Hist Otorhinolaryngol 2019; 253-264

Theodor Kocher, Nobel Prize winner for work in thyroid physiology, pathology and surgery, died more than 100 years ago

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Abstract
Background: Theodor Kocher received the Nobel Prize for thyroid surgery in 1909. The aim of this study is to reflect on how Kocher's work on the thyroid came to be recognized as worthy of the Nobel Prize, the first ever for a surgeon.
Methods: An extensive review of Kocher's publications dealing with the thyroid, and of all publications concerning him and the history of thyroid physiology was conducted.
Result: Kocher's thyroid work is hereby presented in four chapters following a brief biographical sketch: the development of safe thyroid surgery; unexpected consequences of total thyroidectomy: *cachexia strumipriva*; understanding thyroid pathophysiology; and description of the main thyroid pathologies.
Conclusions: Kocher's contributions to thyroidology combine an assimilation of historical data, an impressive chapter in the development of modern thyroid surgery, and a model of medical and scientific inspiration.
"An involuntary experiment in man historically forms one of the foundations of modern endocrinology." [1] This statement found in Tröchsel's remarkable biography of Theodor Kocher (1841-1917), may best describe the career and impact of the thyroid work of this surgeon Nobel laureate who died a century ago.

Key words: *history, Kocher, thyroid, surgery, research*
No financial support, no conflict of interest

The aim of this study is to reflect on how Kocher's work on the thyroid came to be recognized as worthy of the Nobel Prize, the first ever for a surgeon. An extensive review of Kocher's publications dealing with the thyroid, and of all publications concerning him and the history of thyroid physiology was conducted. It was augmented by a review of the key documents at the Kocher Institute in Bern and the Institute for History of Medicine of Bern University.

Kocher possessed an intuitive realization that to understand and master pathological processes required an extensive knowledge of normal anatomy, physiology and biochemistry. Furthermore, good medical and surgical outcomes could only be achieved with a surgical technique based on meticulous hemostasis, application of principles of antisepsis and gentle tissue handling in order to preserve functionality of the surrounding structures as much as possible[2]. Kocher's particular interest in the thyroid stemmed in part from the endemic nature of goiters in his area[3], bringing to him numerous patients. Kocher's thyroid work is hereby presented in four chapters following a brief biographical sketch: the development of safe thyroid surgery; unexpected consequences of total thy-

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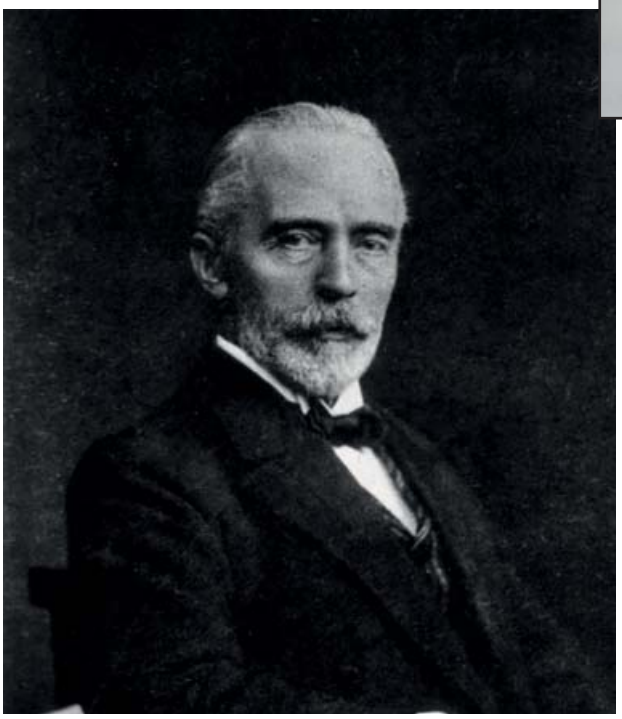
Presented at Kocher Symposium, Swiss ORL Society Meeting, Interlaken, November 16, 2017

roidectomy: *cachexia strumipriva*; understanding thyroid pathophysiology; and description of the main thyroid pathologies.

