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Articoli/*Articles*

LESSONS FROM ANTI-THALASSEMIA CAMPAIGNS IN ITALY, BEFORE PRENATAL DIAGNOSIS

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SUMMARY

The essay reconstructs the antithalassemia campaign carried out by means of population screening and pre-marriage counselling for about twenty years in Italy, immediately after the relationship between microcythemia and Cooley's anemia had been established, as well as its genetic bases. We examine the Italian contributions to the understanding of the genetics and of the clinical treatment of thalassemic disorders, and analyze the approaches to prevention as well as the results obtained by the first campaign against a genetic disease, conceived and largely implemented in Italy by Ezio Silvestroni and Ida Bianco. We discuss the resistances met by the antithalassemia campaign due to the cultural and organizational backwardness of the Italian medical community and of the public health system. Moreover we analyse the explanations and interpretations of the problematic results of these experiences in terms of morbidity reduction. It will be pointed out that the objective of genetic counselling practised in that context assumed the concept of disease prevention at the population level, and it was far from the idea, emerged in the 1970s, of non directive genetic counselling.

Introduction

The beta-thalassemia prevention action undertaken by the health services in the early 'seventies in various countries by means of the genetic screening of the population and prenatal diagnosis, made it possible, on the basis of pre- or post-nuptial

Key words: History of thalassemia - History of genetic screening, Pre-marriage counselling, Ezio Silvestroni, Ida Bianco

reproductive decisions - in particular by the selective abortion of homozygous foetuses - to prevent almost entirely the birth of children suffering from the effects of thalassemia. Several of these national and regional experiments have been analysed and, as far as Italy is concerned, particular emphasis has been laid on the campaign carried out in Sardinia[1]. A number of different socio-ethical problems were reported, associated with the anti-thalassemia campaign, above all in national contexts in which beta-thalassemia involved ethnic minorities, but also in operations at the level of the general population, such as the one carried out at Cyprus[2].

Before the prevention of beta-thalassemia was in a position to exploit the new prenatal diagnosis techniques, the campaign against this disease had been attempted by means of screening and pre-marriage counselling for about twenty years in Italy, immediately after the relationship between microcythemia and Cooley's anemia and the genetic bases of the disorder had been established.

The present article reconstructs this experiment, schematically examining the Italian contributions to the understanding of the genetics and clinical treatment of thalassemic disorders, and analysing the lines of approach to prevention as well as the results obtained. An examination will be made of the premises and methods underlying what was the first campaign against a genetic disease, conceived and largely implemented by Ezio Silvestroni and Ida Bianco. Furthermore, a discussion will be presented of the resistance encountered by the campaign owing to the cultural and organizational backwardness of the medical community and the public health service in Italy and the official stance adopted by the Roman Catholic Church. Lastly, an analysis will be presented of the explanations and interpretations of the problematic results of these experiments in terms of the reduction of morbidity, showing that the objective of genetic counselling in those programmes insisted on the concept of prevention of the disease at the population level rather than according to the idea, which emerged only in the 'seventies in the field of genetic medicine, of merely providing elements of information of use in making an individual informed choice[3].

Silvestroni and Bianco's experience became a reference model for the thalassemia prevention programmes carried out in the 'seventies in Greece and Cyprus, and even though it was hastily judged to be superseded by the advent of prenatal diagnosis, it contains important lessons of still topical interest. In particular, several experiments in health care education carried out within the programme of the campaign against thalassemia in Italy can be taken as models in addressing the current need to promote cultural awareness concerning genetic testing in medicine[4].

Phases and controversies in the Italian contribution to the discovery of the genetics of thalassemia

The fact that the first thalassemia prevention programme was run in Italy was the consequence of the intense studies carried out on this disease by a number of Italian researchers, who made a significant contribution to introducing some form of order into the relationship between clinical signs and the genetic basis of thalassemia.

In 1932, when George Whipple introduced the term *"thalassemia"*[5], Thomas Cooley noticed that the disease had an evident familial incidence[6]. Later, Heinrich Lehndorf assumed that Cooley's anemia was an inherited disease originally due to a genetic mutation[7].

In the same period Ferdinando Micheli and collaborators (1935), Angelini (1937), Jean Caminopetros (1937) observed distinctive, even if minimal, hematological traits in healthy parents[8]. Then Maxwell Wintrobe and William Dameshek recognized the relationship between these hematological abnormalities and minor forms of thalassemia[9]. Meanwhile Jean Caminopetros (1937) postulated that clinically healthy people could transmit the disease as a recessive Mendelian trait[10].

