DAVID MARINE (1880–1976): NESTOR OF
THYROIDOLOGY

JMP MATWINSKI

And so we thought fit to spend our time and pains in writing the lives of
famous persons. ... [1, p. 31]

"The lives of noble Greeks and Romans" have remained through the
centuries living lessons for subsequent generations.
More than any other element of human culture, medicine combines
science and humanism, thus subscribing to the universal ideals of truth,
beauty, and goodness. The life and work of David Marine is an epitome
of this noble proposition.

Origins and Education of David Marine

In his "History as a System" Ortega y Gasset makes an overstatement:
"What nature is to things, history, res gestae, is to man" [2, p. 217]. And
yet, this pronouncement somehow applies to the origins of David
Marine. The French kings Henri IV and Louis XIV decisively in-
fluenced the course of his ancestors' lives. The former issued the Edict of
Nantes in 1598, giving the Protestant minority in France freedom of
religion and protection from persecution. The latter suppressed these
rights one by one and in 1685 revoked the edict. David's Huguenot ances-
tor, Millicent Martin, did not wait for the last act. Instead, he left Brittany
in 1666 for Maryland, thus preceding the exodus of many thousands of
his Protestant compatriots [3]. On both sides of the Atlantic, Marine's
ancestors were farmers, and he was born on a farm at Whidbey
Maryland, on September 20, 1880. The American Medical Association

*Professor of internal medicine, Division of Nuclear Medicine, University Hospital,
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had been founded 33 years earlier, and the American Academy of Sciences was only 17 years old at the time. The Marine family was hardworking, conservative in lifestyle, and moderately prosperous. Some of the older members might have looked like the Iowans of Grant Wood's Gothic Series.

David lost both of his parents before he reached the age of 7. Sadly, no memories of them survive. They left an endowment for the education of David and his two younger sisters. One of them graduated from nursing school, and the other became a teacher. He finished grade school in a nearby village, and lived until age 15 with an aunt on a farm near Dayton, Maryland [2]. Early rural experiences had a profound influence on his way of life and work, his scientific interests, his approach to research, and even on his activities in retirement.

At the age of 16 David entered Western Maryland College at Westminster where he received the best education of the time, with a good background in history and literature. There was relatively little science, but being general and not specialized, it fit well with the other mental furniture of an educated man of the turn of the century. David made good use of that science. His knowledge of German and French proved very advantageous too, since much of the scientific literature between 1850 and 1910 was published in either German or French.

In 1900 David enrolled at The Johns Hopkins University to study anatomy under W. K. Brooks, professor of comparative anatomy. But in his first year he had already decided to become a physician and therefore added German and chemistry to his curriculum. In 1901 he entered The Johns Hopkins Medical School, and in 1905 he graduated high in his class [4].

The industrial revolution and the strong influence of German ideas in science and technology had been the moving forces in the founding of The Johns Hopkins University. It is noteworthy that the opening address in 1876 was delivered by Thomas H. Huxley, a protagonist of a strong science curriculum and a gallant opponent of Matthew Arnold. He insisted that universities should be centers of science. Both The Johns Hopkins University Hospital (in 1889) and the medical school (in 1899) were established on the principle. David studied under a galaxy of scientists and educators, led by the greatest man in American medicine, William H. Welch, William Osler, Franklin P. Mall, William H. Howell, William S. Halsted, and John J. Abel [4, 5].

Under these circumstances it seems natural for an excellent student like David to have considered a career in research. Pathology appeared to be a logical choice, for W. H. Welch was an internationally known pathologist, and all of his teachers, except for J. J. Abel, the pharmacologist, had had considerable experience in that field. Finally, he was deeply impressed by W. S. Halsted and his studies of the thyroid gland.

David’s selection of and success in his work was greatly influenced by his first appointment in Cleveland, then a famous epicenter of endemic goiter. However, Herodotus’s “Fortune commands men” [6, p. 335] was fully counterbalanced by the old saying, “Only in good hands will every flute sing.” Many years later, in 1968, at the age of 88, he described in a letter the manner in which he had made his choice to study endemic goiter:

My decision was made on the morning I arrived in Cleveland from Baltimore on July 1st, 1905. In walking from the Hollander Hotel to the old Lakeside Hospital (four city blocks) to report for duty, I saw many dogs with swollen necks. I stopped three or four of these dogs and found that the swelling was due to the enlargement of the thyroid gland. Professor E. T. Howard (Pathology) met me at 9 a.m. to explain my duties. He said the routine work would require only half my time, and that I should have a research problem as a supplement. I told him that I had already decided on my spare time while walking down from the Hollander Hotel. Professor Howard was somewhat disappointed, as his major interest was in bacteriology, and he could be of little help in the thyroid field. To be sure, I was already sensitized to the thyroid gland by the research work of Professor W. S. Halsted done in 1886-1888, and published in The Johns Hopkins Report in 1896. As a student, I thought his work was excellent, and each year I was getting more interested in research than in clinical medicine [7].

This anecdote was a portent of things to come. Sometimes the opening measures of an overtone herald the dominant theme of the whole work. A research-minded young physician with a rural background noticed goiter in the street dogs of Cleveland and instantly decided to work in the same field as his admired teacher. But there was also an immediate anteclimax to this ambition. David had no experience in medical investigation and had never been exposed to any kind of experimental work. Therefore, it was his lot to be an autodidact in the field of thyroid research. Admittedly, most scientists are self-taught, but investigative thinking and practice are best developed under the guidance of experienced researchers. David’s postgraduate education was different from that of his teachers. After graduation from medical school, most of them had spent one or more years in advanced studies at leading medical centers in Europe and Great Britain. At the turn of the century, a relatively small number of scientists or even artists would embark on an ambitious career without some previous experience abroad. However, “non fit poetae, nascitur.” A few years later, David spent 6 months (December 1913–May 1914) with the thyroid surgeon and Nobel Prize winner, Theodor Kocher, and the expert pathologist in endemic goiter and cretinism, Karl Wegelin, in Bern, as well as with the cancer pathologist, Ludwig Pick, in Berlin. At that time, he was already a recognized thyroidologist and, as first among equals, carried on discussions with
them on the classification of goiter, iodine metabolism, and the relation of iodide-deficient goiter to thyroid carcinoma [5].