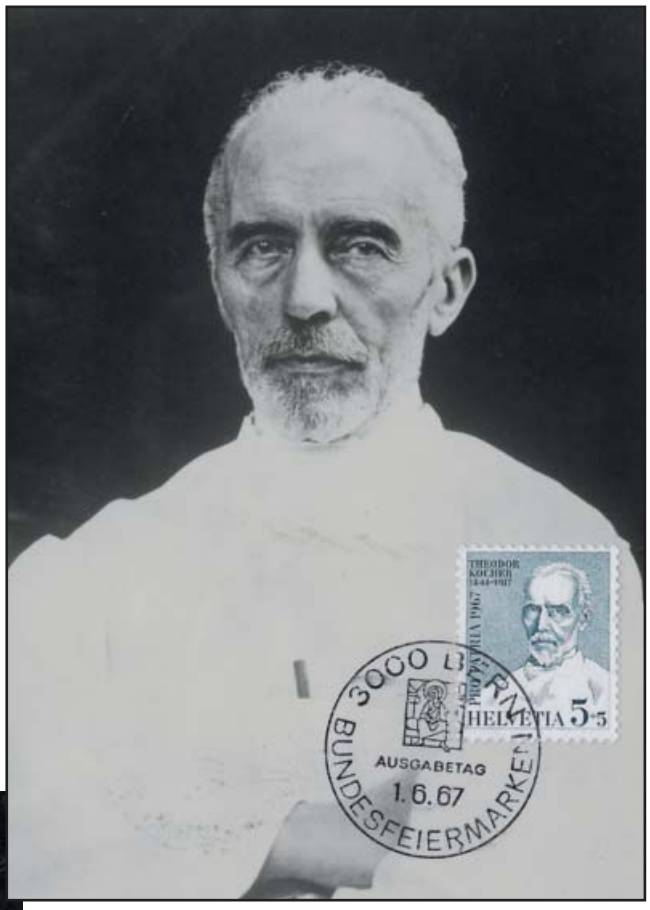
Short biographical sketch

Born in Bern August 25th, 1841, Emil Theodor Kocher *(Figure 1)* studied medicine in his hometown, where he obtained his doctorate in 1865. Upon finishing his formal studies, he trained abroad with the great surgeons Bernhard von Langenbeck in Berlin, Joseph Lister in Glasgow, Thomas Spencer Wells in London, Auguste Nélaton in Paris, and Theodor Billroth in Vienna. In 1866 he returned to Bern, became assistant to Georg Albert Lücke and was appointed privatdocent in surgery. In 1872, at 31 years of age, he succeeded Lücke and became director of the Surgery Clinic at the University of Bern, where he remained until his death on July 27th, 1917 *(Figure 2)*. A prolific writer (approximately 250



1.Portrait of Kocher, post card Switzerland, no date.

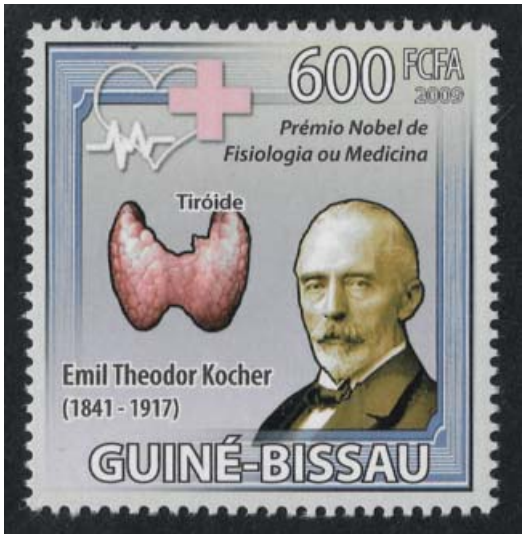
articles and books), Kocher published his surgical textbook, *Chirurgische Operationslehre*, in 1892, based on his vast personal experience. The book achieved five editions in 15 years, was expanded from 208 to 1072 pages, and was translated into English. In 1909 Kocher was



2. Kocher's stamp on maximum card, Switzerland, 1967

awarded the Nobel Prize for Physiology and Medicine for his work on the physiology, pathology and surgery of the thyroid gland[1,4-5], his most significant of many contributions to medicine [6] *(Figure 3)*.

Kocher assigned six eponyms related to the thyroid: Kocher's middle thyroid vein *(Figure 4)*, Kocher II incision (cervical transverse incision for thyroid surgery) *(Figure 5)*, Kocher probe (spoon-shaped probe for the operation of goiter) *(Figure 6)*, Kocher sign (in hyperthyroidism, excessive retraction of the eyelid, or the corollary of lid-lag, where with upward gaze the eyelid rises faster than the eye), Kocher's syndrome (splenomegaly with or without lymphocytosis and lymphadenopathy in thyrotoxicosis), and Kocher-Debré-Sémélaigne syndrome (the combination of hypothyroidism, myxoedema, short stature, cretinism with pseudo-hypertrophic myopathy in infancy and childhood). In addition to these thyroid eponyms,



3. Kocher's Nobel Prize stamp, Guinea-Buisau, 2009

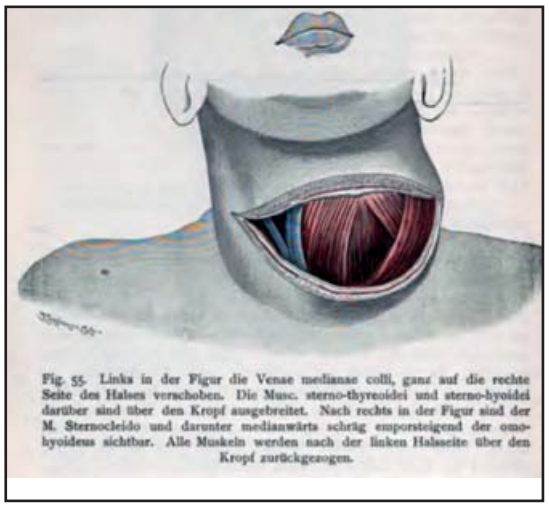
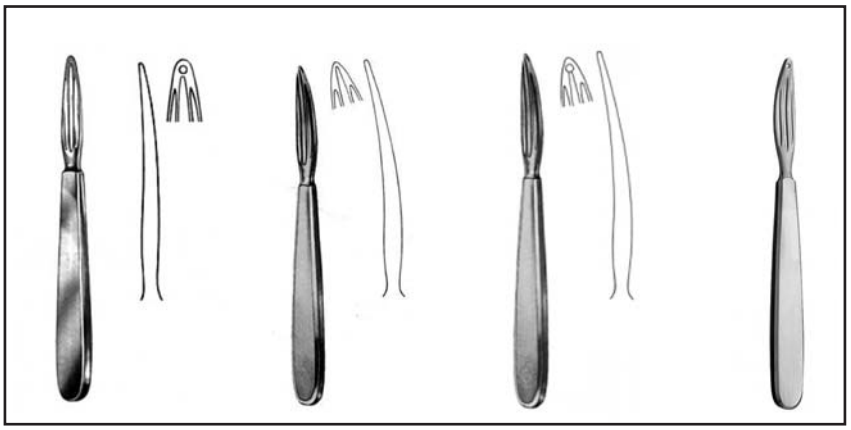
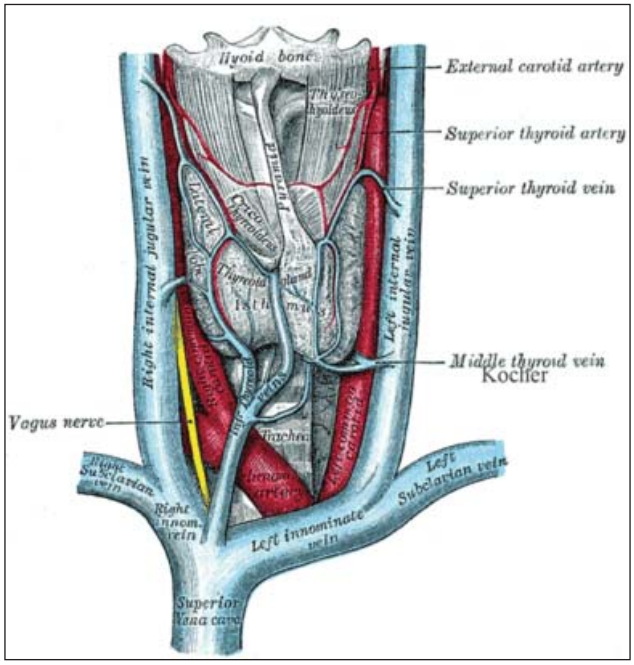


