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Correspondence should be addressed to:
Bernardino Fantini, Institut Louis Jeantet D'Histoire de la Médecine, Université de Genève, CMU Case postale, 1211 - Genève 4.

Articoli/Articles

CAMILLO GOLGI AS CLINICAL PATHOLOGIST:
EPICRITICAL READING OF GOLGI'S WORKS ON MALARIA

LEONIDA SANTAMARIA

Istituto di Patologia Generale Camillo Golgi
Università di Pavia, I

SUMMARY

Camillo Golgi confirmed, in 1885, Marchiafava's and Celli's discoveries about malaria, following a clinical-pathologic research pattern and studying the patient directly. In 1889 he associated the naturalistic-biological point of view and the clinical-pathologic one so that he made possible a differential diagnosis between tertian and quartan fever, independently from the clinical observation; he supplied useful laboratory data for clinical diagnosis and, in doing so, he created the new figure of the clinical pathologist; he distinguished three different kinds of intermittent fevers and, in 1888, he specified the useful time for quinine administration.

The article analyzes, also, his methodological and scientific principles.

Introduction

The idea of dedicating a paper to Camillo Golgi as the forerunner of Clinical Pathology came to me when, by chance, I found a proof of an original holograph drawing of thermometric curves of the quartan and tertian benign malaria (Fig. 1). This finding occurred in a recent tidying-up of the historical library of the likewise historical *Camillo Golgi* Institute of General Pathology of the University of Pavia, where I have cohabited for the last twenty-five years with the Golgi's statue, with his many little and great things and perhaps with his ghost, accor-

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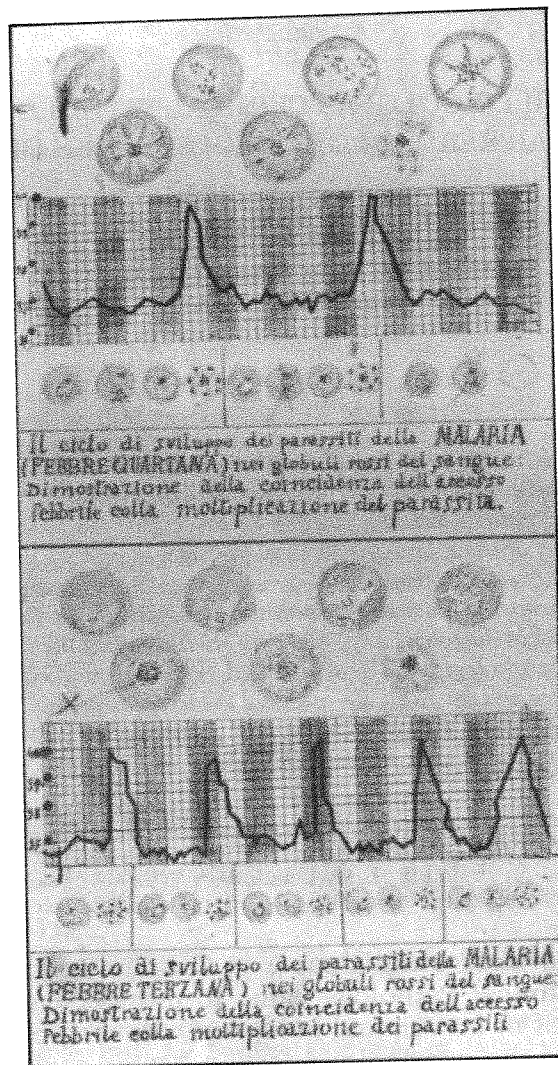


Fig. 1 - A copy of the original holograph drawing showing thermometric curves of quartan and tertian simple fevers with respect to the schizogonic cycle. This holograph drawing should be dated 1889, that is, when Golgi first described the Spring tertian fever. Here the tertian fever appears to be related to *Plasmodium vivax*, because of much more *little bodies* arising from the segmentation process than the ones shown in quartan fever. At that time, the pernicious tertian form was still unknown. (Finding from the historical library of Golgi Institute).

ding to a local tradition, being his successor as director of the above Institute, after Aldo Perroncito, Emilio Veratti and Piero Locatelli. The above drawings had to belong to Golgi's discoveries in 1889, that was four years after his letter *On malarial infection* addressed to Prof. E. Marchiafava and Dr. A. Celli of the University of Rome, in which he first illustrated the *Developing cycle of pigmented bodies living inside the red globules*, that he recognized as *corresponding to the cycle of recurring onsets of fever in quartan fevers (72-hours interval)*. In this connection, I wish to point out the fact that Camillo Golgi is world-wide famous for his method of black staining by means of silver salt impregnation, that in 1873 allowed him to reveal the unique morphology of the nerve cell with dendrites and neuroaxis, which won him the Nobel Prize in 1906. Furthermore, all biologists in this century know Golgi for his discovery of the *internal reticular apparatus* of cells, originally observed by silver impregnation in 1898, called *Golgi's apparatus or complex*. Nevertheless, very few know the studies of Golgi deserved a second Nobel Prize for the discovery on the pathogenesis of malaria fevers, the suggestion of their best treatment through the administration of quinine and the description of preventing procedures, basically consisting of the disinfection of swamps and rice fields introducing fish which might eat up all the larvae of mosquitoes, including *Plasmodium*-bearing *anopheles*, with benefit for mankind.

I was quite impressed reading once again Golgi's writings on the discovery of the schizogonic cycle of the quartan and tertian (48-hours interval) spring benign form of malaria, which allowed him to understand the pathogenesis of intermittent malaria fevers and consequently to identify the administration time rates for quinine, to obtain the best therapeutic effects. Finally, I was also surprised by Golgi's experimental and clinical method used to confirm the parasitic aetiology of summer and falls pernicious tertian fever in his piece of research, lasted only two months, which was the result of his deep learning in the field of clinical pathology.

My goal here is thus to convey this paper with an epicritical spirit and a personal comment on the methodological principles

as adopted in the epistolary format of Golgi's scientific communications, which surprisingly showed also various significant expressions of his humanity.

1. On malaria infection. The developing cycle of pigmented bodies living inside the red globules and the onsets of fever in quartan form

The discovery of the aetiology of malaria was made in 1880 by Laveran in France by identification of spherical, half-moon shaped pigmented *bodies* and moving filaments affecting the red globules of patients suffering from malaria. Five years later, in 1885, Marchiafava and Celli confirmed Laveran's observations and, for the first time, they observed that Laveran's pigmented bodies were not inert, but they moved like amoebas, thus discovering their living parasitic nature and identifying them by the name of *Plasmodia*. In addition, Marchiafava and Celli confirmed the aetiological property of *Plasmodia* by transmitting the infection from man to man through blood injections followed by a microscopic examination. In this respect, after so many years, modern bioethics may provide the justification for this bold experiment on man, considering that, at that time, quinine salts could be used with safe therapeutic effects in the treatment of specific forms of malaria fevers.