Like many individuals who lost their parents at an early age, David followed the pattern of his favorite teachers, wishing to identify with them. His broad and varied interests in goiter have several origins. In his 1925 Lancer Lecture at Johns Hopkins, he said:

One of the most important results of the thorough teaching of the sciences of physiology and pathology is the gradual unfolding to the student of medicine of the limitations of curative medicine. As our knowledge of these two subjects broadens, we are made conscious of the fact that some means of combating disease other than by cure, must be developed, if we are to cope successfully with many of the more serious causes of ill health, incapacity and suffering. My last years as a student in this university created this impression, which has increased during succeeding years. Whether their knowledge of physiology and pathology per se had anything to do with the selection of Professor Welch and Howell as directing heads of this School of Hygiene and Public Health is not, it has always seemed to me singularly fortunate for the school that physiology and pathology should have been given such prominent positions during its formative period. [8, p. 1]

His interest in clinical medicine was inspired by “the young man’s friend,” William Osler. David was the first pathologist to be active in clinical care of patients with thyroid disease, and he studied the effect of iodine and thyroid preparations in patients with endemic goiter and hyperthyroidism; he often presented papers at clinical meetings and published many of his studies in clinical periodicals [5].

David liked and acquired books as “friends that never fail.” While a sophomore medical student, on November 1, 1902, he netted Darwin’s The Origin of Species for $4 at the junk dealer leaving his library [5]. He was most interested in pathology and often quoted Rudolph Virchow, the founder of cellular pathology, anthropologist, public health worker, and leader of the democratic opposition to Chancellor Otto von Bismarck in the German Parliament. He also admired Louis Pasteur, the father of microbiology. Impressed by Pasteur’s universal interest in microbiology, from the contamination of beer to pebrine in silkworms and rabies in dog and man, he accepted Pasteur’s theory of the unity of medicine and his belief that vaccination should be supplemented by environmental preventive measures [5]. But, most devotedly, he embraced Pasteur’s doctrine, “There is only one science, and there are applications of science, the two being linked together like the tree and its fruit” [3, p. 215].

Before engaging in experimental work of his own, David studied the available literature most carefully, as if observing, “The best in him he owes to others” from Osler’s “Books and Men” [10, p. 35]. However, in the hospital he encountered confusion and controversy, even an orthodox standstill. Successful therapy of goiter with iodine had been introduced in 1820 by the Swiss physician Jean-François Coidet, who also warned against the danger of administering large doses of iodine, quoting H. Boerhaave (1668–1738): “At prudenter a prudente medicos, si methodum nescis, abstinens” (it is reasonable for a prudent physician to abstain from the method he has not mastered) [11]. In several studies, 1850–1860, the French pharmacist and botanist Caspar-Adolphe Chatin reported an inverse correlation of the iodine content of the air, water, soil, and food to the prevalence of endemic goiter [12], but his observations were rejected by a committee of the French Academy of Sciences, and only 45 years later were they confirmed by the Swiss chemist Theodor von Fellenberg [13, p. 293]. According to the Swiss surgeon Felix De Quervain, the first goiter prevention was carried out in 1855 in three counties in France. Salt containing potassium iodide, 0.1–0.5 g/kg, was used. Children received tablets of 0.01 g potassium iodide daily, and open bottles with elemental iodine were placed in bedrooms. The prophylaxis was generally effective, but it was soon discontinued and discontinued because of numerous cases of severe iodism and hyperthyroidism due to excessive intake of iodine [14]. Soon, in 1858, the first setback to the iodine therapy of goiter also occurred when Frederic Rillett reported hyperthyroidism as a frequent consequence of iodine therapy of goiter [15]. Ironically, in 1863, Armand Trousseau accidentally prescribed iodine and thereby relieved severe tachycardia in a case of hyperthyroidism. His orthodox switch to digitalis was followed by a relapse of fast pulse. Although he rationally reverted to tincture of iodine, the great Frenchman remained perplexed [16]. In 1867 the French physician, Joseph Saint-Lager, enumerated 43 hypotheses on the etiology of goiter. He believed the cause of goiter to be in the water. If food was responsible for goiter, he thought, people should be advised to leave their homes and, on the roads leading to endemic goiter areas, erect signs, “Abandon all hope ye who enter here” [17]. Defeatism was great. Even the report by Eugen Baumann in 1895, that iodine was a normal constituent of the thyroid, was of no avail [18]. The final blow to iodine therapy and prevention of goiter was delivered in 1910 by the prestigious Theodor Kocher. With the omenous term, “iodine based,” (iodine-hyperthyroidism), he warned that, in patients with nodular goiter, this disease was caused by large doses of iodine [19]. It seemed that the road to progress in this branch of medicine was hopelessly closed, but actually the stage was set for a solution to the goiter problem.

The Research and Scientific Accomplishments of David Marine

The philosophy of Marine’s scientific work was based on four principles: (1) The investigation of one problem from many sides is preferable
in the study of many problems from one side. (2) An understanding of thyroid anatomy and function in health and disease in general was a prerequisite for the successful solution of the problem of endemic goiter in particular. (3) Endemic goiter is the same disease in man and animals.

(4) Because of the limitations of curative medicine prevention of endemic goiter in man and animals is mandatory. The persistent adherence to the above principles is evident in all of Marine's publications.

The normal thyroid gland.—For Marine, the definition of the normal thyroid was a point of departure in a lifelong exploration of the numerous, enigmatic, and perplexing problems of thyroid disease. The first integrated values for the size, weight, structure, and iodine content of the normal thyroid in man and many animals were reported by Marine and co-workers in 1908 and 1909 [20, 21]. No one has studied the normal thyroid gland in more species (in all laboratory and most domestic animals, including poultry, as well as in many wild species, ranging from the bear and the turtle to the alligator). Surprisingly, the anatomy and iodine concentration of the thyroid of other vertebrates were similar, despite great differences in body organization and environmental conditions.

The average normal weight of the adult human thyroid was 24 g, or 0.23 g/kg of body weight. The normal size was 50-60 mm in transverse diameter, the height and thickness of the thyroid lobes were 50-60 mm and 10-20 mm, respectively. The relatively uniform thyroid follicles with 0.3-0.5 mm in diameter were lined with cuboidal epithelium and were surrounded by a little stroma. The iodine content varied considerably, but its minimal concentration, consistent with normal anatomical structure, was remarkably constant, about 0.2 percent dry weight. The average iodine content was 492 μg and 2.171 mg/g of wet and dry thyroid tissue, respectively. The average total thyroidal iodine was 95 μg [21]. This work met a definite need; these normal human thyroid gland values were adopted as standard references in many countries around the world.