Alan Moncrieff and Lionel Ernest Whitby had already suggested the involvement of a Mendelian mechanism in 1934[11]. Ignazio Gatto proposed in 1941-42 that thalassemia was a hereditary condition, lethal in the homozygote (*"omozigote-malattia"*) and representing in the heterozygote only a minor and non pathological trait (*"eterozigote-stigmata"*)[12].

In 1943, Ezio Silvestroni and Ida Bianco described an inborn and hereditary hematological anomaly in healthy people that

they subsequently called microcythemia[13]. At the same time, Silvestroni and Bianco established the genetical relationship between thalassemia and microcythemia by studying several people with Cooley's anemia[14]. At the end of these investigations, Silvestroni and Bianco showed conclusively that microcythemia was a Mendelian character, and its homozygotic condition corresponded to Cooley's disease[15]. These results tallied with the evidence obtained from independent studies conducted in USA by Dameshek[16], and especially by William Valentine and James Neel at University of Rochester[17].

Silvestroni and Bianco's results were greeted unenthusiastically and even vigorously challenged by the Italian scientific community. A bitter controversy arose over the nature and priority of the discovery of microcythemia, as well as over the demonstration of the relationship between this condition and Cooley's anemia. Several Italian physicians had for various reasons had the occasion to study microcythemic individuals, and had reported forms of familiarity in the hematological features of the types of thalassemia; they also described, without understanding it, the link between Cooley's anemia, Rietti-Greppi-Micheli's disease and the microcythemic condition[18]. Silvestroni and Bianco, who were still only young assistant physicians at the time and enjoyed no effective academic protection, were isolated inside the medical community. Indeed, in the pure feudal style prevailing in the Italian universities in the 'fifties, Ezio Silvestroni was systematically failed in his competitive examinations for the award of a chair, and soon had to abandon all hope of academic success. Both members of the couple were then pushed out of the university in 1957 as the result of a change of management of the Clinical Medicine Institute where they worked as assistants[19]. Partly for this reason, and partly due to the envy and opposition they encountered, their proposals on prevention received a very cool reception from those responsible for Italian health care policy.

From epidemiological investigations to the prevention model

Between 1943, the year in which they began their research on microcythemia and 1948, Silvestroni and Bianco carried out extensive epidemiological studies throughout Italy and were the

first in the case of thalassemia to draw up an accurate map of the distribution of the disease in Italy[20]. Their research results pointed to an alarming situation, characterized by the presence of numerous microcythemic foci scattered over the country, in particular in the Po valley area and the islands, i.e. Sardinia and Sicily, where the incidence of carriers sometimes exceeded 20% of the population.

For about twenty years, until the mid '60s, the extensive root and branch epidemiological study carried out by Silvestroni and Bianco in the whole of Italy, involving about 100,000 subjects, was based on using a rapid method they themselves had devised to diagnose microcythemia[21].

Starting from an understanding of the genetic relationship between microcythemia and thalassemia, Silvestroni and Bianco suggested that it was possible to implement prevention by avoiding marriage and procreation between microcythemics. In the session of the Accademia Medica di Roma held on 30 November 1946, the two researchers announced the results of their C.N.R. funded research on the frequency of microcythemia in the Ferrara area and in the neighbouring regions (2,393 subjects examined). The results confirmed the link between microcythemia and Cooley's anemia. According to Silvestroni and Bianco they also demonstrated

> *the possibility of using suitable prophylactic measures for the purpose of preventing (that is, by preventing marriages between microcythemia carriers) the onset of this form of the disease*[22].

Silvestroni reaffirmed this idea in 1949, at the 50th Congress of the Società Italiana di Medicina Interna, pointing out that

> *"also in America there is growing awareness that our present understanding of the hereditary nature of Cooley's anemia means that eugenic counselling can be given to young couples in whom one or both partners are microcythemia carriers"*[23].

In the course of the same Congress other speakers described possible strategies for the prevention of thalassemia, also in the wake of the eugenic ideas popular at the time. Giovanni Di

Guglielmo proposed the sterilization of microcythemics while, when participating in the discussion, the anthropologist Sergio Sergi, a leading figure in the eugenic debate in Italy, suggested performing a compulsory blood test on the entire school population, which had also already been suggested by Silvestroni and Bianco.