At the end of the same year, Golgi communicated to Marchiafava and Celli, by the letter *On malarial infection* presented to the *Regia Accademia di Medicina di Torino*, in the Session of 15th November 1885, that he had already undertaken the study on quartan malaria fevers in Pavia, through microscopic examination of blood. He confirmed their experimental data and agreed on the denomination of *Plasmodia* to identify the whitish bodies which moved like amoebas into the red globules. Furthermore, he communicated his personal fundamental discovery that *Plasmodia* get roundish, pigmented and undergo a process of segmentation which ends up with the destruction of the red globules inducing simultaneously the onset of a fever spike.

From a closer reading of this letter, it is surprising and fascinating to see how Golgi, an already famous scientist, humbly approached the malarial patient admitted to the hospital compartment he granted by the S. Matteo Hospital Administration Board to carry out clinical studies on malaria. He carefully wrote the patient's clinical chart and he carried out straightly the microscopic examination of the changes affecting red globules. The letter exactly reports his own words as follows:

through persistent blood tests I could follow the course of the disease throughout the whole period of recurrence of 4 fever spikes repeating with mathematical regularity, at a fixed hour every 4th day.

In his *clinical diary* (CD), the first patient was a countrywoman from Trivolzio, who being pregnant at the 9th month, was admitted in the obstetric-gynecological compartment directed by Prof. Cuzzi. Golgi approached the patient's bed and meticulously described his microscope observations of blood samples carefully collected from her finger at fixed times before the onset of the fever spike. Thus, he could identify the red globules (obviously not stained and sometimes treated by a drop of osmic acid solution) containing great pigmented bodies, many different forms undergoing a slightly marked segmentation process and some others showing an already completed segmentation, thus evidencing *the gradual changing of forms which characterises the last developing phase of pigmented bodies* and which corresponds to the onset of fever spike.

He repeated the examinations during the first and second day of apyrexia; during the 4th day, through careful microscope observations, he studied blood samples an hour before the onset of fever, three hours after the disappearance of fever spike and five hours after the onset of fever. Therefore, he could check the volumetric increase in the endocorpuscular bodies undergoing a slightly marked segmentation process and in some others with segmentation in progress that subsequently disappeared. During the days of apyrexia, on the contrary, the pigmented bodies were present in the blood-stream. In the days of the onset of fever spike, the splitted forms appeared again showing a gradual in-

crease in number just before the onset of fever spike.

The administration of a strong dose of quinine (quinine sulphate, 1.5 g) in the morning of the second day of apyrexia caused an apparent decrease in the pigmented bodies after three or four hours and the day after, that was the day of the onset of fever, he observed that fever was absent at the usual time (12 a.m.), while

into the blood it was possible to notice the progressive growth of the pigmented bodies (so that) their development might turn out to be only slowed. At 5 p.m. the patient had a new onset of fever spike even though less intense than in the other days (CD).

This is the classical scheme of the *clinical-pathological research* (a definition that Golgi himself introduced four years later) which allowed him, in the study of the following 39 cases of malaria in 1884-85, to identify the typical forms of *simple quartan fever, double quartan fever, triple quartan fever and irregular quartan fever*. As a conclusion to this study, Golgi drew his first table of the schizogonic cycle of the quartan fever (Fig. 2). In this table, he illustrated *the pigmented bodies next to the complete development, at completed development, and finally with segmentation in progress*. As regards the fact that all the forms of segmentation rapidly disappear just before the shivering and throughout the first phase of fever, he assumed that

the little globules, which are released and only exceptionally visible in blood smears, go standing in some organs (spleen?) to appear again the day after, thus inducing again the onset of fever spike characterized by the presence of little not pigmented bodies (Plasmodia) which represent the first phase of a further new cycle (CD).

According to Golgi's original description, it was clear that Plasmodium induces changes in the red globules, which consist of the accumulation of pigment mass gradually concentrating towards the centre of Plasmodium, thus showing, at the beginning, irregularly located stripe shapes or pigmented trabecula and, thereafter, more central irregular or starry masses. Therefore, it is possible to observe the development of segmentation processes along with the formation of

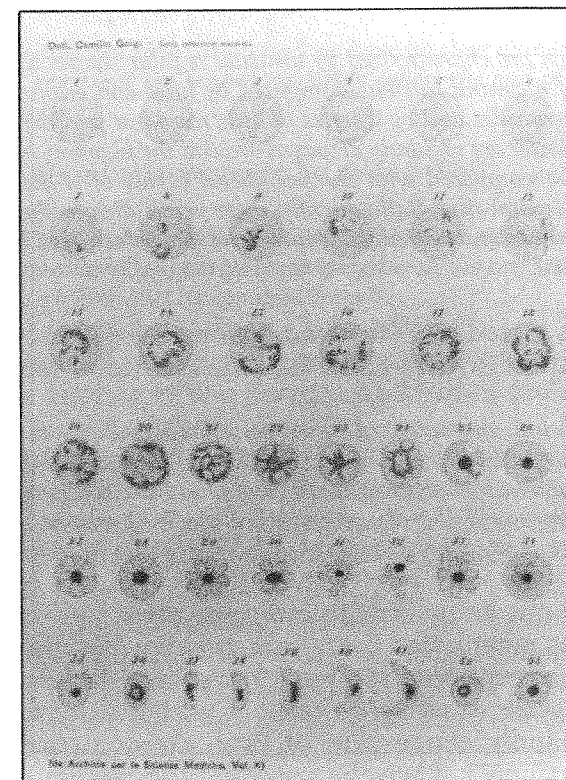


Fig. 2 - Experimental data concerning Golgi's first study (1895) on 40 cases of quartan fever in the *typical pure, double, irregular, daily intermittent* forms. These data explain the discovery of the Plasmodia schizogonic cycle into the red globules in the *typical pure* or simple form.

N. 1-6: Amoebic mobility of *Plasmodium malariae*.

N. 7-12: Little pigmented bodies moving like amoebas observed in the first day of apyrexia.

N. 13-18: Big pigmented bodies, second day of apyrexia.

N. 19-32: Pigmented bodies almost completely invading the globule, centralization of the pigments, segmentation process and aggregation of the pigments as *peripheral petals of a daisy*, breakdown of the red globule and release of the little globules, onset of fever and disappearance of the little globules.