During 1915-1916 Marine and Rogoff established that the thyroid of the dog takes iodine within seconds, whereas it needs 8 hours to produce the hormone. These observations were made by injecting iodide intravenously in hemithyroidectomized dogs whose ureters were ligated. The iodine and hormone content of the control and experimental thyroid lobes were determined chemically and by radicle biosynthesis, respectively. If the experiments were terminated after 30-48 hours, an increase in iodide concentration of the remaining hyperplastic thyroid lobe was noticed [22]. One year earlier Marine and Feiss had observed only thyroidal iodine uptake but no synthesis of the hormone after 1-5 hours in vivo perfusion of the thyroid lobe with iodine-enriched blood. The highest accumulation of iodine occurred in the hyperplastic goiter [23].

However, iodine in large doses can inhibit production and excretion of thyroid hormone in normal, colloid, and especially in hyperplastic thyroid tissue. The secretion of thyroid hormone, manifested by its metabolic effect, was decreased in newborn pups with hyperplastic goiters receiving large doses of iodine [24]. The iodine concentration mechanism in vitro was strikingly inhibited by potassium cyanate [23].

In 1909, Marine and Lennart carried out lobectomies and subtotal thyroidectomies (removal of five-sixths of the normal gland) in dogs [24]. If given an optimal amount of iodine, the regenerating thyroid remnant retained a normal histological structure and the animals remained euthyroid. Large doses of iodine were less effective than small doses in preventing hyperplasia of the thyroid remnant [21].

The steplike enlargement of the thyroid associated with multiple pregnancies was described in 1874 by Tait [25]. Such goiter development was preventable by administration of iodine. The effect of the thyroid on heat production during pregnancy was not well understood. Marine observed that, irrespective of the number of fetuses, the heat production (calculated from the respiratory quotient) was higher in control pregnant rabbits than in rabbits that were partially or totally thyroidectomized 7 days after breeding. Therefore, the increased thyroid function (per se) was partly responsible for the elevated heat production during pregnancy and lactation. According to Marine, the pregnant mother and newborn most often develop goiter if their increased iodine requirement is not met [26]. After the presentation of this study in 1924, Walter B. Cannon asked: “Did Doctor Marine make any examinations of the thyroid glands of the offspring? Is it not possible that the thyroid gland of the offspring might play a part in the heat production?” Marine answered: “We have made some observations, but we do not know whether the fetal thyroid can assist the mother in maintaining the increased metabolic rate. We have tried that with the administration of iodine. Iodine given to the thyroidectomized rabbits will not increase heat production, but it is carried over into the fetal thyroid. Therefore, I think that the thyroid hormone formed in the fetus cannot be transmitted back to the mother” [26, p. 190].

Transplants of most endocrine organs were carried out with Manley. More than 250 auto- and homografts of thyroid lobes under the skin and in various organs were studied in rabbits from 1913 to 1916. Wherever implanted, the thyroid autografts grew, synthesized hormone, and responded to lack of supplement of iodine. The destruction of homografts was slowed down if the thyroids of both the donor and the host were inoculated with large doses of iodine [27]. In 1934 Marine and Rosen obtained thyrotropin (by the method of L. Loeb and R. B. Bassett), which stimulated the thyroid auto- and homografts in the guinea pig [28].

In 1917, Rogoff and Marine iodized in vitro whole bovine serum. Its
globulin fraction was most active in tadpole metamorphosis. However, it was less potent than an equivalent amount of thyroid extract, and was inactivated by alkaline hydrolysis [29].

**Hyperthyroidism.**—In 1907 Marine reported that patients with hyperthyroidism can have (1) uniform diffuse hyperplastic goiter, (2) diffuse or nodular hyperplasia of thyroid follicles in a preexistent nodular goiter [30], or (3) focal nodular hyperplasia in the hyperplastic-collodial goiter [31]. The most common form is exophthalmic goiter (a term coined by George Bock of Ann Arbor, Michigan, and preferred by Marine to all other eponyms [32]). Today, exophthalmic goiter, containing a functioning adenoma, is known as the Marine-Lehmann syndrome [33]. The iodine concentration of the adenoma is lower than in the surrounding tissue, even after administration of iodine [33]. Marine also reported in 1913 that direct thyroid surgical specimens from hyperplastic thyroid patients contained less thyroid hormone than an equal amount of commercial desiccated thyroid. He proved this by comparing the disease-aggravating effect of both preparations in patients with hyperthyroidism [34]. In 1909 and 1911 Marine and Lenhart stressed that lymphocytic infiltrations occur especially in the hyperplastic goiter of Graves' disease as part of a systemic lymphoid hyperplasia [30, 33]. In 1909 Marine stated, "The severity of cases varies with the degree of thyroid and lymphoid hyperplasia" [31]. This concept was broadened by him in 1911: "We have found close parallelism between the percentage of mononuclear cells in the circulating blood and the extent of the active lymphoid and thyroid hyperplasia" [33]. Finally, he grasped the continuum of hyperthyroidism of Graves' disease and of ultimate hypothyroidism (Hashimoto's thyroiditis had as yet not been described): "The exophthalmic goiter is the most frequent forerunner of myxedema in adults, and Myxedema Oid had pointed out, all cases of myxedema are preceded by an acute thyroid hyperplasia with or without symptom complex of exophthalmic goiter" [35].

Marine planned the therapy of hyperthyroidism by changing the structure and function of the thyroid gland. His approach was based on anatomic reasoning: (1) the identical hyperplastic goiters in euthyroid dogs in Cleveland [29] and hyperthyroid man [33] are both iodine deficient; (2) after administration of iodine to dogs, the hyperplastic enlarged thyroid becomes a colloid goiter, which grows smaller and functions like a normal thyroid [24]; and (3) by inference, iodine should have the same effect on exophthalmic goiter. In 1911 and 1912 Marine reported the prophylactic use of iodine in 15 patients with exophthalmic goiter [34, 35]. But, without a curea and too early for his contemporaries, this method of therapy had to wait for 12 years to be reinduced by H. N. Plummer. He recommended it, at first, after surgical treatment of Graves' disease for prevention of thyroid stor [36].

From 1933 to 1940 Marine and Rosen produced exophthalmus increasing endogenous thyrotropin in rabbits (animals fed allafin at given injections of methyl-cyanide developed goiter) and in guinea pigs by injection of thyrotropin. They considered that exophthalmus in experimental animals was due to the thyrotropin effect on the eye directly or indirectly via the sympathetic ganglia of the hypothalamus [37, 38].