Fig. 55. Links in der Figur die Venae mediianae colli, ganz auf die rechte Seite des Halses verschoben. Die Musc. sterno-thyreoidei und sterno-hyoidei darüber sind über den Kropf ausgebreitet. Nach rechts in der Figur sind der M. Sternocleido und darunter medianwärts schräg emporsteigend der omo-hyoideus sichtbar. Alle Muskeln werden nach der linken Halsseite über den Kropf zurückgezogen.

5. Kocher II incision (from his 1902 textbook)

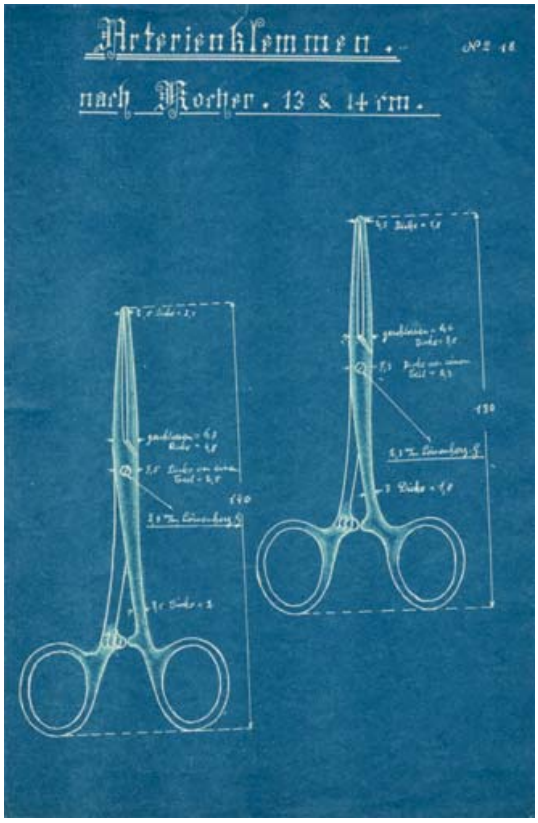


6. Kocher probe (from various modern instruments catalogues)



4. Kocher, middle thyroid vein
(from Gray's anatomy, 1918)

Theodor Kocher attached his name to various surgical techniques, instruments, or other signs and clinical syndromes[7]: Kocher operation or Kocherization/Kocher maneuver (mobilization of the duodenum before performing other procedures, notably exposing the papilla of Vater), Kocher's incision (oblique arched incision to open the knee joint), Kocher I incision (oblique subcostal incision parallel to the costal margin on the right side of the abdomen for cholecystectomy), Kocher's method (technique for reducing antero-internal dislocation of the shoulder), Kocher method I (method to fix the bottom of the uterus to the abdominal wall), Kocher method II (technique of invagination for the radical operation of the inguinal her-