N. 33-34: Persistent daisy shapes.

N. 35-43: *Different (elliptical, oval, stick shaped, half-moon shaped) forms of pigmented free bodies observed in only one case out of the 40 patients under examination in Pavia.*

It is a rare case of tertian malignant sickle form still unknown to Golgi at that time, but later on He succeeded in identifying it in *the long intervals malarial intermittent fevers* (Archivio Sci. Cliniche, Vol 1890; 14) and finally in the pernicious forms, in 1893, while he was developing his conclusive research at the Medical Clinic of the University of Rome, whose Director was Guido Baccelli.

bodies which are characterized by unusual regular shapes and elegance, made up of a central nucleus composed by little and crammed heap of pigmented granules and by a series of little round or pyriform bodies (5-8-10). The latter are regularly disposed around the pigment mass, so that they may be compared with the peripheral petals of a daisy wrapped around its central ring. Subsequently, these petals disjoin the mass, pass in circle and are quite rapidly assumed and likely destroyed by the white globules (CD).

Golgi was kissed by Fate when, among the 40 cases he kept under examination in 1884-85 he had the chance to face a case of

blood alteration, characterized by the presence of half-moon, elliptical or free oval shaped bodies and of Plasmodia into the red globules. Clinical symptoms showed a very irregular type of blood alteration, characterized by the presence of half-moon, elliptical or free oval shaped bodies intermittent fever, along with daily fever spikes within no fixed time (CD).

Golgi did not know how to interpret these half-moon shaped or oval forms, which had been already described by Laveran. He realised the exceptionality of such case and he constantly kept the patient under observation (that is without therapeutic treatment), for kindly concession of Prof. Grocco (the Director of that compartment). Then, he reported the results of his observations of this unique case in his Table, figures 35-43 to be faithful to his research method.

Only this specific case, among the 40 cases under observation, deserved further investigations, however, Golgi did not take it apart from other cases and included it in his report together with many personal considerations which need to be partly referred. He supposed that:

most probably the half-moon shaped forms undergo a process of segmentation, which may be compared with the one affecting the pigmented bodies into the red globules, and it is also possible that such process might develop according to the onset of fever The extreme irregularity of the fever type, thus being no mean to specify which forms corresponded to the different moments of apyrexia or fever attacks, was certainly the main problem related to the definition of specific rules underlying the development of the bodies; obviously - ended Golgi - we are facing forms

belonging to different generations and we have no clear data to verify that some forms represent the beginning, while others the end of the developing cycle (CD).

Speaking about tertian fever he stated that:

a priori the parasite that induces this kind of malarial infection might have a different developing cycle if compared with the one which characterizes quartan fever and its combinations.¹

In this connection, we can remark that Golgi anticipated, by intuition, the finding of the pernicious form of malaria.

2. *On the developing cycle of the malarial parasites in tertian fever. The role of the clinical-pathologist in the differential diagnostics between double quartan and double tertian fevers*

Four years later, in 1889, in the work *On the developing cycle of the malarial parasites in tertian fever. Observations by Dr. Camillo Golgi, Professor of General Pathology and Histology*² he finally succeeded in associating the *naturalistic-biological general point of view*, concerning the parasites, with that special clinical-pathological point of view for the differential diagnosis between tertian and quartan fever through simple blood test, which allows to find the biological and morphological differences of the corresponding endocorpuscular parasites (Fig. 3).

Indeed, he could point out that the amoebic parasite which is present in the tertian (spring benign) form showed special and peculiar biological and morphological features, by allowing the expert observer to formulate, without a shadow of a doubt, the differential diagnosis between tertian and quartan forms independently of traditional clinical monitoring. In fact, in the first phase, that may develop a few hours after the onset of fever, he observed that:

endocorpuscular protoplasmic bodies move in such a lively way (that is the reason why they are called Plasmodium vivax) to make it rather difficult to recognize the different forms that the parasite assumes

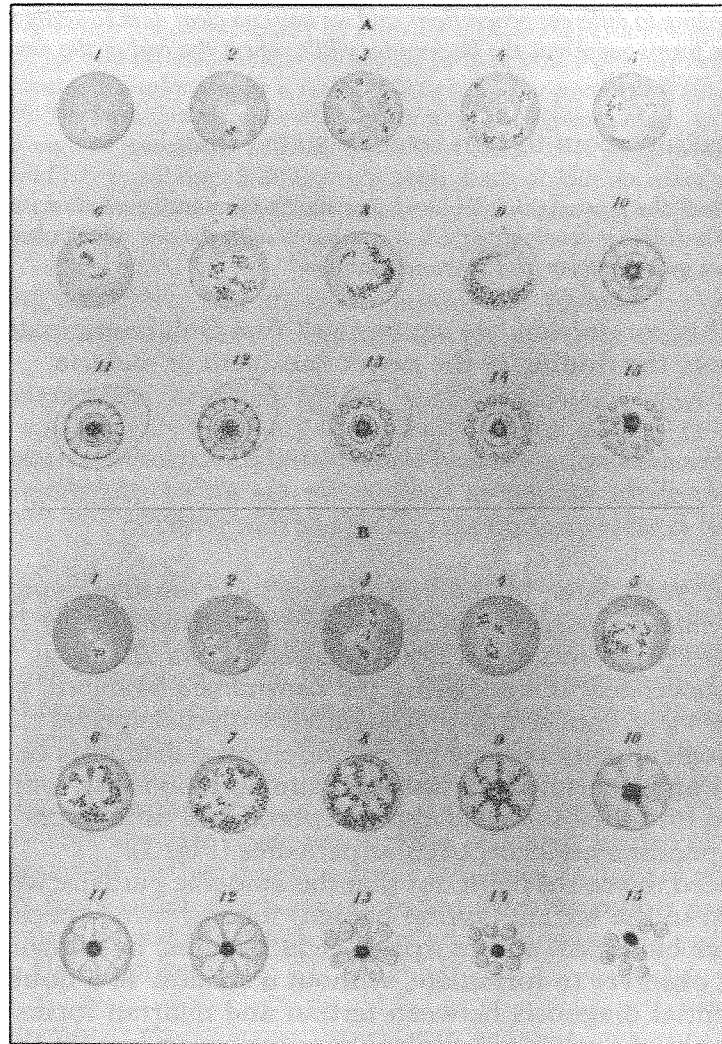


Fig. 3 - The schizogonic cycle. A) In the tertian form as induced by the *Plasmodium vivax*; the differential diagnosis is made easier by its vivacious amoebaic movement, causing the swelling of the red globules and bringing about a segmentation process ending with the formation of 15-20 little globules. B) In the quartan form as induced by *Plasmodium malariae*; the segmentation process ends into formation of 6-12 little globules. These data allowed the Pathologist Golgi also to become an expert Clinician in the monitoring of the complicated malarial fevers forms.