**Benign and malignant tumors of the thyroid.**—In 1913, Marine classified 114 human benign epithelial thyroid tumors into total, intermediate, and simple adenomas. He postulated that adenoma can exhibit cyclic growing, involuting, and colloid resting stages. In a group of 56 cases the iodine content of the adenoma was usually lower than in the surrounding tissue. Iodine in large doses had little effect on the structure of the adenoma [39]. In 1913, Marine and Johnson studied two human undifferentiated, metastatic carcinomas and one metastatic follicular carcinoma of the dog. To determine whether structural and functional differentiation are interrelated in malignant tumors as in normal thyroid, large doses of iodine were given for a prolonged period of time to both patients and the dog. In one patient and the dog, biopsy of tumors were taken before iodine was administered. No iodine was found even in differentiated (follicular) parts of the metastases of thymic carcinoma. The uptake of iodine in the primary tumor at metastases of the dog was 10 times lower than in the normal part of the thyroid gland. Therefore, he concluded that the thyroid iodine uptake serves best to differentiate normal from neoplastic thyroid tissue [39].

**Endemic goiter.**—Leonardo da Vinci knew more about goiter than medical profession until the end of the eighteenth century. The study of Rudolf Virchow, Theodor Billroth, Theodor Kocher, and others of the nineteenth century were descriptive in nature. Therefore, Marin realized that in order to control endemic goiter, it was imperative to study the whole subject ab ovo experimentally.

Rudolf Virchow wrote in 1865, "It has long been held that there are many varieties of goiter (among others: struma parenchymatosa, cysts, vascular, lymphatica, calcifica, etc.). That is wrong." Marine quotes this statement as an aprioristic idea, or a subtle abstraction of a great pathologist, which needed experimental confirmation [20]. This study proved difficult because of variations in and structural complexities of the human goiter. "In the present work, we first attempted to use human material, but were forced to turn back and study series of dog, sheep, and ox thyroids in order to find basic types of anatomical changes" [21]. With that goal in mind he simplified the anatomical classification of goiter into the following categories: (1) normal thyroid, (2) hyperplastic goiter, (3}
colloid goiter, and (4) "complication goiter." The diffuse, uniform hyperplastic goiter occurs in most animals. The colloid goiter is relatively frequent in man and in fowl. The "complication goiter" is most common in the adult human. It consists of more or less homogeneous mixtures of hyperplastic and colloid follicles and various types of exhausted and degenerated thyroid tissue. Inner irregularity and outer nodularity develop pari passu in this type of goiter [20].

Gaius Marcus Vitruvius, the Roman architect and writer of the first century B.C., thought that water was responsible for endemic goiter. "Aquae fuit in Italia et in Alpibus nationi Medullorum est genus aquae, quam qui libant effectuum tergis gauturibus" [40] (The Aequei in Italy and the Medulli in the Alps have swollen necks from the drinking water). The belief in a goitrogen in the water was held by many people in Europe and Asia, as well as by the Indians of the Great Lakes. On the same principle, Vitruvius rejected Chalin's theory of iodine deficiency of water as the cause of endemic goiter [41]. That was inevitable before Casimir Funk's vitamins were recognized in medicine in 1912. "Indeed, between 1905 and 1910, Lenhart and I frequently heard the criticism that it was difficult to conceive a deficiency of something causing something," remembered Marine [41]. Therefore, and not by chance, he and Lenhart examined the thyroid glands of mountain trout from Yellowstone Park, Utah, and California, sea-bass from the Atlantic Ocean, goldfish from local dealers, as well as pike and other fish from Lake Erie. "We observed goitrous changes only in the fish obtained from Lake Erie. It was very common in the pike and bass, rare in the sheephead and herring, and absent in the carp [42].

In order to explore the cause and mechanism of goiter development, Marine measured the iodine in the normal thyroid, as well as in the hyperplastic and colloid goiters of sheep, dogs, hogs, cattle, and fish. The iodine content per unit weight in the hyperplastic goiter was always low and varied inversely with the intensity of the hyperplasia. The total iodine was always below normal and became relatively lower as the goiter increased in size. In contrast, the iodine concentration of the colloid goiter was near normal or even normal. Depending on the size of the goiter, the total iodine was normal or even above normal [20]. These observations were confirmed in experiments involving prodigious variations on the theme. The design of the experiments was simple. In separate groups of dogs one thyroid lobe was removed for control studies of structure and iodine content. One-half of the animals remained on the same iodine intake (the "status quo group"), while in the other half the iodine intake was increased significantly (the "higher iodine group").

There were six variations in the experiment: (1) Dogs with normal control thyroid tissue. The remaining lobe of the status quo group became hyperplastic and contained less iodine (primary hyperplasia), while the remaining lobe of the higher iodine group became slightly enlarged but retained normal structure and iodine concentration. (2) Dogs with hyperplastic control lobe. In the statusquo group all deviations from the normal progressed further, while in the higher iodine group colloid involution and normal iodine concentration in the remaining lobe were observed. This lobe grew smaller (colloid involution). (3) Dogs with colloid involution of the control lobe. The remaining lobe in the statusquo group became hyperplastic and further enlarged while its iodine concentration was decreased (secondary hyperplasia). The size and structure of the remaining lobe of the higher iodine group remained histologically unaltered, but its iodine content was increased [44].

Although such correlations between iodine concentration and anatomy were found in diffuse, uniform human goiters, they were not observed in irregular, nodular goiters. By a spark of poetic intuition, Marine showed that this discrepancy was due to age-time-dependent morphological complications. He reminisced in 1954 about the "simple" experiment he had carried out in 1907:

One of the dogs (A-106) was said to be eleven years old and had a large, palpably irregular goiter. On June 5, 1907, Lenhart and I removed one lobe weighing 29.5 gm, which contained many old scarred areas and hemorrhagic cysts, with scattered intact areas showing large irregular colloid-filled follicles lined with flattened epithelium which was classified as "colloid goiter with multiple hemorrhagic cysts." After 40 days, we removed approximately one-half of the remaining lobe which weighed 15 gm and was similar both grossly and microscopically to the first lobe removed. After 57 days, we removed a portion of the remaining half lobe which weighed 3 gm. Microscopically, there were scattered areas, but the follicular epithelium, though irregular, was mostly columnar, and was classified as "moderately hyperplastic." A fourth specimen removed 88 days later, weighed 4.5 gm and was very vascular and soft. This we classified as "marked hyperplasia." This and other similar experiments established in our minds that compensatory hyperplasia in these long-standing and morphologically highly complex goiters was essentially identical with that observed by Halsted for normal thyroid of dogs. I think it was the most satisfying group of experiments we ever did. [41]

This study was first reported in 1909. The iodine content of the first degenerated thyroid specimen was lower than that of the subsequent, more colloid samples, declining again as the thyroid tissue became hyperplastic [43]. In order to convince the doubting Thomases, Marine sequentially performed seven partial thyroidectomies in one dog during a period of 18 months. By omitting or giving iodine, he alternately produced hyperplasia or colloid involution of the thyroid remnant [44].