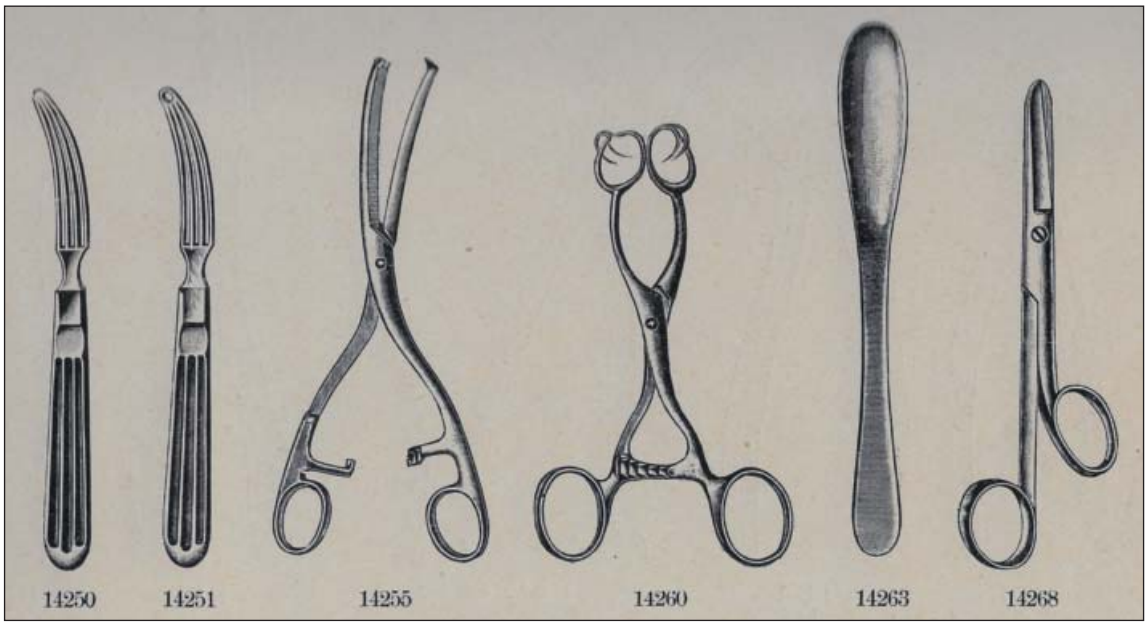


7. Kocher arterial clamp

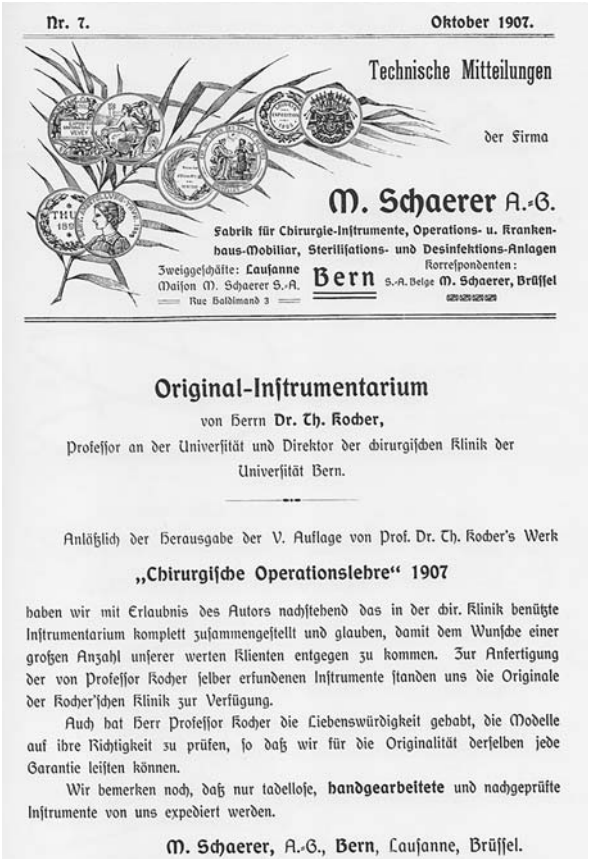
nia), Kocher fracture or Kocher-Lorenz fracture (distal fracture of the humerus) Kocher reflex (contraction of the abdominal muscles following moderate compression of the testicle) and Kocher clamp or surgical forceps for arterial hemostasis *(Figure 7)*.

Development of safe thyroid surgery

The first attempts to surgically remove, "in the neck between the skin and the trachea, a tumor" date back to Celsus who wrote in the first century AD: "A linear incision is made over the middle of the tumor down to the tunic; then the morbid pouch is separated by the finger from the sound tissue, and the whole is removed along with its covering."[8] This tumor was often named "bronchocele" [9], and it is not clear whether it truly was a thyroid tumor or simply an adenopathy or other lump of the neck[10]. Little progress was known until the 18th century. A typical procedure was to insert two setons (hair ropes) through the tumor, which were regularly moved to try to extirpate some small pieces of the tumor[11]. The first successful partial "*extirpatio strumae*", i.e. thyroid extirpation, is credited to Adolf Friedrich Vogel (Johann Friedrich Ackermann) in 1771[12-13] and then more extensively to Pierre Joseph Desault in 1791[14-15]. Up until the end of the 1860's, extirpation of the thyroid gland, was considered a high-risk procedure, or even butchery, with a high-mortality rate approaching 75% essentially because of hemorrhage. Extirpation of the thyroid gland with goiter was limited to cases not responding to parenchymatous iodine injection, especially for problematic local compression of the trachea in cases of "plunging goiter". Kocher performed his first thyroid surgery in 1872. Two years later, he wrote: "The chief danger of extirpation is the high degree of hemorrhage, which is due to the numerous arteries, but much more from the colossally developed venous plexus on and around the thyroid gland [...] A further remote danger is the injury of the laryngeal nerve [...] The wounds after exposure to excision of the gland were always treated openly, that is to say, not only no suture was applied, but removal of the edges of the wound was effected by the insertion of pledgets [*bourdonnets*] soaked in phenyl water solution (1:40) or phenylglycerol solution (1:10)."[16] More than thirty years later, Kocher explained in his Nobel lecture that: "It was also due to strict asepsis that one of the most serious, and, before Lister, most dangerous operations could be undertaken without substantial risk, that is the removal of a goitrous thyroid, which so often proves urgently necessary on account of severe respiratory disturbances."[17] In introducing Lister antisepsis [18], preparing a bloodless field with systematic ligatures of the main vessels [19] and use of his newly designed clamp[20], isolating the laryngeal recurrent nerve[21], and application of good anaesthetic technique, it was finally possible to correctly extirpate the thyroid gland by careful dissection of the external capsule, removal of the isthmus and preservation of the parathyroid glands[22]. With these recognized prerequisites, Kocher achieved unprecedented surgical success[23]. These precepts were accomplished with the introduction of a new transverse incision allowing better aesthetic results [24], and executed using his own specific thyroid instrumentarium [25-26] *(Figure 8-9)*.



8. Kocher's instruments for thyroid surgery, from Schaerer 1905. 14250/14251 thyroid probe, 14255 thyroid crimping instrument, 14260 thyroid barrels tongs, 14263, thyroid spoon, and 14268, thyroid ligature scissors.



Nr. 7. Oktober 1907.

Technische Mitteilungen

der Firma

M. Schaerer A.-G.

Fabrik für Chirurgie-Instrumente, Operations- u. Krankenhaus-Mobiliar, Sterilisations- und Desinfektions-Anlagen

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Original-Instrumentarium

von Herrn **Dr. Th. Kocher,**

Professor an der Universität und Direktor der chirurgischen Klinik der Universität Bern.