(besides, the red globule affected by parasites appears swollen). This lively activity (and the swelling of the globule) do not affect protoplasmic bodies of the quartan form.

In the second phase, during the day of apyrexia, Golgi described

the transformation of the haemoglobin in melanin (that is in haematic pigment) along with the progressive uncolouring of the same globular substance,

a process which develops more quickly in the tertian than in the quartan form. Finally, in the third phase, the segmentation process takes place according to the onset of fever spikes that lasts one or two hours (by reaching 39.5- 40° C) and it is followed by shivering. He also described different forms of segmentation, which wholly produce 15-20 little bodies in the tertian fever and usually from 6 up to 12 in the quartan form. Besides, the pigment shows a more irregular shape in the quartan than in the tertian form. *In this connection, the diagnosis of double and triple quartan or double tertian fevers is no longer considered a problem by the clinical-pathologist.* Indeed, clinical pictures are just the expression of intercalated additional generations of a single *Plasmodium* type.

This progress of pure clinical pathology stands for all the philosophic issues of this speech, aiming at underlining Golgi's ethical values, by being a scientist who constantly keeps in mind his duties as a medical doctor. He was the one who first provided precise laboratory data to support clinical diagnostics, thus shaping the new picture of the clinical pathologist. In this line, when he was formally charged to supervise the construction of the new S. Matteo Hospital in Pavia, according to modern medical trends, he arranged to support each clinical structure with a suitable laboratory of analysis.

In the development of the above-mentioned scientific work, he happened to observe again Laveran's half-moon *bodies* and other *flagellum* like forms, just the same as the ones he noticed in the unique case out of the 40 cases of quartan fever he examined and described in his first work, in 1885, but this time they were associated with much more malarial fever cases which proved to be particularly resistant to quinine. In this connection, he thought that:

by now (1886) it is better to consider these analogous forms separately, since, though being strictly related to malaria, they cannot be observed in the most typical malarial infections, but, on the contrary, they can be usually associated with irregular fevers. Let's add that their biology is surely different from the one which characterizes other forms undergoing a well known endocorpuscular development (ASM).

3. The quarrel with Tommasi-Crudeli on the claimed *Bacillus malariae*

In the interval within the publication of his first work in 1885, dealing with the quite complete pathogenesis of malaria, and the above-mentioned report dated 1889 on the differential diagnosis between the endocorpuscular malarial parasites of the tertian and those of the quartan forms, Golgi had to face a rough scientific quarrel set out by Professor Tommasi-Crudeli a member of the *Regia Accademia dei Lincei*. In fact, during a session of the Accademia, Tommasi-Crudeli announced that:

*from the air surrounding Pola d'Istria, a region which was contaminated by malaria, Dr. Bernardino Schiavuzzi had obtained the pure culture of a bacterial schizomycete absolutely identical to the bacillus which was previously described and denominated Bacillus malariae by Tommasi-Crudeli himself and by Klebs. Tommasi-Crudeli added that if it is possible to induce, by means of the schizomycete isolated by Schiavuzzi, fevers showing all the clinical and structural characteristics of malarial fevers, we will come to identify their aetiology.*³

In fact, Tommasi-Crudeli considered the amoebic bodies described by Marchiafava and Celli as a degeneration of the protoplasm of the red globules, according to his general studies on the protoplasm of the red globules in many types of fevers. Accordingly, he interpreted the process of segmentation of malarial parasites described by Golgi as heaps of granular sediment resulting from a strong action on the red globules just like the one induced by electrical discharges.

Subsequently, Schiavuzzi injected in two different rabbits a culture of *Bacillus malariae* and observed that, in infected animals, the red globules are subjected to those changes described by

Marchiafava and Celli as characteristic of the malarial infection, while the animals showed up and down peaks in temperature range, as in malaria fevers. Therefore, in 1887, during a novel session of the *Regia Accademia dei Lincei*, Tommasi-Crudeli stated that:

it is no longer possible to speak of Plasmodium of malaria and, both in Italy and abroad, literature on the so called Plasmodium is a mere expression of infatuation.

He thus concluded his speech saying that:

*Marchiafava-Celli's and Golgi's concern on the nature of changes which can be strictly related with malaria had to be considered brilliantly solved.*⁴

In the paper *On the claimed Bacillus malariae by Klebs, Tommasi-Crudeli and Schiavuzzi*⁵, Golgi thus commented these adverse reports confessing that the above-mentioned

declamations and the echo that followed could only drive me sad, just on account of the pretentious tone expressed, but they did never win me to get the slenderest shade on my convictions.

He obtained from Dr. Schiavuzzi a colture of the claimed *Bacillus malariae* and repeated the experiment, previously carried out by Schiavuzzi, on nine rabbits thus finding that the changes in temperature range showed by each rabbit perfectly agreed with the physiology of the rabbit itself, but sometimes they were affected by abscessual processes. As regards the alterations in blood cells, he denounced the inadequacy of the microscope observations as reported in Schiavuzzi's and Tommasi-Crudeli's figures. Golgi firmly declared:

*Now, the problem is not to look through the microscope as a scientist but with the simple attitude of a profane (not expert man); well, in this connection I have to say, against my will, that to find the courage to point out such a correspondence certainly means not to wish to accomplish differential examinations, not only with respect to the alterations one has the pretentiousness to identify, but neither with respect to those figures representing those alterations.*⁵

For what concerns the anatomopathologist surveys of the claimed malarial infection carried out by Schiavuzzi and by Tommasi-Crudeli, Golgi thus ended:

*Dr. Schiavuzzi's assertions on such matter are so little serious, as well as, in their whole, his experiments are illogical.*⁵

According to an old saying, Golgi was generally known as a troublesome man, since the scientific controversies he had to face were quite rough, but, as far as the above-mentioned quarrel is concerned, we could agree with him today and say that *by no means he was completely right*. In this connection, it seems to be right and proper to add that the controversy involving Golgi and Tommasi-Crudeli had been exhaustibly documented; in fact Golgi's *eminent assistants* Dr. A. Cattaneo and Dr. A. Monti and his colleagues such as Mosso, Maragliano, Sternberg, Osler (from Philadelphia), Councilmann and Metschnikoff had confirmed through further studies the pathogenesis of malaria in various aspects concerning schizogony and leukocyte phagocytosis (*phagocitism*). With such authoritative support and positive criticism, he could argue his general definitive although scornful conclusion:

*The claimed Bacillus malariae described by Klebs, Tommasi-Crudeli and Schiavuzzi, has nothing to do with the malaria infection.*⁵

4. Phagocitism in malaria infection. A clinical pathological classification of the three forms of malaria

Golgi has studied *the phagocitism in malaria infection*⁶ for long time and he has also stressed Metschnikoff's attention on the same subject⁷. Besides, he contributed to increase the knowledge *On the intermittent long intervals malaria fevers*⁸ according to Hippocrates', Galen's and Tulpius' old medical science, who had also identified quintan, seventh, ninth fevers and, in particular, to Celsus who had pointed out the difference between daily, tertian and quartan fevers. Celsus had also identified types of fevers which were lasting longer by saying *interdum etiam longiore circuitu quaedam redeunt, sed id raro fit*⁹. He

had compared all his observations with those carried out by his contemporary colleagues, underlining that *it is rather necessary, in the field of the scientific clinical monitoring to take into account criteria outcoming from the new knowledge*. In this study he had distinguished three types of intermittent fevers as follows:

1. intermittent fevers strictly related to the evolving cycle of parasites developing within two days (simple and double spring tertian forms);
2. intermittent fevers strictly related to the evolving cycle of parasites developing within three days (simple, double and triple quartan forms);
3. intermittent fevers strictly related to the presence in blood of those forms whose nature is rather uncertain, which develop throughout an irregular period of time and are commonly named half-moons.

This classification, as proposed in 1890, is surprisingly the most appropriate one nowadays, especially, in defining the tertian benign form (the spring form) as being induced by the *Plasmodium vivax*; the quartan form by the *Plasmodium malariae* and finally the tertian (summer-falls) malignant or pernicious form by the *Plasmodium falciparum*. At that time, Golgi did not know this last form very well, and, indeed, he confessed that: *in my observations these forms appeared in a very restricted proportion*. He was just aware of the fact that this last type of fevers was particularly resistant to the action of quinine. Three years later, he will carry out a strenuous research work on such forms in the Medical Clinic directed by Guido Baccelli in Rome, by being involved in another famous scientific debate with Baccelli, on the parasitic nature of these forms¹⁰.

5. The progress of photographic demonstration

In 1890 Golgi pointed out *Photographic demonstration of the development of the malaria parasites*¹¹ the importance of the photographic documentation to support rigorously the experimental data; a new procedure that even Laveran himself had judged

a little bit artificial. At that time, photographic technology did not offer itself as a satisfying method of choice and he expressed all his disappointment on it by stressing on the fact that this technique

is surprisingly difficult...: little movements of micrometric screw, different individual costumizing parameters, little variations of light etc. are enough to show slightly different figures¹¹.

Nevertheless, he found that:

some pictures He took showed greater sharpness and regularity as compared with the drawings that support all His previous reports¹¹.

6. Prime-time for the therapeutic administration of quinine and the general rule for the elimination of a parasitic generation

In 1888, Golgi referred to the *Società Medico-Chirurgica di Pavia* (Session March 17th) his observations on *The prime-time, throughout the developing cycle of malaria parasites, for the administration of quinine in order to prevent next onset of fever spike, by stopping its development¹²*. Golgi was particularly concerned about such question because, according to his own words:

I had the chance to discover the relationship between the developing cycle of malarial parasites and the periodic recurrences of the fever spikes and to check, at the same time, how to different types of fevers corresponded different species or varieties of malarial parasites¹².

Well, his duties as responsible for the hospital compartment had to include also the study of a therapy more directly concerned on clinical issues and, in the specific case, a study on the action of quinine on these parasites. In this connection, he arranged his research project in order to associate quinine administration time rates, *per os*, according to the ordinary therapeutic dose (not specified, it is supposed to be lower than 1 g), with the onset of fever and, in particular, with drug administration time rates, within four, five, six, eight and even ten hours before the

expected onset of fever. These time rates were fixed by Golgi according to the fact that the greatest relative quantity of quinine circulates into blood within the first six hours after ingestion¹³.

He applied this therapy in the treatment of simple quartan fever, the most common form of malaria in Pavia; he observed no significant effects on the approaching of the fever attack, but, later on, he could observe the subsequent disappearance of the young generation of parasites along with the suppression of the relative onset of fever and finally the stable remission of the disease. Analogous effects implying the complete remission of the disease are also induced by a therapy based on quinine bichloride which must be hypodermically injected four hours before the fever spike in cases of inveterate quartan fever. On the contrary, in the treatment of simple quartan fevers, if quinine sulphate is administered on the first day of apyrexia, the colony of parasites partially disappears and partially persists by undergoing an irregular development process; the first onset of fever may not arise or may be alleviated, but the infection is not completely healed thus inhibiting a complete regression of the disease leading to recurrences.

These fundamental observations demonstrated that the parasite, at the latest stage of its growing, when it breaks the red globule, is no more protected and find itself to be the massive target for drug and white globule aggression, while when it is again inside the red globule the action of quinine is partially efficacious.

According to those observations, Golgi found a general rule to eliminate completely a parasitic generation and he confirmed its validity by converting the triple quartan form (three daily onsets of fever caused by three subsequent generations of *Plasmodia*) into the double quartan form and the double quartan into a simple form along with the subsequent elimination of the above-mentioned three generations and finally the complete recovery through daily administration of quinine according to his general rule. It follows that Golgi, in his studies on the action of quinine on malarial parasites, did not act as a pharmacologist, but once again he was a true clinical-pathologist, really interested in the study of the aetiopathogenesis of the disease.

The above-mentioned rule was verified also in the cases of tertian fever (Spring benign form induced by *Plasmodium vivax*) along with the further discovery that the *Plasmodium vivax* shows higher sensibility than the *Plasmodium malariae* of the quartan form; the first one can thus be influenced by quinine even during the phase of endocorpuscular development, probably on account of the damage affecting the red globule that is revealed by a consistent swelling process. This process, according to Binz's and Rossbach's opinion (as reported by Golgi), perhaps is the expression of a sort of competition for oxygen between quinine and haemoglobin in favour of the drug or, on the contrary, quinine produces a stronger bond between oxygen and haemoglobin. In both cases, *Plasmodium* is indirectly damaged.

As regards the intermittent fevers induced by malaria with the presence of half-moon bodies into the blood, Golgi confirmed his previous observations by pointing out that these parasites showed high insensibility to all common anti-malarial agents and he formally reported such information even though he only had few chances to face such cases in his laboratory examinations in Pavia.