According to these experiments, the structural changes of the thyroid are preceded by a decrease in the thyroidal iodine concentration from 0.2 percent to 0.1 percent of dry tissue [44]. The goiter develops by
primary hyper trophy and hyperplasia of the thyroid cells. Subsequent replenishment of thyroidal iodine is followed by colloid involution of the hyperplastic goiter. Finally, repeated reduction of iodine intake below normal levels to secondary hyper trophy and hyperplasia of the thyroid cells of the colloid goiter. During this process, the follicles increase in size because of cell hypertrophy, while subsequent involution of cells leads to an enlargement of the follicular spaces. With each repetition of this cycle, there is a progressive enlargement of follicles in colloid goiter [44].

Frequent or continuous formation of the hyperplasia-colloid inversion repetitive is an inevitable cause of exhaustion and necrosis of some thyroid cells. Cystic degeneration, hemorrhage, fibrosis, and calcification of thyroid tissue. The nodularity of the goiter is a consequence of the irregularity in the growth and structure of the thyroid. Prolonged repetition of hyperplasia may lead to hyperthyroidism (toxic nodular goiter) and also in either benign or malignant neoplasia. Because of thyroid exhaustion, it can also cause congenital goitrous cretinism in the newborn and goitrous myxedema in elderly individuals, especially women after many pregnancies. This phenomenon became known as “Marine’s Cycle” [45, 46].

In reflecting upon these studies, Marine, at the end of the chapter on the problem of “cycle” in the irregular, disfiguring goiter, wrote, “I think it was the most satisfying group of experiments we ever did.” [41]. At that moment, the reader both rediscovers Marine’s cycle and shares in the joy of his beauty. This aesthetic experience brings to mind a sonnet written by Michelangelo while painting the frescoes on the ceiling of the Sistine Chapel [48, p. 25]:

I've grown a goiter by dwelling in this den—
As cats from stagnant streams in Lombardy,
Or in what other land they hap to be—., .

Thus, in dealing with the subject of goiter, the scientific experiment and the verse of poetry are equally imaginative, and each in its own way makes a contribution to progress.

Prevention and therapy of endemic goiter.—Because an inverse correlation between thyroidal iodine concentration and thyroidal cell hyperplasia exists in man and animals, Marine proposed that absolute iodine deficiency was the dominant cause of endemic goiter. To prove this hypothesis, he tested both the prevention and therapy of hyperplastic goiter with iodine in animals and man. The effect of iodine on the goiter of the Lake Erie pike was studied by Marine and Lenhart in 1910 at the State Fish Hatchery at Put-in-Bay, Ohio. Pike of uniform age and size were kept in 80 ft. troughs, filled continuously with Lake Erie water. The control fish had a mild to marked hyperplastic goiter, diffusely spread around the ventral aorta between the first and third gill. Experimental fish received one drop of Lugol’s solution per day. Colloid involution of the hyperplastic goiter was observed within 20 days in the experimental fish [43].

However, the most rewarding studies were carried out in the brook trout from 1909 to 1915 at the Blooming Grove Hatchery in Pennsylvania. The fish were kept in small tanks in 11 houses downstream along a brook. The age, size, crowding of the fish, and pollution of the water increased progressively in the same direction as the prevalence and size of the goiter. In the last tanks, the level of water was so low that the fish rubbed against the ground, and the large, ventrally bulging goiters were exacerbated. In contrast to amphibia and reptilia, the thyroid of fish has no capsule. Therefore, a large goiter can invade surrounding structures. By compressing the gills, the hyperplastic goiter was preventing normal respiration, and, by invading the muscles and bones, it was disturbing the feeding. The urchers were infected with bacteria and fungi. The large hypothyroid fish were “excessively fat, weak, sluggish and cumbersome creatures with little resistance when taken by hook and line.” The wild fish in raceways outside of the tanks, even in polluted water, were goiter free. The life of the goitrous and especially the hypothyroid fish was observed after the trout were fed chopped California sea fish, or after one part of iodine was added per one million parts of water. Thus the fisheries in the country were saved from financial ruin. Marine learned that age, body size, overfeeding with meat, and pollution of water with fish excrement contributed to the development of goiter. He showed that the invasive, hyperplastic thyroid in fish was not a thyroid carcinoma, as European experts claimed. However, he was convinced that prolonged excessive thyroid hyperplasia can lead to cancerous alteration. His homographs of such tissue, in 1909, failed to grow, but he ascribed that to deficiency in technique and physiological requirements [47, 48].

Marine liked dogs, and because their nutrition and goiter are similar to human, he used them from 1907 to 1910 to solve some basic questions about the cause and prevention of goiter in man and mammals. Newborn pups developed large, hyperplastic thyroid if, early in pregnancy, their mother was subtotally thyroidectomized and thereafter was fed an iodine-deficient diet. Her second litter of pups had normal thyroids if, before and during pregnancy, she was given iodine. In the iodine-deficient Cleveland area, one-half of a litter of pups given 1 mg of iodine per week had a normal thyroid gland, while in the same kennel, the other half not receiving iodine developed goiter. In one litter of 6-week-old congenitally cretinous goitrous pups, the thyroid tissue consisted of fibrotic stroma and rare, mostly exhausted follicles. Given a few milligrams of iodine per day for 2 months, all pups began normal devel-
opment, while thyroid biopsies showed gradual regeneration of follicles and disappearance of the stroma [44].

During 1916–1917 Marine carried out a practical experiment in the prevention of goiter in farm stock (chickens, hogs, cattle, and horses) on a farm at Pemberton Meadows Valley, British Columbia. The farmer could not rear any animal to maturity because of goiter and cretinism. After adding a few milligrams of iodine to the food every week, “Mr. Homaye stated that they had no difficulty in absolutely controlling goiter by this very simple and inexpensive means” [49].