Anläßlich der Herausgabe der V. Auflage von Prof. Dr. Th. Kocher's Werk

„Chirurgische Operationslehre" 1907

haben wir mit Erlaubnis des Autors nachstehend das in der chir. Klinik benützte Instrumentarium komplett zusammengestellt und glauben, damit dem Wunsche einer großen Anzahl unserer werten Klienten entgegen zu kommen. Zur Anfertigung der von Professor Kocher selber erfundenen Instrumente standen uns die Originale der Kocher'schen Klinik zur Verfügung.

Auch hat Herr Professor Kocher die Liebenswürdigkeit gehabt, die Modelle auf ihre Richtigkeit zu prüfen, so daß wir für die Originalität derselben jede Garantie leisten können.

Wir bemerken noch, daß nur tadellose, **handgearbeitete** und nachgeprüfte Instrumente von uns expediert werden.

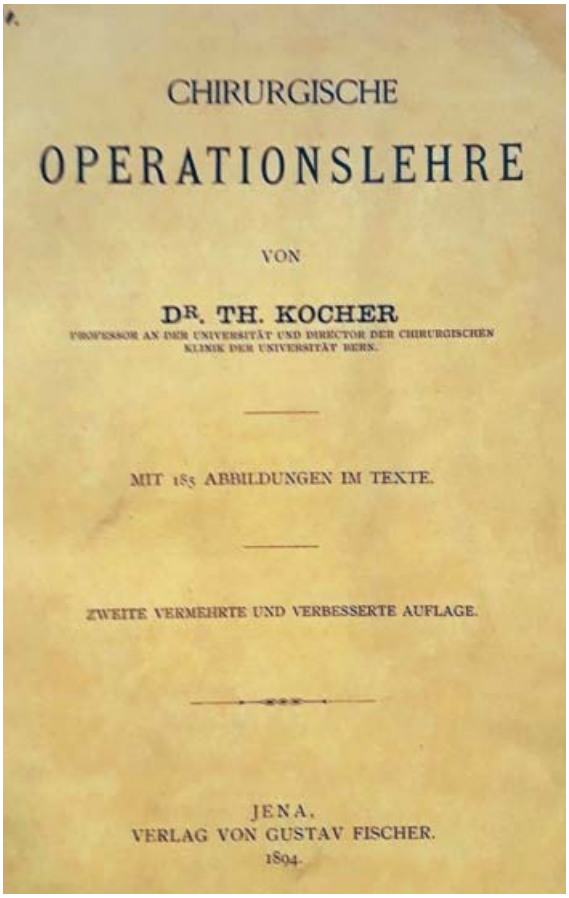
M. Schaerer, A.-G., Bern, Lausanne, Brüssel.

9. Kocher instrumentarium, Schaerer, 1907

Kocher regularly published his sequential statistical results after 1000 surgeries in 1895 [27], 2000 surgeries in 1901[28], 3000 surgeries in 1906[29], and finally after 7052 operations made in his surgical department in 1917, of which 5314 were performed by Kocher himself[1]. His relentless pursuit of perfection and painstaking attention to detail in refining thyroid surgery[30] decreased mortality from 14.1% in 1883 (31) to 0.18% in 1898[32] *(Figure 10, p.258)*.

It was not until the second edition of his textbook of surgery, in 1894[33] *(Figure 11, p.258)*, that Kocher described in detail the extirpation of the thyroid. "The excision of a goitre is an operation which in many instances is very easy, but in certain cases is attended with great difficulty […] It is difficult to give a general description of the procedure to suit all cases, as modifications may be called for in individual operations. The most important point is to make a very large skin incision […] When it is important to avoid disfigurement, the transverse curved incision (or collar-incision) is to be recommended as the best […] A very thin layer of connective tissue, the outer capsule of the goitre, is now all that lies upon the gland. This must be carefully divided and stripped to either side from the surface of the goitre […] Now follow the dislocation of the goitre […] The chief vessels are now ligatured […] Next follow the

10. Kocher in operating room, post card Switzerland, no date



11. Kocher textbook, 2nd edition, 1894

isolation of the isthmus […] After luxating the goitre, the isthmus is ligatured and divided", and finally it is excised. In the 4th edition in 1902, Kocher greatly expanded the text and added: "Up to the present we have performed excision of the thyroid gland in 2160 cases of goitre; we are thus in a position to speak with authority regarding the best way of performing the operation. Our procedure, which is both definite and simple, guarantees excellent results, but it must, of course, be slightly modified in individual cases."[34] Kocher's last publication, a few weeks before his death, presents an historical report about thyroid surgery and summarizes the evolution of his surgical technique[35].