1.1 Silvestroni and Bianco's prevention model: general principles

Formulated in the early '50s, Silvestroni and Bianco's prevention model was based essentially on the identification of carriers by means of mass screenings and on pre-marriage prevention. At the time, this was the only possible course of action after the link between microcythemia and Cooley's anemia had been demonstrated, and was set up and implemented some two decades before the advent of prenatal diagnosis[24].

> *"The search for microcythemia,* wrote the two Roman researchers, *has an obvious importance, not only for the purpose of identifying Cooley's anemia in patients that are already sick and anemic [...] the presence, always clearly identifiable in parents suffering from Cooley's anemia, of the complex of hematological characters representing microcythemia, affords early recognition of all those families that, in their turn, may give birth to children suffering from Cooley's anemia, and is a precious element in ensuring an adequate and feasible prophylaxis of this disease. It thus became possible in those regions, such as the Ferrara area, characterized by a high incidence of Cooley's anemia, by identifying microcythemia carriers through the special blood test centres, to avoid marriages between microcythemia carriers, which would be sufficient (except in rather rare and hard to interpret cases of families in which the disease is declared when only one parent is a carrier of the anomaly) to avoid the onset of new cases of Cooley's anemia."*[25]

Silvestroni and Bianco on several occasions called for the microcythemia test to be made compulsory for couples planning to get married.

1.1.1 The importance of health care education and information

From the outset the two researchers grasped the importance for the purpose of prevention of information and health care and "eugenic" education. In the long report he delivered to the

50th Congress of the Società Italiana di Medicina Interna held in Rome, Silvestroni appealed to the state for help in carrying out a sweeping national awareness campaign on the problem, a campaign of education able to set in motion the formation of a eugenic sensitivity, that is, aimed at reducing the number of marriage between carriers, the only instrument available at the time to prevent Cooley's anemia[26].

Silvestroni's ideas and proposed prophylaxis aroused a strong echo in the media (see, among others, *La Settimana Incom*, 3 November 1949, *L'Elefante*, 5 November 1949)[27].

In order to disseminate knowledge about thalassemia and methods of prophylaxis, Silvestroni and Bianco in 1951 made a documentary film, which they immediately set about screening for physicians, health care professionals and the general public.

1954-1971: prevention of thalassemia in the framework of the radical changes in health care policy in Italy

Only towards the mid '50s did the Italian health authorities begin to take an interest in the problem of thalassemia. In that period Silvestroni and Bianco finally succeeded in getting the political will of the academic world to converge with that of the health care authorities. Sufficient funds were now forthcoming from different sources to be able to undertake a programme of prevention, which was actually the first in the world for thalassemia.

1.2 The birth of the Rome Microcythemia Centre

Amid numerous difficulties, Silvestroni succeeded in raising the level of awareness of the Alto Commissariato per l'Igiene e la Sanità Pubblica – ACIS[28], a body that had already, on various occasions, made available small financial contributions for the research and population studies carried out together with Ida Bianco. As immediate objective he proposed to set up a centre for the campaign against microcythemia.

Silvestroni at the time was assistant lecturer in general clinical practice and medical therapy at the University of Rome. His academic position was therefore comparatively weak for the purpose of carry out a project that was quite burdensome and

presented complex organizational obstacles. Premises and funding were needed to set up the centre, purchase equipment and get the centre operational. Instrumental in this connection was the help offered by Vittorio Puntoni, then Head of the Faculty of Medicine and Director of the Institute of Hygiene. Puntoni had realized the importance of the work being done by Silvestroni and Bianco as well as the social significance of a research centre for microcythemia and the prevention of Cooley's anemia. He had invited the two researchers to write a long article, published in 1953 in *Annali di Sanità pubblica*, which summarized their research results and pointed to the need to carry out effective prevention measures through the direct action of the national health care authorities[29].

In 1954 Puntoni had the centre set up inside his institute, in premises that had been freed by the transfer of the museum and the library of the history of medicine, and sponsored Silvestroni's request to ACIS in a formal letter sent on 25 July 1954 to the ACIS Alto Commissario, Tiziano Tessitori[30].