The first pilot study in individual prevention and therapy of goiter with iodine was carried out by Marine from 1912 to 1918 in children at the Lakeside Hospital Medical Dispensary in Cleveland [50]. In cooperation with the Department of Obstetrics of the Western Reserve University School of Medicine, he also studied goiter prevention with iodine in a large group of pregnant women [8]. “Attempts to apply the plan of goiter prevention in man on a large scale were beset with the difficulties, obstacles, and hazards which society seems always to have interposed when new methods of controlling disease (however meritorious) have been proposed. Many interesting stories could be told of our efforts and failures to make the experiment” [45]. Finally, Marine and Kimball carried out, from 1917 to 1920, the first scientific large-scale goiter prevention program, in fifth- to twelfth-grade schoolgirls in the Public Schools of Akron, Ohio. At that time, 49.9 percent of the girls had a slight goiter (grade 1; small, visible, and palpable goiter), 6.4 percent had a moderate goiter (grade 2; marked bulging goiter), and 0.2 percent had a marked goiter (grade 3; excessive deformity of the neck). Thyroglossal duct, as a sign of intrauterine goiter development, was found in 13.4 percent of the girls at single and multiple nodules in 1.01 percent.

The method at that time consisted in the administration of two grams of sodium iodide in 0.5 gram doses, distributed over a period of two weeks and repeated each month and yearly. At that time, it was pointed out that this amount of iodine was excessive and far beyond the needs of the individual or the ability of the thyroid to utilize or store it. This demonstration was carried out for a period of two and one half years, and the results are briefly as follows: 2100 pupils taking 2 grams of sodium iodide twice yearly, only five developed thyroid enlargement, while 2100 girls not taking the prophylactic, 495 developed thyroid enlargement. The thyroid glands of 773 pupils out of 1182 with thyroid enlargement, after the prophylactic treatment, decreased in size. These figures demonstrate in a striking manner both the prevention and the corrective effects of minute doses of iodine. [50]

Hyperplastic goiter in dogs [24]. In 1923 Marine proposed goiter therapy with USP desiccated thyroid 0.1–0.2 g per day for 2–3 weeks, followed by 10 mg of iodine per day for the same period of time, to be repeated twice a year [49]. At that time he noted that a large dose of iodine can temporarily lower the metabolic rate in a patient with hyperplastic goiter [52].

Studies of endemic cretinism.—While in Switzerland in 1913–1914, Marine had noticed that small stature and low intelligence, deaf-mutism and cretinism, were the horrible shadows of endemic goiter [3]. Although very rare in overt form in humans in the United States, endemic cretinism in domestic animals in goitrous areas was a serious problem at the turn of the century. “My first visit to Michigan was in March 1907, when I made a horse and buggy visit to several farms between Ann Arbor and Pontiac, to add to our collection of thyroids of cretin goitrous dogs and calves, also the thyroids of cretin lambs” [41].

In 1907 he reported a case of endemic hypo-thyroid cretinism in a bullocker. “The puppy on admission was anemic, apathetic, pot-bellied. His hair was coarse, eyes weeping, he had a large symmetrical swelling of the thyroid and expanded pulsation, accompanied by a bruit.” Treatment with desiccated thyroid and iodine produced colloid involution of the hyperplastic goiter and a general improvement of health [53]. In many of his articles Marine quoted B. A. Morel: “Le goitre est la premiere etape sur le chemin qui conduit au cretinisme,” adding his own translation: “Goiter is the first halting place on the road to cretinism.” In 1924, he stressed that iodized salt was the best means of prevention of both endemic goiter and cretinism in the whole population and that prevention of endemic goiter should also contribute to the decrease in incidence of hyperthyroidism and thyroid tumors [54].

Studies of goitrogen in food.—After the Akron experiment Marine and his co-workers became champions of absolute iodine deficiency as the dominant cause of endemic goiter. However, in 1909 he wrote: “And it is our belief that one or more chemical substances will be found which are antagonistic to or inhibit the normal absorption or assimilation of iodine” [21]. And, in his 1924 Harvey Lecture, he restated that “goiter may develop because of relative iodine deficiency caused by factors which interfere with the absorption or utilization of iodine” [45].

Only 3 years later such a goitrogenic factor became the subject of intensive inquiry. As if foreseeing the future great importance of such substances in other nutrients, like cassava (tapioca) and soybeans, Marine spent 6 years working in that field of research. In 1927 Chesney of The Johns Hopkins Medical School observed development of large goiter in rabbits used in studies of syphilis [55]. His co-worker, Webster, consulted on this observation with Marine. Thereafter, Chesney, Clawson, and Webster reported that a diet of cabbage, and not syphilis, had
caused the thyroid enlargement. They established that administration of
iodine to goitrous animals was followed by severe, usually fatal hyperthyroidism [56]. Finally, Webster and Chesney demonstrated that the
goitrogenic effect was preventable when cabbage and iodine were given
simultaneously [57]. Marine, Baumann, and Gipra noted seasonal varia-
tions of the goitrogenic effect of cabbage and also showed that other
types of Brassica plants, such as cauliflower and turnips, were goitrogenic
[58, 59]. At that time Webster joined Marine’s group; they reported that
the goitrogenic effect of cabbage varied with the location of origin and
was increased by boiling the cabbage [58, 59]. They also noted that the
volatile ether extract of cabbage was goitrogenic in rabbits [60]. Since
Thio-ureas are characteristic constituents of the Brassica plants, Marine
and his co-workers injected rabbits with these compounds and their
cystine precursors. They were the first to observe that methyl
thiourea was goitrogenic [61].

Public health approach to endemic goiter.—Although the Akron
experiment was the first success in the prevention of goiter in a large number
of individuals, “a political storm seized on the Akron experiment as an
invasion of personal rights and stopped it” [62]. However, Marine did
not give in. During the following 35 years, by way of lectures and publi-
lications, he stimulated public health studies and goiter prophylaxis both
at home and abroad. The first statewide goiter prevention program
was started in Michigan in 1922 by the Advisory Committee of the Pediatric
Section of the Michigan State Medical Society, under the leadership of
Marine’s father, Walter L. Cowie, chairman of the Department of Pediatrics,
University of Michigan School of Medicine. In close contact with Marine and Kim-
ball, the committee prepared a plan for the prevention of goiter, and its
denier, W. H. B. H. E., developed a method for the iodization of salt [63]. At
the same time, the Michigan State Department of Health, under Com-
missioner R. A. R. D., carried out a survey of goiter prevalence in
schoolchildren (supervised by Kimball) and also determined the iodine
content of the drinking water in four counties in Michigan. An average
goiter prevalence of 38.5 percent and an inverse correlation of iodine
content in water and goiter prevalence was found [64]. In later years,
this survey proved useful for the evaluation of the effect of iodized salt.
On March 13, 1924, the advisory council (“Salt Committee”) obtained
the approval of the Michigan State Medical Society for a general goiter
prophylaxis, and with the concurrence of the State Health Board goiter
prevention was started in the fall of 1924. Goiter prophylaxis was op-
tional: both iodized and noniodized salt was available, at no difference in
cost to the consumer. One part per 10,000 (0.1 percent) sodium iodide
was added to table salt only [65]. Thus, despite many organizational
problems and even the fact that “the United States Department of Ag-
culture, Bureau of Chemistry, at first had insisted that each carton of
salt should be labeled with the skull and crossbones, because iodine is a
poison” [65], this effort ended as an overwhelming scientific and social
validation of general goiter prophylaxis with iodized salt. It inaugurated
the first ecological prevention of a noninfectious disease throughout
the United States and the whole world. On September 13, 1924, the Ann
Arbor News, under the heading, “Urge Families to Use Iodized Salt,”
announced that iodized salt was available, warned citizens about an out-
break of a severe type of smallpox in Toledo, Ohio, and reported on
preparations for the season of infantile paralysis [66]. Shortly thereafter
the use of iodized salt spread throughout the country. In 1925 a reduc-
tion of goiter prevalence in schoolchildren in the four counties of Michi-
gan (from an average 38.6 percent in 1924 to an average of 1.4 percent)
was reported by Brush and Altdorf [67]. Goiter prophylaxis in the
United States was probably at its zenith in 1955, when only iodized salt
was used in 75.8 percent of households, both iodized and noniodized salt
in 2.9 percent, and only noniodized salt in 26.2 percent [68, p. 189].