In 1891, in an extensive report on the *Gazzetta Medica di Pavia*¹⁴, Golgi stressed again his attention on *The action of quinine on malarial parasites and on the corresponding onsets of fever* and he quoted Guido Baccelli, Director of the Medical Clinic of the University of Rome, who had carried out for the first time a therapy based on intravenous administration of 1 g of quinine in order to induce the direct contact between the specific drug and the blood globules, reported on the *Riforma Medica*, January 1890. Nevertheless, in this connection Golgi pointed out that even such treatment had to be necessarily applied during the last phase the parasites proliferation (sporulation) and both oral and hypodermic administration of quinine are thus efficacious only if practised some hours before the onset of fever spike. He quoted Baccelli again for *his brilliant intuition, as a master in the field of direct clinical observation on patients*, by suggesting that the onset of fever might be induced by a sort of chemical action developed by a substance which is released when the parasite undergoes sporulation. In this connection,

Golgi was sorry to stress the fact that he had insufficient instruments of analysis to carry out deeper observations in this direction, but he remembered his surveys on the changes of blood colour (from light red to dark red) he could observe by taking blood samples from the fingertip of a patient during the parasite sporulation phase.

7. *Study on the pathogenesis of pernicious malaria in Rome. Golgi stresses the evidence on the parasitic aetiology of this form of disease in his debate with Guido Baccelli*

The admiration expressed by Golgi on Baccelli's *brilliant intuition, in the field of direct clinical observations on patients* took the latter to revise all the problems concerning the *intermittent fevers in Rome*, when he noticed that almost always these forms showed greater severity on summer and at the beginning of falls. In this connection, Baccelli was mainly concerned about the fact that such stronger virulence could be *evidenced but not proved by considering only the morphology of the parasite* so that, as he stated at the end of other four previous nosogenic considerations, he came to the conclusion that *the nosogeny of malarial fever is essentially and simply chemical in nature*.

This assertion challenged both the parasitic aetiology of malaria according to Marchiafava's and Celli's report, and, above all, the relative pathogenic mechanism as suggested by Golgi. At this point, Golgi, who was already known as the clever and lucky scientist in the study of quartan and tertian malarial fevers, was stung to the quick and immediately asked hospitality to his famous colleague in order to study, in his Institute of Medical Clinic at the University of Rome, the summer-falls pernicious malaria forms with Laveran's circulating half-moon bodies, which he very rarely had the chance to observe in Pavia. Formally, Golgi's demand was not really based on his disagreement with Baccelli's above-mentioned assertion, but on account of another claim put forward by the same Baccelli, that is, *the doctrine on the nosogenic process of malarial fevers is still partially unknown*.

At any rate, Golgi did go to Rome and he did undertake his observations with the assistance of Baccelli's direct collaborators, such as the clinicians Professor Rossoni and Doctor Tausig, and the anatomopathologist Doctor Bastianelli. He spent in Rome two months (July and September 1893; he came back to Pavia in August). During these months he got acquainted with the most varied clinical forms as called primitive fevers, relapsing fevers, light or mediocre fevers, pernicious and very serious fevers. He stressed his attention first on less severe and irregular forms in order to make it

easier to track the developing cycle of the parasites along with the different clinical symptoms and to the duration of the onset of fever¹⁴.

In this connection, he firmly followed his general method of scientific investigation, whereby, as he stated:

always convinced that the reason of facts must emerge, not by comparing many cases, but by observing the succession of phenomena unfolding a single subject; rather more than observe a great number of patients, I had care to follow single cases, searching in each of them the connection between clinical symptoms and parasitological findings¹⁴.

By this general method, Golgi only needed two months - July and September 1893 - to demonstrate to Baccelli the inconsistency of his nosogenic interpretation of summer-falls intermittent fevers as being induced by a mere chemical factor independently of the presence of amoebas, which may be occasionally observed into the blood and only during the final phase of apyrexia. According to Baccelli, the presence of the parasite had to be considered only an accidental but not aetiopathogenetic factor.

Golgi methodically analyzed little samples taken by needle from the spleen and the bone marrow, as well as blood samples taken from the patients' fingers.

Thus,

he found out the new fact that, whenever the test of spleen content is carried out (beginning of apyrexia, advanced apyrexia, imminence of the fever spike, advanced fever spike, deffervescence), it constantly turns out to

show (in the spleen) positive data concerning the presence of the parasites, but it also shows that in different periods the same parasites undergo different developing stages¹⁴

including the so-called Laveran's half-moon bodies (the Laverians), which are generally considered a distinctive feature of this form of malaria. In reporting his original observations, Golgi sharply stressed Baccelli's attention on the fact that:

his study was mainly based on a method that had been already persistently used by other distinguished clinicians, aiming the same goal¹⁴

and he clearly suffered from proud going on saying:

it is not up to me to explain how we came to achieve different results; I could only say that most probably the methods I followed were clearly modulated by personal laboratory practise¹⁴.

Besides, on account of the autoptic observations of the cases of terminal pernicious forms, carried out by Dr. Bastianelli, Golgi explained that the *brassing* process affecting the red globules (that is early necrosis for wrinkling) induces the fixation of the malarial parasites in all their developing phases, not only in the spleen but also into blood vessels (causing trombosis) of other organs, including intestine and brain. In this way, he showed the mechanism of most varied clinical pernicious symptoms, such as choleric and parietic symptoms. In all these observations, Golgi as a pathologist, played a very important role even in the field of clinical monitoring of pernicious malaria and his work is still generally considered a high contribution to the progress of medical science.

Golgi hands us down his latest and successful work *On the summer-falls malarial fevers in Rome* in a long letter addressed to Guido Baccelli in October 1893 and published by the *Gazzetta Medica of Pavia*, November-December 1893¹⁵. Formally, this letter is a sort of scientific report, that he submitted to the judgement of his colleague, on what he observed and studied within two months about the summer-falls malaria fever at the Medical Clinic of the University of Rome. Substantially, however, this re-

port mainly represents a sort of doctrinal performance of rational speech in terms first of argumentative dialectics, that often turns out to be extremely persuasive (rhetorical) dialectics, later followed by a logic synthesis aiming at fighting against Baccelli's assertion that *the nosography of malaria fever is essentially and simply chemical in nature*. Only at that time, Golgi opposed his clinical-pathologic observations, that he kindly called impressions, in order to demonstrate, in an extremely logical way as well with a high convincing power, the imperative error made by his colleague. Finally, he reminded Baccelli that:

*the most important experimental data are concerned with the reproduction (of malaria) in healthy people, which can be induced by injections of special types of malarial fevers along with the corresponding parasitic species*¹⁵.

