine and the formation of calcium stones; and (5) abnormally high serum calcium.

"All of these changes are secondary to, or associated with, a parathyroid hyperplasia or parathyroid tumor." They also cited a personal communication with Dr. E.F. DuBois and Dr. J.C. Aub who had studied a similar case (Captain Charles Martell) 2 years earlier and who had removed from the patient two normal parathyroid glands, which resulted in considerable clinical improvement.

The resolution of Elva Dawkins' problem is an example of the contribution of a thoughtful medical student. Fortuitously, a patient with such severe hypotonia was seen by a medical student who was studying the effect of calcium concentrations on muscle tone. He asked the right question: Could the calcium level be a factor in Mrs. Dawkins' hypotonia?

Isaac Y. Olch (1897-1987), the first surgeon in this country to remove a parathyroid adenoma, was born in Providence, R.I., in 1897. After attending Brown University and Johns Hopkins School of Medicine, he received his MD in 1921 and interned on the surgical service at Johns Hopkins School of Medicine, spending considerable time with Joseph Bloodgood in surgical pathology. He moved to Washington University School of Medicine and worked with Dr. E.L. Opie in pathology before starting his residency with Dr. Evarts Graham. He joined the faculty as an assistant professor and was very active in surgical pathology.

Wilder's patient was a 35-year-old woman with generalized osteitis fibrosa and giant cell tumors of the maxilla and femur. She underwent excision of a tumor measuring 5 X 3.5 X 3 cm; subsequent diagnosis was parathyroid carcinoma (Dec. 1, 1928). Four months after surgery she had improved greatly and gave up use of crutches. Her serum calcium level was 8.3 mg/dl, and roentgenography showed increased density of bones. After 12 years no disease had recurred, which makes the diagnosis of carcinoma "suspect" (written communication, J. van Heerden, MD, 1990).

Snapper reported a 56-year-old man with a 7-year history of leg pain, pathologic fractures, and a diagnosis of osteomalacia. His serum calcium level ranged from 19 to 22 mg/dl. Professor Lanz removed this patient's 24 X 14 mm adenoma, on Feb. 28, 1929. The serum calcium level fell to 8.5 mg/dl on day 5 and to 7.2 mg/dl on day 12. The patient was confused and disoriented and was treated with calcium lactate (4 gm daily), parathyroid extract (Collip), and an intravenous calcium compound. After 4 weeks the serum calcium level was 9.4 mg/dl. Snapper's description articulates dramatic
improvement after parathyroidectomy. "The patient remained a small bent man with crooked legs, but the unfortunate man chained to his bed in agony had been changed into a cheerful man who had no more pain and who recorded with delight his daily improvement in walking." Recurrent hypercalcemia was present at 3 years; reoperation was performed at 14 years (serum calcium level of 15.9 mg/dl and serum phosphorus level of 3.8 mg/dl) and additional parathyroid tissue was removed. Seventeen years later the patient was dying of renal failure caused by bilateral nephrocalcinosis (written communication, E.E. Mason, MD, 1990).

Boyd et al. cited a 19-year-old man with progressive bowing of his extremities (Fig. 7) and a serum calcium level of 17.6 mg/dl. A parathyroid tumor measuring 35 X 25 mm was removed by Frank Peterson of the University of Iowa (April 12, 1929). The postoperative serum calcium level was 5.0 mg/dl, and there was "mild tetany." Recurrent hypercalcemia was present at 3 years; reoperation was performed at 14 years (serum calcium level of 15.9 mg/dl and serum phosphorus level of 3.8 mg/dl) and additional parathyroid tissue was removed. Seventeen years later the patient was dying of renal failure caused by bilateral nephrocalcinosis (written communication, E.E. Mason, MD, 1990).

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Barr and Bulger also reported a 38-year-old man with a serum calcium level of 13 to 16 mg/dl and with a giant cell tumor of the mandible who underwent removal by Dr. J. Barrett Brown (June 12, 1929) of a 2.5 cm palpable adenoma. At Olch's suggestion, 1 cc of tumor was transplanted into the rectus abdominis muscle. The patient was well at 7 years. The transplanted tumor was not palpable (written communication, P.M. Weeks, MD, 1990).

Dr. D.B. Phemister (June 24, 1929) excised a 1 X 1.5 cm tumor from a 59-year-old woman who had severe skeletal deformity (Fig. 8). The postoperative serum calcium level of 6.9 mg/dl was accompanied by paresthesias, and the patient was treated with calcium lactate, 2 gm three times daily. Nine months later the serum calcium level was 12.5 mg/dl and the phosphorus level, 5.7 mg/dl.

The last of these 10 patients was reported by Hunter. Dr. A.J. Walton removed a 30 X 30 X 37 mm tumor in a 44-year-old woman in November 1929. The preoperative serum calcium level ranged between 12 to 16 mg/dl. Paresthesias were noted after surgery. The patient was much improved at postoperative day 10, and the bone pains were gone.
teoporosis (osteopenia), giant cell tumors (osteoclastomas), bony deformity, pathologic fractures, nonunion, and loss of height. The muscle weakness, extreme flexibility of joints, severe bone pain, and deformity resulted in complete disability. Renal calculi, which was commonly an associated finding, was not a common initial complaint. However, complications of renal insufficiency and urinary tract infection were probably the cause of late deaths in these initial patients. Follow-up in general was strikingly brief; hypercalcemia recurred in three of these 10 patients. Postoperatively, tetany was also a greater problem than today, causing the death of Beck's patient and of the most celebrated patient of the time, namely Captain Charles Martell (Fig. 9).