In Europe, public-health work on goiter started in the early 1930s.
Switzerland led the way by introducing a similar goiter prophylaxis in
1922 [69]. During World War II all work on goiter was interrupted. In
1950, Marine’s idea of goiter prevention was taken up by the World
Health Organization (WHO), and Kinball, as the WHO consultant, vis-
ited several South American countries [65]. The first international
cooperative study of endemic goiter was carried out in 1951 by J. B.
Stanbury, with co-workers from the Massachusetts General Hospital,
and by H. Perinetti and his colleague in Argentina [70]. One year later,
in 1952, the WHO Goiter Study Group, with Kinball representing his
72-year-old teacher [71], prepared a worldwide program for the
investigation and prevention of endemic goiter. This program more or less
vigorously pursued aims to prevent endemic goiter in 200 million indi-
viduals inhabiting large goitrous areas around the world. The elimin-
ation of smallpox and great success with poliomyelitis, together with the
justifiable expectations for the prevention of endemic goiter, all so
alarmingly frequent in 1924, could point the way for medicine at the
dawn of the third millennium.

Finally, at the age of 74, in the James D. Bruce Memorial Lecture of
the American College of Physicians, the pioneer of goiter prevention
put the finishing touches on his portrait of endemic goiter [41]. With deep
understanding of the intricate roles of man and environment in the
development and prevention of goiter, he perceived the thyroid gland
as functioning within the realm of three worlds. Endemic goiter was pre-
dominantly caused by the uneven distribution of iodine in the inorganic
world. This was most aggravated during the last glaciation, when ma-
ture, iodine-rich soil was swept away and the new crystalline soil without
humus could not retain iodine. The northern regions of the United
States were in the goiter belt. In 1924, Marine reproduced a map of the Wisconsin Drift, which roughly corresponds to the endemic goiter area of the Great Lakes States, extending westward through the Dakotas, Montana, Colorado, Idaho, Utah, Oregon, and Washington, as well as to the southeast into the states of the Appalachian Range [44]. In the organic world it was recognized: (1) endemic goiter as an adaptation to chronic absolute iodine deficiency; (2) endemic or sporadic goiter due to relative or inadequate, brought about by (a) an increased requirement of thyroid hormone during growth, pregnancy, lactation, and chronic infection; and (b) a disturbance in the thyroid hormone synthesis of goitrogenic carcinomas and their precursors, as well as 5-iodo-2-thio-oxoacetate in a great variety of vegetables; (3) relatively infrequent goiter due to homo- and heterozygous inborn errors in iodine metabolism and over-sensitivity to goitrogens in phenyl-thiocarbamate poisoning; and lastly, (4) sporadic or even endemic goiter resulting from a combined interplay of various factors. Finally, in the social world he experienced that scientific advances can both solve and create problems. In many areas endemic goiter was virtually eliminated by the supplementation of iodine in salt, while in others the refinement of salt, with the consequent loss of iodine, was the cause of goiter. The efforts toward goiter prevention were confronted at times by the phantom of Jod-Basedow, while at other times they were impeded by conservatism, ignorance, self-interests, and economic and political difficulties which often stand in the way of progress. The common errors of mistaking the complex for the simple, and the beginning for the end, were known to Marine. Already in 1909 he rejected iodine deficiency as the sole, linear cause of goiter, postulating a multiple causation, complex in nature [21]. Also, from the very outset to his last lecture in 1954, he favored iodization of all salt for human consumption. To ensure an optimal, uniform intake of iodine for the entire population and to avoid adverse effects from excessive iodine intake (especially Jod-Basedow), he preferred a general prophylaxis with iodine 1:100,000 parts of all salt (10 mg KI/kg), rather than the present optional use of 1:10,000 parts of iodized table saltly. He envisioned that 50 years would have to pass before nodular goiters, existing at the beginning of goiter prophylaxis, were naturally eliminated. Therefore, he suggested that limited periodic goiter surveys would be advisable in order to adjust the iodine supplement of salt [41].

As if foreseeing our present health hazard and high intake of iodine from various known and unknown sources, he warned, “iodine, like other food, has been greatly abused” and “iodism and the possibility of aggravating exophthalmic goiter are the dangers worthy of consideration” [34]. Marine understood goiter prophylaxis basically as a permanent irrigation system, preventing deficiency of and flooding with iodine. He considered goiter prevention an integral part of the national nutrition program, which should become the responsibility of the Public Health Service. Therefore, he wrote, “In conclusion, I should like to emphasize that simple goiter is the easiest of all known diseases to prevent, and that it may be excluded from the list of human diseases as soon as society determines to make the effort” [49].