Unexpected consequences of total thyroidectomy: *cachexia strumipriva*

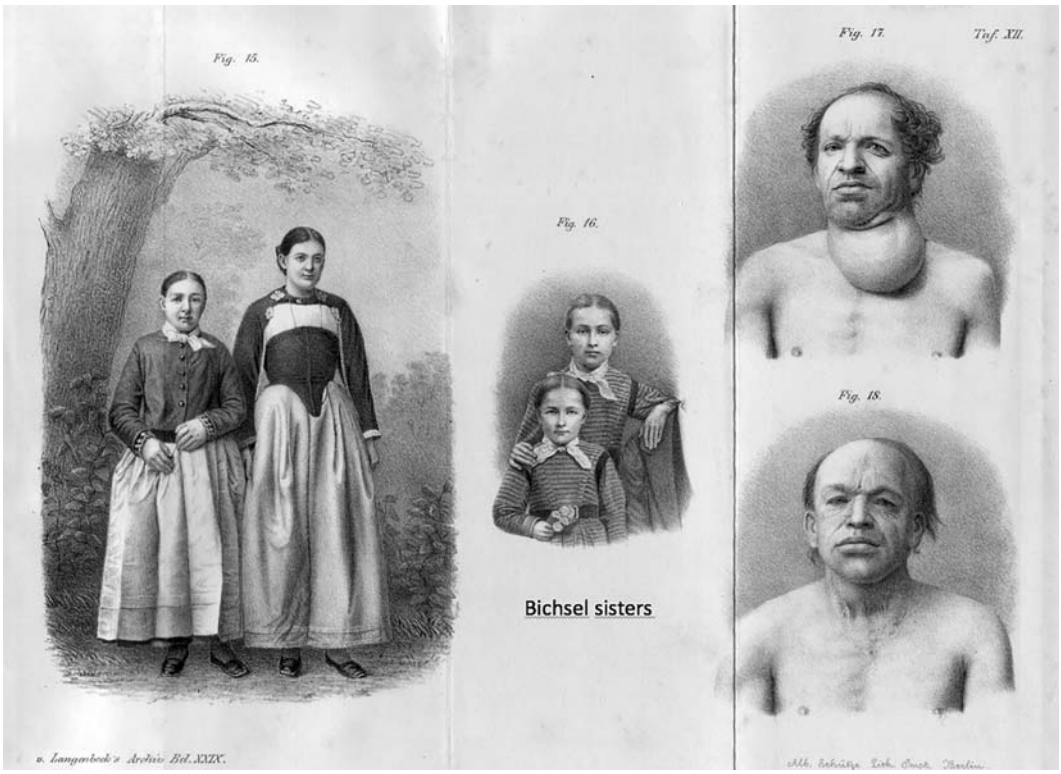
By 1856 Moritz Schiff had shown by experiments on dogs that total extirpation of the thyroid gland produced a sequence of physical troubles which led to death[36-38]. His work remained unknown for more than twenty-five years. Kocher did not first make reference to Schiff when he reported the phenomenon of surgical thyroid deprivation. In

April 1883, Kocher explained: "Unfortunately the physiologists know next to nothing about the physiological significance of the thyroid gland, and this may have been the main reason for surgeons tacitly assuming that the thyroid gland had no function at all. Once one had achieved certainty that total removal could be happily performed from a technical point of view, one did not hesitate, in cases of disease of both halves of the thyroid gland, to take out the whole organ […] I shared this opinion for a long time. It was just one case, on whom I had operated in 1874 – and about whom the doctor had occasionally mentioned that the girl in question had since undergone a complete and substantial change in the nature of her character. Indeed, he had recently informed me that she had become entirely cretinoid [Bichsel's sister[39]]. This was so important to me, that I now took all pains to see the girl with my own eyes. This was not easy, because the doctor had died soon after his verbal message. We insisted all the more because colleague Reverdin, in Geneva, mentioned to us that he had seen two cases in whom decreased mental capacity had followed excision of goitre. I was astonished to a great extent by the conspicuous looks of the individual in question […] According to the mother, the two sisters were said to have resembled each other so much at the time of the operation that they were frequently confused for each other. Whilst the younger sister during the nine years has now grown up to a blossoming young woman of very pretty looks, the sister operated on has remained small and exhibits the ugly looks of a semi-idiot. This having been ascertained […] I immediately sent invitations to all my operated for goitre to present themselves for examination."[31]

In fact, the description of this postoperative clinical complication had already been described in 1882 by Jacques-Louis Reverdin *(Figure 12)*. He depicted sequelae after total extirpation of the thyroid: "Two or three months after the operation, the patients mostly presented a state of weakness, pallor, anemia, accompanied in two of them by a state of edema of the face and hands, without albuminuria."[40] Reverdin thus modified his surgical practice and no longer practiced total thyroidectomy[41]. Observing these results, Kocher reexamined his thyroid patients, and described the postoperative hypothyroidism he called "*cachexia strumipriva*" which led him to also discourage total thyroidectomy *(Figure 13, p.260)*. Kocher wrote: "Of the 18 patients with total excision who presented themselves for examination, only two show a

12. Portrait of Reverdin

state of health as good as or better than before the operation. The remaining 16 patients with total excision of the diseased thyroid gland all show more or less severe disturbances in their general condition […] They are obviously progressive […] If we have to give a name to this picture, we cannot fail to recognize its relation to idiocy and cretinism […] We prefer, for the time being, to use an entirely innocuous name for this symptom-complex […] For the nutritional disturbances which accompany the disappearance of goiters after iodine administration (Virchow), the name goiter cachexia or cachexia iodica has been used; we see no objection for the time being, to the use of the name *cachexia strumipriva*." [31-42] In the same year, Reverdin spoke of "operative myxoedema"[43]. The term myxoedema itself was actually coined in 1878 by William Ord[44-46], who initially thought that cretinoid features were due to excessive mucus formation and deposition under the skin[47]. The importance of this discovery is widely acknowledged in the literature[48-49], and emphasized by Kocher in his Nobel lecture[17] even without a precise explanation, but it has generally been credited to Reverdin



13. Cachexia strumipriva (from reference 31)

as of the International Conference of Goitre in Bern in 1927[50-51].

Cachexia strumipriva directly influenced Kocher to limit his practice to unilateral thyroid lobectomy, practicing only an enucleation of the pathological tissue on the other side, saving total resection for intractable compression or cancer. In July 1883 he tried to reverse the postoperative consequences of total thyroidectomy by implanting human thyroid tissue into the patient's body to correct the loss of postulated thyroidal function[52]. He thus performed the first organ transplantation in the modern sense of curing a complex internal disease by replacing an organ[53-54]. Schiff, in I884, demonstrated that the symptoms of thyroid deprivation could be averted by making thyroid transplants before performing complete extirpation of the gland[55]. He proved the thyroid gland had a secretion which is necessary to life[56]. He paved the way for the administration of thyroid extract in the treatment of myxoedema which was introduced in 1891 by George Murray[37,57]. In his Nobel lecture Kocher explained that their "finding, which seems so simple and yet is so exceedingly important, that the administration of thyroid juice was quite sufficient to compensate for the deficiency of thyroid function, was of great significance for the theory of thyroid function. This finding has become a cornerstone of the structure and doctrine of internal secretion and organotherapy."[17] From these clinical observations, Kocher initiated new physiological experiments in an effort to understand thyroid function. He added: "It was just this ability to make all the organs accessible to direct observation, and to alter the conditions in which they exercise their functions, that broadened our knowledge of the physiology of the body extraordinarily."[17]