This monitoring procedure, as it had been first verified by Marchiafava and Celli (1895) for quarantan fever, might be carried out also to demonstrate, without a shadow of a doubt, the parasitic aetiology of tertian pernicious summer-falls forms. We may add, however, that this pernicious form could not ethically permit such experimental approach because of the high insensitivity of this form to quinine.

8. *Epicritical study on Golgi's methodological and behavioural principles and on his philosophical values as a scientist and as a man*

An epicritical reading of Golgi's works on the aetiopathology of malaria and on its treatment with quinine contributes to draw a complete picture of Golgi not only as a doctor-scientist-pathologist-clinician, but also showing an unexpected picture of Golgi as a man.

For what concerns Golgi's method of analysis, he stressed on the extreme accuracy of the haematological tests he constantly carried out since the first cases of quartan fever and throughout the whole developing cycle consisting of 4 recurring onsets of fever, repeating themselves with mathematical regularity, at a

fixed hour, every 4th day. He referred that this research was carried out through *insistent blood tests* to underline the need for a practice that might turn out to be boring. Nowadays, we can properly say that such unsurpassed method allowed Golgi to describe the schizogonic cycle and to show the presence-absence of *Plasmodia* into the blood before and after the onset of fever.

Another peculiarity concerning Golgi's method of analysis in his first approach to clinical experimental studies was the gradual development of the procedure of analysis. He started to observe simple forms of quartan fever and thereafter he passed on double forms of quartan fever, by discovering that the first ones distinguished themselves from the others for the presence of one or two intercalated generations of the same parasite. The methodological accuracy allowed Golgi to observe all the symptomatic peculiarities showed by his first 40 patients, who represented a sufficient range in order to formulate precise rules for schizogonic growing phases connected with the onset of fever. He also reported the disappearance of the parasites from the blood after the fever spike; thus promoting his hypothesis of the hiding of *Plasmodia* into other internal organs, for example into the spleen. In this process of analysis Golgi highly improved his skills in clinical monitoring through microscope so that he could also check in only one case, out of the 40 patients he first examined, the presence of anomalous elliptical, oval, rather half-moon shaped bodies, which were completely abnormal if compared to the ones he previously observed. Besides, they appeared for the first time in coincidence with the fever spikes. Golgi could not define such bodies, but, however, he included them in his report in order to make complete his first important clinical experimental study on malaria¹⁶.

The fortuitus discovery, as Golgi sincerely declared in 1888, of the relationship between the developing cycle of malarial parasites and the periodic recurrences of fever spikes in quartan fevers, thus showing, at the same time, that different types of fevers may be induced by different species or varieties of malarial parasites, gave Golgi the chance to explain the matter concerning the onsets of fever within two consecutive days, and it allowed him to demonstrate the cyclic recurrence of two intercalated parasite generations.

Therefore, when he identified the morphological differences among the parasites of *Plasmodium vivax* in the spring tertian form and those of *Plasmodium malariae* of the quartan and of *Plasmodium falciparum* of the summer-falls tertian form, for the first time in medical science he embodied the clinical-pathologist ability to manage, through microscope examinations, diagnostic problems arising when the above-mentioned malarial forms are complicated by daily fevers induced by the cyclic recurrence of more generations of the same or of another parasite¹⁷.

The accuracy of his clinical observations supported by microscope diagnostics induced him also to undertake a therapeutic study, more as a clinician than as a pathologist, in order to make the highest haematic concentration of quinine coinciding with the terminal development stage of the schizogonic cycle. He, thus, found the prime-time for the therapeutic administration of quinine and the general law for the elimination of a parasitic generation, by transforming the double quartan into simple quartan form and he finally obtained, through a further rational administration of quinine, the complete remission of the disease¹⁸.

In 1893, in the Medical Clinic of Rome, crowded by patients suffering from pernicious complicated malaria, Golgi once more carried out his examinations according to his main methodical principle in the treatment of many difficult clinical cases, that is, at the beginning, *less serious and less irregular cases* had to be inspected, exactly as he started his research work focusing on simple quartan forms of malaria. In that occasion, Golgi came to formulate the following crucial statement on his method of pathological-clinical investigation:

always convinced that the reason of facts must emerge, not by comparing many cases, but by observing the succession of phenomena unfolding a single subject, rather more than observe a great number of patients, I had care to follow single cases, searching in each of them the connection between clinical symptoms and parasitological findings.

This successful scientific philosophy won him the chance to find confirmation on the parasitic aetiopathogenesis of the disease even in case of pernicious malaria, thus denying Baccelli's

creed about chemical aetiology, after only two months of specific clinical-pathologic investigations carried out on samples taken from internal organs and from autopsy^{19,20}.

Golgi's reports clearly draw the picture of the man of science, whose work is strongly characterized by methodological accuracy and scientific determination, but, nevertheless, they show many signs of human distrust, drawing an unusual picture of Golgi as an ordinary man. Indeed, he confessed that he felt all the sadness of the scientific affront brought forward the solidity of his research work, at least two times, either by colleagues whom he despised, or by colleagues he admired. He might also be considered rather vainglorious for he achieved positive results whether the others had failed by following the same research technique. On the other hand, he acknowledged, with intellectual honesty, that he was helped by chance since the beginning when he discovered the *Plasmodium* schizogonic cycle and he found the relationship between the developing cycle of the parasites and the onsets of fever spikes in different malaria forms.

Such accounts might be an impulse to bring about a psychological study on Golgi, in order to understand better his whole identity as a human being. Such analysis could be extremely punctual because, according to old saying from Pavia, Golgi is also remembered as a shy man in performing his public lectures, arid in friendship and in his affections and finally even atheist or agnostic in front of the Transcendental²¹.

In this connection, it is necessary to stress the attention on few dialectic considerations in order to understand better Golgi's rational philosophy. First of all, it must be remembered that Golgi always planned his project works and adopted, from time to time, a specific method of analysis, mainly according to rational issues and to the so called *demonstratio quia* technique, that is based on a *posteriori* logical conjectures.

Nevertheless, such method also implied the use of intuition to formulate *a priori* an hypothesis or to foresee the possible development of a research work²². (According to such issues, and by the way, it can be suggestive to remember that Golgi, as a music scholar, was also actively involved in art, which is pure intuition²³). It is important to point out that his logical methods of

analysis associated with a high power of imagination led him to discover the pathogenesis and to find the suitable therapy for such a complex disease, along with observations which have been enduring throughout more than a century. This very last issue makes us understand that the intellectual degree reached by Golgi as a scientist is very high.