On the following 18 September, Tessitori informed Puntoni that a grant of 4,450,000 Lire (the equivalent to about 155,800 Euro in January 2002 values) had been offered for the creation of a microcythemia study centre directed by Ezio Silvestroni[31]. In his letter Tessitori expressed the hope that

> *"the problem of microcythemia, of the social importance of which this High Commissariat is fully aware, may be thoroughly studied and determined, above all with regard to Cooley's anemia."*[32]

ACIS' primary objective was thus prevention and the Centre was actually the beginning of the first Italian, and indeed world, campaign of thalassemia prophylaxis. The mandate received by the Centre was however more comprehensive, and ranged from clinical practice to experimental research, thus basically covering the same ground as Silvestroni had already travelled over with Ida Bianco:

1. organization of the health care services for the care and treatment of those suffering from Cooley's anemia and other microcythemic anemias in all the Italian regions badly affected by these diseases;

2. extension of epidemiological research, in order to determine more precisely the extension and extent of the microcythemic phenomenon in Italy as a whole;
3. research and application of the more effective means of treatment against Cooley's anemia and the microcythemic anemias;
4. implementation of pre-marriage prophylaxis against Cooley's anemia;
5. performance of studies and research in the field of microcythemia.

Also the Rockfeller Foundation recognized the importance of Silvestroni and Bianco's research and results and in 1954, by means of a genetics research programme coordinated by Giuseppe Montalenti, it decided to financially support the two physicians and the newly created Centre in order to ensure greater development of

> *"the eugenic aspect of the microcythemic problem, the establishment of official registers of persons carrying this gene, and marriage counseling in some form."*[33]

However, the Italian geneticist did not take up the suggestion and allocated most of the available funds to research on population genetics.

In 1955 the Centre opened a free day hospital service for the vetting and care of thalassemia patients. Subsequently, in 1956, work began on networking the peripheral centres in the Italian regions with the highest incidence of thalassemia. With the help of a new financial contribution, first from ACIS and then from the newly established Ministry of Health (instituted by Law 13 March 1958, no. 296), between 1956 and 1961 seven microcythemia centres or sections, as they were called, were set up and carried on their activities in close collaboration with the Rome Centre[34].

1.3 1961: Thalassemia as a social disease and the birth of the ANLMI

On 5 December 1961, the Consiglio Superiore di Sanità, when finalizing the last hearings regarding the determination of social

diseases for the purposes of applying the Decreto del Presidente della Repubblica 11 February 1961, Chapter II of which provided for the institution of *"special social disease centres for the protection of the health of the population"*, convened Silvestroni on the subject of microcythemia and Cooley's anemia.

In his report Silvestroni pointed out the need for state intervention owing to the epidemiological dimension of thalassemia, the high cost of treatment for the patients, unaffordable by the majority of Italian families, but above all in order to achieve large-scale implementation *"as a means of immediate and certain effectiveness, of pre-marriage prophylaxis against this disease"*[35].

> *"The onset of Cooley's anemia* – Silvestroni went on *–is determined by the homozygous condition of the microcythemia and it is thus possible to avoid it by preventing marriage between microcythemics and recommending marriage between microcythemics and normal subjects. This led to the need for a systematic census and registration of microcythemics by means of screening all elementary school children, of a vigorous and effective eugenic information campaign among the microcythemic populations, and the organization and functioning of special marriage counselling centre.* And he concluded, *on the basis of his previous experience with the network of centres coordinated by him, that "Of course, all these tasks of health care, study and research, census taking, eugenic propaganda and pre-marriage prophylaxis against Cooley's anemia can be carried out only by ad hoc specialist Centres that guarantee these tasks are carried out immediately and fully."*[36]

Microcythemia and Cooley's anemia were thus recognized as *"pathological forms to be defined as social diseases"* by decree of the Ministry of Health of 20 December 1961. The Ministry of Health had the task of setting up the relevant health care Centres. In order to be recognized by the Ministry and have access to the social disease funds, the network of centres set up by Silvestroni and Bianco nevertheless had to have legal personality. To this end, on 16 November 1961 the Associazione Nazionale per la Lotta contro le Microcitemie in Italia – ANLMI was set up in Rome, with its main office at the Institute of Hygiene at the University and with Vittorio Puntoni as Chairman and Vittorio Del Vecchio as Vice Chairman. On these new bases and finally

having been given a permanent position in Italian health care policy, the work of expanding the network of microcythemia centres could be resumed. In 1963, a nine-year convention stipulated with the Ministry of Health finally guaranteed ANLMI the funds it needed to be able to define a rational programme of development with some certainty of its duration in time.