Understanding thyroid pathophysiology

The understanding of the physiopathological function of the thyroid gland is intimately related to the comprehension of the development of goiter and its associated general symptoms. Goiter had been described since Antiquity[58] and the Middle Ages[59], and had mainly been found in mountainous areas, notably in the Alps. Pliny the Elder made a connection to the quality of the drink-

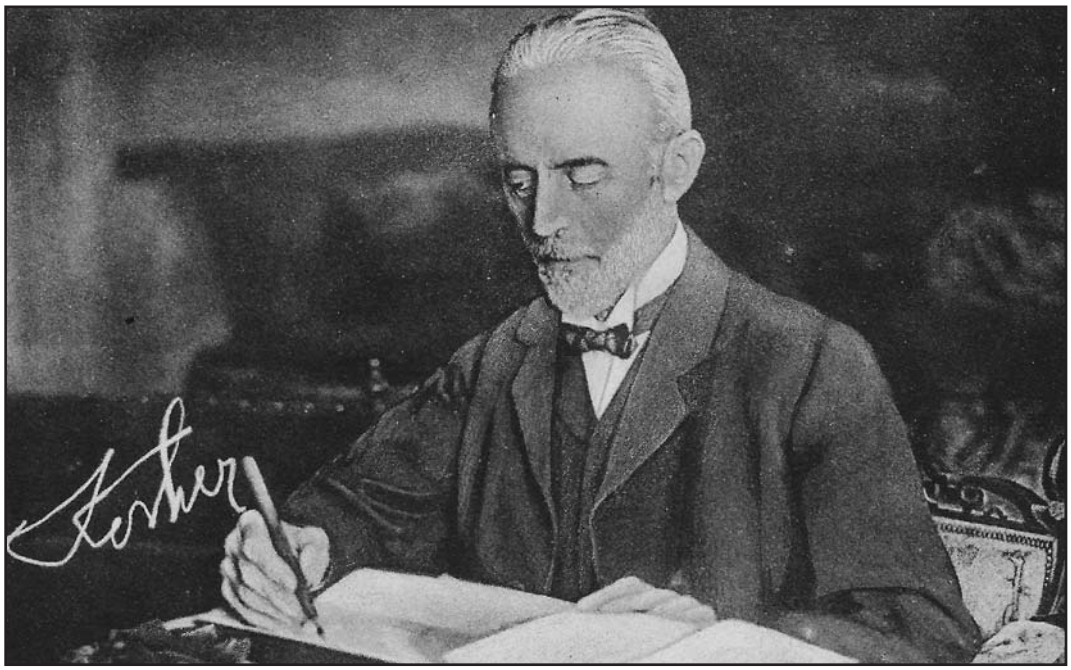
ing water: "Man and swine alone suffer from swollen throat, usually due to bad drinking water."[60-61] During the Renaissance, Paracelsus was the first to suggest a relationship between goiter and cretinism: "Goitre is a mineral growth comparable with the flader [knot in a tree, more particularly to a knot of the sort which is found in bird's-eye maple] […] That is why all goitrous people are more likely to be foolish and skillful, because the mineral in it is untimely."[62-63] At the turn of 1800, François Fodéré wrote: "For so many centuries, that a disease as evident as goiter exists in the sub-sub-alpine valleys, conjectures have been made upon the nature of the causes which produce it; but it has resulted from the various opinions more obscurity than light was emitted, more false theories than utility for the patients who were the object of it." [64] For Fodéré, and in referring to Morgagni, the thyroid gland was "destined to produce a lubrifing mucous to the larynx and trachea, always dryed by inspirated air." [64-65] Goiters were related to "excess of atmospheric humidity", associated with "relaxation of the tissue of the thyroid gland, and the collapse of its mucinous ducts". He demonstrated that the quality of water was not associated with goiter. A few years earlier, Vincenzo Malacarne postulated that the cause of cretinism was brain damage due to impediment of cerebral blood flow by the goitrous swelling[66].

A key advancement was the discovery of iodine by Bernard Courtois[67] in 1811, and the demonstration by Gay-Lussac that it was a new element[21]. At nearly the same time, Jean-François Coindet[68-69] hypothesized that the traditional treatment of goiter with seaweed was effective because of its iodine content, and he successfully treated goitrous patients with iodine[70]. Nevertheless, the medical community of the day did not yet appreciate the importance of an iodine-deficient diet as a root cause for endemic goiter[71-72]. In 1850, Adolphe Chatin was the first to suggest prescribing iodine to prevent goiter, and hypothesized that iodine insufficiency was associated with goiter[73-74]. After reading Kocher's 1883 report, Felix Semon suggested that myxoedema was due to thyroid insufficiency[75].