David Marine, the Man

The dignity of a great man, reflected in the world of noble ideas and ideals, is in many ways similar to the grandeur of a mountain, mirrored in a lake below. We admire them both, without ever knowing them well. Like his farmer ancestors, Marine lived for work. The first phase of his studies (1905–1920) took place at the Cushing Laboratory for Experimental Medicine, Western Reserve University, in Cleveland, Ohio. Here as associate professor of experimental medicine he lectured in endocrine pathology to medical students. He carried out the second part of his investigation as chairman of the Department of Pathology and director of the Research Laboratory at Montefiore Hospital, New York (1920–1945). Simultaneously, he held an appointment as assistant professor of pathology at the Columbia University Medical School. Marine assembled a remarkable team of investigators. Among 20 co-workers over the years, the greatest contributions were made (in chronological order) by C. H. Lenhart, W. W. Williams, H. O. Feiss, J. M. Rogoff, O. T. Manley, S. H. Rosen, A. A. Johnson, O. P. Kimball, E. J. Baumann, A. Ciprana, A. W. Spence, B. P. Webster, J. Lerman, A. E. Meyers, and others. During his career as a pathologist and later as chairman of the Department of Pathology, he worked 7 days a week, and in the early years of his retirement he spent his days from dawn to dusk on his cattle farm, or in his vegetable and flower garden in the late years of his long life.

At the age of 42 he married a high school teacher, Mary Elizabeth Nuttle, from the village where he had gone to school, and she made a warm and pleasant home for him [5]. Marine was a serious man, but with a healthy sense of humor, punctuated by a twinkle in his grey-blue eyes. He expected little from life and probably was happy most of the time. He was a friendly man but had few close friends. For many years his co-workers Lenhart, Baumann, and Webster were closest to him. A teetotaller, his social activities were at a minimum. He had little time for anything except his work.

A conversation, recorded on tape in 1968, follows verbatim [72]:

Q: You had a surgeon who made transplants of the thyroid with you? A: Yes. Q: What conditions for work did you give him? A: I gave him three conditions: the first was that he work, the second was that he work, and the third was that he work. Q: What did he answer? A: He said, “I can meet all three conditions.” And he did.
Marine and Manley performed about a thousand transplants of endocrine and other organs. Marine proudly subscribed to Pasteur's ideal of science for the good of mankind, but in search of scientific truth, he was intolerant of the conformist "ciu bono." In 1926, he reported a 5-year observation that 64 of 257 cats, mostly of street potpourri origin, had more or less extensive calcifications of the adrenal cortex. To document whether or not this phenomenon was characteristic of cats only, he histologically examined the adrenal cortex of 125 cattle, 150 pigs, 200 sheep, 238 dogs, and 2,300 rabbits [73].

Marine was devoted to education. He generously shared his knowledge and the fruits of his work with his co-workers. Most of them began thyroid research under his guidance and continued in it for a long time. He liked to teach students whenever he had an opportunity. He may not have been the greatest lecturer but his students were inspired by him. His own words may illustrate that best:

Q: Now, Doctor Marine, I would like to ask you about the Akron experiment. Who helped you with it? How did you get to it? A: Well, Kimball... I was lecturing to the second-year class in Pathology, and Kimball was a second-year man at that time... In the class, I made a statement that any doctor who has charge of young girls between the ages of 6 or 7 and 15 would be guilty of criminal negligence if he allowed goiter to develop in these girls. After the lecture was over, he, Kimball, came down and said: "That was a very serious statement you made, and if true, something ought to be done about it." I said: "Why, my dear man, I have been trying to do something about it for five, six years." He said: "Well, I taught school in Akron for eight years before I started medicine, and I know the political machine there from A to Z. If anything could be done anywhere, it could be done in Akron." I said: "We'll jump in the car and we will go to Akron tomorrow." So we went to Akron. Kimball called the School Superintendent and he came, and with him, his whole School Board. Q: Do you remember his name? A: I don't remember the name. Q: Wasn't he a Ph.D.? A: Yes, he was a Ph.D. from Hopkins, and he asked what school I was graduated from, and I told him Johns Hopkins... He sort of put his arm around me and said: "Same school for my Ph.D., and I know you're not a damn crook." That's all he said. "Anything we've got here in Akron, you can have."

In 1952, at the meeting of the WHO Study Group, Kimball claimed that Marine had taught him all about endemic goiter, he steered his interest into goiter prevention, and that this had given meaning to all his life. According to Kimball, the enlightened superintendent of schools in Akron was H. V. Hotchkiss [74].

Most of Marine's work was supported by the Western Reserve University and by Montefiore Hospital in New York, but research funds were also obtained from the American Medical Association and the Ella Sachs Foundation. Fellowships were granted by the National Research Council and the Rockefeller Foundation. His handling of grants may be illustrated by the following conversation:

Q: Who supported it and how much money did you spend on it? [the Akron
In November 1976, Bertha Polite, Marine's housekeeper for the last 15 years, found a document showing that he once returned to the American Medical Association $79.50 from a grant of $250 [75]. In that respect, Marine had never changed. According to E. M. Bluestone, retired director of Montefiore Hospital, Marine's salary, as chairman of the Department of Pathology, was about $10,000--$12,000 per year. At the time of his retirement, the hospital board wanted to recognize his excellent services with a gift of $10,000. Marine thanked them but declined the honorarium, stating that his salary had been adequate and fair [76].

Since his youth, he had been interested in history. Concerned that "backlash might destroy the past," he devoted considerable time, in retirement, to collecting Indian archaeological artifacts in Sussex County, Delaware, and became the main contributor to the local archaeological bulletin. Together with the sense of history, he developed an interest in the age of voices and became an expert dendrologist [5]. He read much about antique furniture, and refurbishing old pieces was his only hobby. During his relaxing hours, Marine found great pleasure in listening to classical music [3]. He remained interested in goiter and read medical journals until age 91, when, in 1971, he had a cerebral vascular accident with a permanent motor aphasia [75].

At the moment, the poetic prose of Sir Rabindranath Tagore could have spoken for David Marine. "On the day when death will knock at thy door, will you know who is the visitor? Oh, I will set before you the full vessel of my life. I will let him go with empty hands. All the sweet sluggishness of all my sunny days and summer nights, all the earnings and gleaning of my busy life I will place before you at the close of my days when death will knock at my door" [77, p. 42].

David Marine died on November 28, 1976, at the age of 96. He was laid to rest next to his wife at the Hillcrest Cemetery in Federalsburg, Maryland. They are survived by one son, David N. Marine, physician [3].

Contribution of David Marine to Thyroidology: An Attempt at a Summary

During the past 30 years considerable advances have been made in the field of thyroidology. However, Marine made most of his contributions

REFERENCES

and the James Bruce Memorial Lecture of the American College of Physicians in 1954. He received the highest E. R. Squibb Award of the Endocrine Society in 1955. In 1960 he was awarded the Kober Medal, the highest honor of the American Association of Physicians. The Award of the American Thyroid Association in 1968 was "in recognition of his fundamental contributions to the cause and prevention of goiter."
75. B. Polite. Personal communication, 1976.