Although the story of Charles Martell (1889-1932) has been told on numerous occasions,16, 35, 36 a few highlights are worth reiterating. Symptoms of pain in the groin, leg, and hip began at the age of 22 years. During the next 3 years, in addition in pain in his heels, leg, and back, he had fractures of the left clavicle, right humerus, and several vertebrae. He had also lost stature and had become pigeon-breasted. At the end of urination, he passed fine white gravel. He was completely disabled at the age of 27 years, and at the age of 30 years (January 1926) was hospitalized at Bellvue Hospital, New York, N.Y., under the care of Dr. Eugene DuBois. Roentgenograms showed severe osteopenia, compressed vertebrae, cystic changes in the femur, and numerous pathologic fractures. The serum calcium level was 14.8 mg/dl and the phosphorus level was 3.3 mg/dl. He had shrunk a total of 7 inches, exhibiting marked kyphosis and extreme muscular hypotonia with unusual flexibility of many joints. With the provisional diagnosis of hyperparathyroidism, the patient was transferred to the Massachusetts General Hospital and, after metabolic studies, underwent removal of a normal parathyroid gland in May and again in June 1926 (one of five nodules excised at the first operation and one of six at the second operation proved to be parathyroid). Both procedures were performed by Dr. E. P. Richardson. Although no change occurred in the Captain's calcium metabolism, his physicians convinced themselves that he had improved clinically and published their observations in 1929 (2 years after parathyroidectomy).37 The case was published under the title "Parathyroidectomy in Osteomalacia"37 and lead to confusion about the cause of osteitis fibrosa cystica since clinical improvement seemed to be obtained by the removal of two normal parathyroid glands. No real change occurred in the patient's condition, and by 1931 he was dependent on crutches. After four additional cervical exploratory operations (three by Dr. Oliver Cope), 90% of a 3 cm tu-

Fig. 9. Charles Martell. (From Bauer W, Federman DD. Metabolism 1962;11:21-9.)

Mandi23 writes of two patients who were operated on before 1930. Both had generalized osteitis fibrosa, and the condition improved after excision of a parathyroid tumor.

The clinical picture of hyperparathyroidism as manifest in these initial patients is essentially unknown today. In most patients the diagnosis is established by routine screening of serum electrolytes, and many have relatively few symptoms.34 In a sense, the most common method of diagnosis is by serendipity. This too has a precedent.

Dr. J. Morelle, from Louvain, in 1932 had on his service a patient with primary hyperparathyroidism. He instructed a medical student to draw blood to measure serum calcium level. The student carefully followed Morelle's directions, but he went to the wrong bed. The patient's serum calcium level was elevated! Here was the first diagnosis of hyperparathyroidism by serendipity.

The long-term but subtle effects of excessive parathormone secretion is reflected in the skeletal changes described by von Recklinghausen—bony cysts, os-
mor was removed from the mediastinum by Dr. E. D. Churchill. The remainder of the tumor was sutured on its pedicle and placed in a superficial position in the sternal notch. Death from tetany occurred 6 weeks after surgery.38

Dr. Oliver Cope, who has made monumental contributions to the surgery of hyperparathyroidism, commented at another time,

"Leaving a good portion of an adenoma does not seem to be too good an idea... some of our other patients treated in this way have turned out to have further hyperparathyroidism and a remnant had to be removed eventually. For a time we had an idea that it would be good to leave a portion of the adenoma to minimize the post-operative tetany. This has not proved to be necessary... .39

RECENT DEVELOPMENTS

Our present concept of parathyroid gland hyperfunction is the antithesis of the concept that prevailed at the time Mandl transplanted parathyroid glands into Albert Jahne because of a presumed parathyroid deficiency. Although the pathogenic mechanisms are still unclear, a number of exciting developments have occurred that should further our understanding of this disease.

The intact immunoparathormone assay has provided a more precise means of differentiating hyperparathyroidism from other causes of hypercalcemia. This method has advanced to the point that intraoperative monitoring of the immunoreactive parathyroid hormone level is possible.40 Studies on dispersed cells from adenomas, hyperplastic glands, and carcinomas have disclosed altered "set points" at which calcium regulates the secretion of parathyroid hormone. Increased parathyroid cell proliferation in combination with deranged calcium-regulated parathyroid hormone release, results in primary hyperparathyroidism.41 Localization procedures have been of help primarily in patients undergoing reoperation, in reducing morbidity, and in increasing the success of the operative procedure.42 Radiolabeled monoclonal antibodies hold the promise of a specific and sensitive method of identifying parathyroid tissue.43 Amino acid sequencing has led to an appreciation of those segments of the hormone that are responsible for active binding to its receptor and biologic activity. This permits the design of a molecule that binds to receptors but has no biologic activity, resulting in a very effective hormone antagonist.44 DNA probes suggest that parathyroid adenomas are more likely clonal than multicellular in origin. This has obvious implications with reference to our ability to discriminate between adenoma and hyperplasia and should help resolve the inadequacy of histopathologic criteria for differentiation.45

Since hyperparathyroidism was described in Herr Bleich almost 100 years ago, more precise methods of diagnosis and of localization of the lesion and excellent results from surgical correction have evolved. As we improved our understanding of this disease, our management should be less empiric and more rational, based on etiologic mechanisms, pathophysiology, and natural history.

In conclusion, we see the end result of the effort made by those hubristic fish that 100 million years ago had the courage to crawl ashore. Had these fish been more dif-fident, no glands of Owen would have been discovered and perhaps we would not have the problems of hyperparathyroidism today.