In the meantime, during the first Congress held in Rome in May 1961, Silvestroni and Bianco presented the results of fourteen years of Italy-wide epidemiological campaigns and the analysis of over 100,000 subjects tested[37]. Thanks to the abundance of case histories and the collaboration of the Institute of Probability Calculus of Rome University, Silvestroni was able to postulate the presence of about 2 million microcythemics in Italy, from whom the birth of 1,000 cases of the disease per year could be expected. The figures referring to the number of sick persons were however overestimated as alpha-microcythemia, which does not lead to thalassemia even in homozygous conditions, was not known at the time.

In those years, however, the extent of another alarming epidemiological phenomenon began to emerge: the appearance of microcythemia and thalassemia in previously unaffected zones, as the effect of migratory flows from the areas of origin. As regularly happens in history, the epidemiological dynamics was associated with economic pressures and needs. In this way it was not just by chance that the 5,800,000 persons that migrated towards the industrial triangle of Milan-Turin-Genoa between 1951 and 1965 mostly came from the microcythemic foci distributed over the national territory: the Po delta, the southern and island regions. Towards the mid '60s, the incidence of microcythemia in the industrial regions of the North practically doubled (compared with the postwar period[38]).

1.4 Expansion of the network of centres over Italy

In early 1965 16 such microcythemia centres were in operation in Italy. In the same year the centres provided care for a total of 1,338 patients, carried out 17,414 medical examinations and blood tests, performed 5,484 transfusions, and 40,147 miscellaneous tests and screened 76,235 persons for microcythemia.

A root and branch network had thus been created, the first in the world, for the prevention and treatment of thalassemia. At the beginning of the seventies, Cypriot and Greek governments took this organization as a model for thalassemia prevention policies. In Cyprus a programme for the prevention of beta-homozygous thalassemia, founded on public education, population screening, genetic counselling, started in 1973[39], while the national Greek programme for thalassemia prevention began in 1974[40]. Services were provided through the Central Unit of Prevention of the "Thalassemia Center" affiliated with the "Laikon" Hospital in Athens and 21 "Units of Prevention" affiliated with hospitals in other towns in Greece, mainly in areas of high prevalence. Like Silvestroni-Bianco's, the Greek programme was based on:

1. raising public awareness (through the mass media, articles in the press, education in schools, posters, a series of leaflets for prospective parents, booklets specifically directed at high schools for teachers and students)
2. screening tests for the identification of carriers
3. genetic counselling.

1.5 From the State to the Regions: the crisis in the microcythemia centre network

In the early '70s, just when ANLMI was establishing its model as the prototype for prevention plans throughout the Mediterranean area, its activity was practically completely blocked by an Act of Parliament. In 1971, the establishment of the regional organization and consequent decentralization and transfer of power from the state to the regions meant that the microcythemia centres would be transferred under the direct authority of the regions. This meant essentially that the national network created by the ANLMI would be broken up, the coordination of the activities largely interrupted, together with the exchange of experiences acquired in the various different areas, and the possibility of any comparison or measurement of the effectiveness and of the regulation of the preventive action taken in the various Italian thalassemia foci would be impaired. The consequences are seen to be all the more serious when it is considered that the ANLMI, among other things, supported almost entirely the prevention of thalassemia and the treatment of Cooley's anemia patients throughout the whole of Italy[41]. The microcythemia centre of Cagliari, situated in the region with the highest thalassemia incidence in Italy, did not open again until January 1975, when also the Rome centre resumed regular functioning on the basis of a five-year convention stipulated with the Lazio Region.

The construction of the prevention model

Right from the early '60s, Silvestroni and Bianco were obliged to carry out their epidemiological research and to try and start up prevention in Italy without any permanent or productive collaboration (except in the case of Ferrara), with funds that were scanty in proportion to the task, and often able to count on material help exclusively from some local authorities who were more sensitive to the problem.

The work of health care information and education, of central importance in the prevention model, thus ended up by being carried out unsystematically, at the same time as the numerous screening campaigns carried out in various Italian regions. Together with the health care personnel that received them locally and accompanied them in their *"haematological censuses"*, the two, particularly in public meetings held in schools, verbally passed on information concerning these diseases and gave advice on how to prevent them. Whenever carriers were identified, their families were contacted and examined, and so further information was passed on concerning thalassemia, and the rules for premarriage prevention were recommended.