May be Golgi, as a man and scientist, has found himself in the paradoxical situation well described by Tommaso d'Aquino:

*The believer is similar to someone who has science and intelligence but whose knowledge is not perfect, as well as that of a man who has an evident vision thus being similar to the one of a man full of doubts, suspects, questions*²⁴.

On the other hand, we can check, through our epicritical reading, that Golgi behaved as a believer in the value of his scientific research which otherwise he developed by means of dialectic doubt and according to the mental process of logical synthesis. Indeed, when Tommasi-Crudeli, on account of his claimed discovery of the *Bacillus malariae*, contested the parasitic nature of the disease and when Baccelli tried to demonstrate the claimed chemical aetiology of pernicious malaria fevers in Rome, Golgi came to confess that such adverse assertions certainly drove him sad, but they did never win him to get the slenderest shade on his convictions.

It could be outlined a comprehensive profile of Golgi as an aristocratic thinker highly concerned with the immanent-transcendental issue of free will, who may be well considered rather the symbol of the perfect *religious* misunderstood by his contemporaries; this may easily explain how Golgi's presumed inner contradictions as a human being had been amplified only by an old and maybe rather inadequate tradition.

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10. See § 7.
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16. See § 1.
17. See § 2.
18. See § 6.
19. Today, this rule cannot be applied in clinical experimental research carried out on many subjects who are constantly monitored by *équipes*, including in turn many different expert physicians. The inherent mistake concerning this kind of research is corrected by statistics. Nevertheless, today Golgi's rule is still valid in the development of the so-called pilot studies, whose aim is to foresee, through the analysis of single few cases, the possible trend of a clinical experimental research. See also: *Gli studi di Camillo Golgi sulla malaria*. Collected by Professor Aldo Perroncito. Roma, Luigi Pozzi, 1929, pp.1-262. (*I Classici della Malaria* series, published by the Scuola Superiore di Malariologia, Rome).
20. See § 7.
21. Perhaps Golgi was not really interested in the appraisal of his contemporary scientists and, according to his last wills, he refused a religious funeral.
22. See § 1.
23. It is little known that Golgi, besides being an eminent scientist, was also a devoted musician. He deeply studied music and he managed to adapt it harmoniously to the flute, the instrument he played according to paternal tradition. In this connection, I had the chance to talk to professor A. Rossi, a musician from Pavia, who is the fortunate owner of two original scores of music by Donizetti *arranged for two flutes by Camillo Golgi*, as the holograph in the cover page shows (fig. 4), and of some piece of music by Verdi *arranged for flutes, violins and piano by V. Golgi*, Golgi's Father, a doctor from Cava Manara in the outskirts of Pavia. Professor Rossi had these scores from Colonel Pizzoccaro's family, whose house in Cava Manara was a sort of chambermusic concert hall, according to the customs of that age, where people had the chance to play and to listen to their favourite lyric plays once again, but properly arranged just for few instruments. As regards to this, it is interesting to report the judgements of Maestro Bruno Villani, Director of F. Vittadini Musical

Civic Institute of Pavia, on the score of the romanza *Elisir d'amore* and *Il furioso* by Donizetti, arranged for two flutes by Camillo Golgi (today only the part concerning the 1st flute survives) showing a changing in tonality from re to do maggiore, with the melody mainly entrusted to the 1st flute and with arpeggio of accompanied written at intervals of third. From the reading of the score, Maestro Villani found that Golgi surely had to be an excellent flute player, since in his transcriptions virtuous cadenzas originally intrusted to the tenor or soprano's trills, are still maintained.

24. S. th. II, 2, q. 2, a. 1.

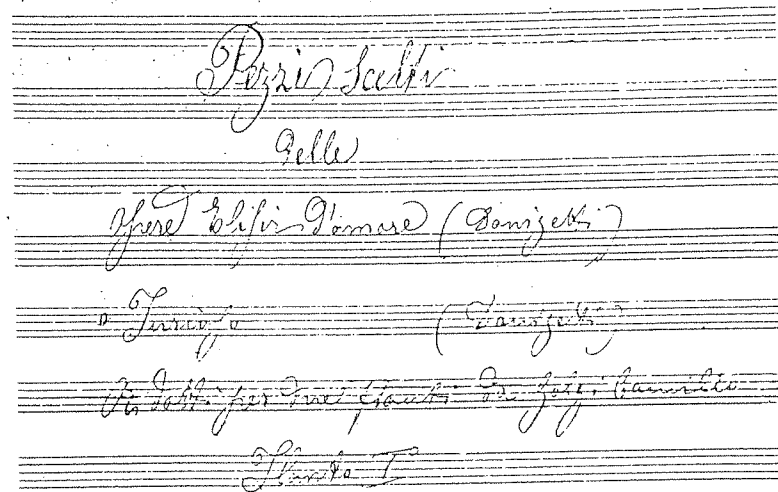


Fig. 4 - Cover page with handwriting of the score of music by Donizetti arranged for two flutes by Camillo Golgi.

Correspondence should be addressed to:
Leonida Santamaria, Istituto di Patologia Generale Camillo Golgi, Università di Pavia,
Piazza Botta, 10 - 27100 Pavia .

Articoli/Articles

SOME ASPECTS OF CAMILLO GOLGI'S
PARLIAMENTARY ACTIVITY

BRUNO ZANOBIO

Istituto di Storia della Medicina
Università degli Studi di Milano, I

GIUSEPPE ARMOCIDA

Cattedra di Storia della Medicina
Università degli Studi di Pavia
Sede di Varese, I

SUMMARY

The Authors present some considerations about the senatorial activity of Camillo Golgi.

His presence in Parliament confirms definite and not negligible interest in political affairs, especially those concerning health and universities.

This year sees the 150th anniversary of the birth of Camillo Golgi. As part of the celebrations and amid the various commemorative events aimed at up-dating and expanding the studies on different facets of his scientific life, we felt this was an ideal opportunity to present a short resumé of his political career as Senator of the Kingdom of Italy. Authors of a recent commemorative book on Golgi's life and scientific works, while defining him as resolute in his speeches to the Senate, also described him as a *stranger to politics*¹. This same observation was made by Tommaso Detti in reference to another Senator who like Golgi was one of the leading figures on the Italian scientific scene at that time.

He believed that

*the names of Bizzozero and Golgi, were not strongly associated with politics and, in any case, they were totally alien to any democratic sympathies*².

Key words: Camillo Golgi - Parliamentary activity