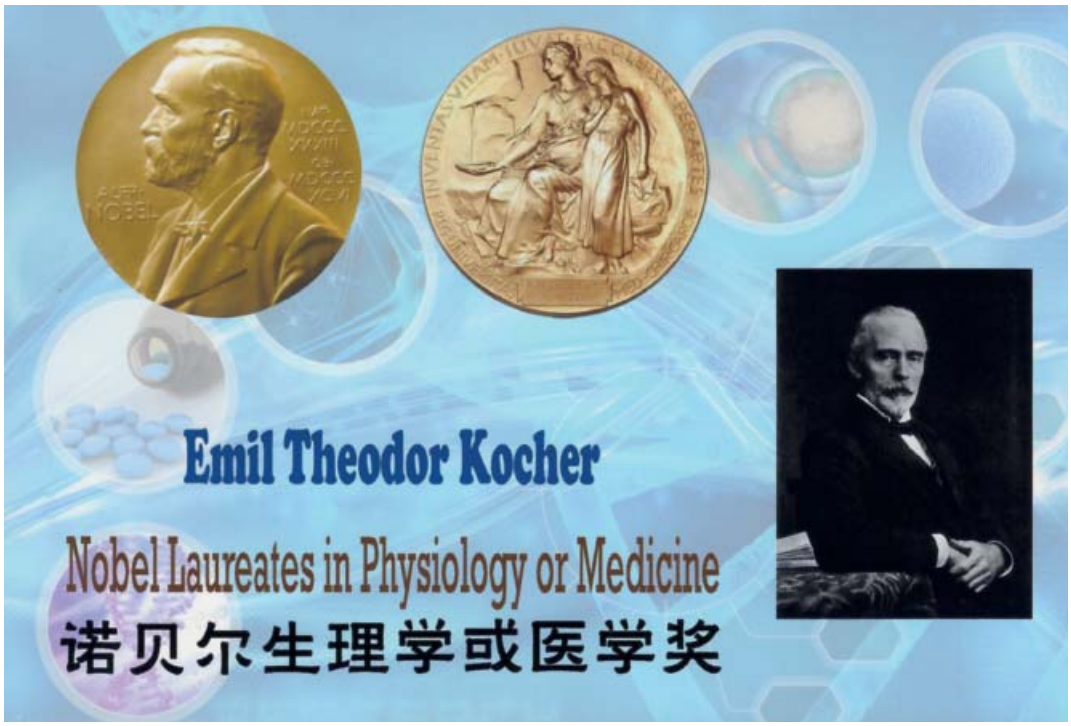
Confronted with his *cachexia strumipriva* and the suspected relation between goiter and iodine deficiency, Kocher was able to explain, both increased and decreased function as well as normal function of the thyroid. In 1887, he thought that thyroid gland is a "secreting organ, and might be of service in removing something detrimental from the blood."[76] He regarded it as "useful in removing some excretion or modifying something in the blood which might be otherwise injurious." He added a few years later that "The concomitant occurrence of goiter and cretinism is not only a matter of local distribution, but also of reproduction within families, and we may admit that our present knowledge of the use of these two sufferings is the minimum of the actual fact. It is to be assumed that the relations are much more constant and regular than we are able to show at the hour […] The injuries which produce the goiter never lead, even though they are so powerful, directly to cretinism, not even in its mildest degrees. Cretinism is produced only then and only when the glandular degeneration of the thyroid gland, or just as well as by any other harmfulness, causes the function of the thyroid gland to be lifted or severely affected."[77] The link between goiter, myxoedema, and iodine was definitively established when, in 1896, Eugen Baumann discovered iodine in the thyroid[78]. In 1909, Kocher stated that, "The main point is that it could be confirmed that the thyroid cells deal with the iodine in such a way that it is delivered into the vessels in an organic compound, and displays the most important physiological effects; and that we can remove this thyroid compound from animals and supply it to a human to compensate for the defective functioning of his thyroid gland."[17]

Description of the main thyroid pathologies

The different forms of thyroiditis were described at the turn of the 20th century[79]. In 1906 Kocher wrote: "Thanks to the scientific work done, we are pretty well informed about all affections depending on deficiency of thyroid tissue or thyroid function, including cachexia thyropriva and tetania parathyropriva. We cannot say the same of another category of diseases connected with alterations of the thyroid body - I mean exophthalmic goiter. There exists still such a divergence of opinion as to the nature of the



14. Kocher at his bureau, post card Switzerland, 1916



15. Kocher at Nobel lecture, post card China, 2011

disease, that it influences our practice strongly, and in part in a regrettable way."[80] *(Figure 14, p.262)* Kocher differentiated "thyroprival disorder", i.e. insufficient function of the thyroid, hypothyroidism or "thyropenia, as one could call this condition", which he named "cachexia thyropriva", and "thyrotoxic disorder", i.e. hyperfunction or hyperthyroidism[17]. He first used the term cachexia strumipriva and then, as he stated in 1895, "better thyropriva"[27]. He wrote in his Nobel lecture: "We have now gained the understanding that at the bottom of these dyscrasias can lie a qualitative or a quantita-

tive plus or minus of some internal secretion which is indispensable for the normal function of the organs."[17] More specifically, "It seems certain to me that every deficiency of the thyroid or its function, however small it may remain, betrays itself by some symptoms, however mild and isolated they may be, which allow us to discover the reason for the changes and to make good the deficiency. We have come to understand from our numerous operations for goiter, in which the disease has varied considerably in severity and form, that every person requires his own, quite definite quantity of functional thyroid substance, if he is to remain quite healthy."[17] Concerning Grave's disease, Kocher explained that "We have gained, during recent years, a clear comprehension of the etiology of Graves's disease and of the differences in the symptoms and prognosis of different cases, and this has naturally brought us to the choice of different ways of treatment."[81]

Conclusion

Kocher's contributions to thyroidology combine an assimilation of historical data, an impressive chapter in the development of modern thyroid surgery, and a model of medical and scientific inspiration[82]. His evolving understanding and refinements even today demonstrate a classic progression: a relevant clinical problem, observation of patients, experimental studies, observation of the effects of different therapies, new experimental studies[83], and finally research of prophylactic measures. Kocher stated at the end of his Nobel lecture: "We will […] merely mention that it is to be hoped that progress in our knowledge of the great role which the thyroid plays in the development and normal existence of the body may direct the attention of wider circles to the necessity for opposing with prophylactic measures all the effects which thyroid diseases can produce."[17] *(Figure 15, p.262)*

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