Starting in 1954, with the opening of the Rome microcythemia centre and the subsequent establishment of the local sections in various Italian cities starting in 1956, their work of dissemination became more intense. Above all at the level of the locations in which Silvestroni and Bianco's work had begun and where the greatest sensitivity had been shown by the local authorities, the local health authorities and the educational and child care institutions, such as at Ferrara and Rome, the growth of health care education regarding microcythemia was given a strong impulse.

In 1956, in Ferrara, the systematic screening of the school population was begun, accompanied by the compilation of a hematological register for the province[42]. In the early '60s, under pressure from the thalassemia emergency, the Municipality of Ferrara, in collaboration with the microcythemia centre, also opened a pre-marriage counselling bureau. In 1963 the Ferrara microcythemia centre concluded the screening of the entire school population of the province[43].

The identification of carriers at school led to the investigation being extended to entire family groups and thus to the compilation of personal records drawn up for the provincial hematological archives. The family was thus able to receive preliminary genetic counselling in the form of a written communication couched in very simple and clear terms and of an interview. The counselling was aimed at *"creating a pre-marriage eugenic mind set"*[44].

Health care education was given at school, in preparation for the microcythemia test days, in the pediatric consulting rooms of the Opera Nazionale Maternità e Infanzia – ONMI (National Maternity and Childhood Organization), directly in the microcythemia centres and consulting rooms, by means of printed material and individual interviews, and meetings with entire family nuclei. Starting in 1956, microcythemics identified in the school screening programme began to receive a pro-memoria in the form of a card describing their status of carrier, and accompanied by several precise pre-marriage eugenic indications[45].

This root and branch information work actually led to an appreciable increase in the level of eugenic awareness of the Ferrara population. This is shown by the increased demand for microcythemia testing at the centre also from young people and engaged couples[46].

To a lesser degree than in Ferrara, the elementary school screening tests were carried out by all the other ANLMI microcythemia centres. From the end of the war until the mid '60s, in a period in which the mass media and the health care information received by the population in general had little effect, and medical and health care personnel lacked training in dealing with the disease, they certainly represented one of the most effective means for reaching and informing also the adult population.

It was attempted to use the compulsory state school system to carry out pre-census and intra-census popularising campaigns, with meetings and letters to parents requesting permission to carry out the tests, and sensitising the teachers. As would be expected in view of the logic specific to the preventive approach, measurable prophylactic effects were long in coming. Over the years it became clear that screening the children at school was comparatively ineffective. The very young age of the subjects made the transmission and comprehension of the educational content difficult, as well as its use, in view of the complexity of the message and the fact that its object was to prevent individual behaviour that would occur only many years later. Furthermore, the information on the carrier's status was abstract and perceived only fleetingly even by adult individuals.

Consequently, towards the mid '60s, the ANLMI further attempted to gear the action to age groups and the specific population. With the collaboration of the municipalities and marriage counselling bureaus, it was attempted to intercept the population at a fertile age and about to reproduce. In several Italian regions, the microcythemia centres began yearly to distribute printed information material to the marriage registry offices of the local administrations, to be distributed to couples gathering the documents they needed to get married.

In May 1967, the Rome microcythemia centre began screening students at Rome University. By 1975, the year in which the Centre, finally funded in an appropriate manner, began the programme of systematically screening school pupils in the final year of secondary school in the Lazio Region, about 47,000 university students had undergone microcythemia tests and received information and sometimes genetic counselling[47].

After 1975, following the indications of the Rome microcythemia centre, the screening of pupils, aged about 13 years, attending the final year of compulsory schooling was begun in regions with the highest incidence of thalassemia. Annual screening and the preparatory and educational action associated with it resulted in increased awareness of the problem and of the rules for preventing it, a chain dissemination of the information which then led to a considerable increase in the demand by

young people of child bearing but post-school age and young married couples (which tripled between 1975 and 1980)[48].

Debate and controversies regarding the prevention of thalassemia

The measure of the scant consideration given to the problem of thalassemia in Italy is eloquently expressed by the lack of vivacity of the debate on prevention in scientific circles at both the political and the cultural level. The rare occasions of stimulus to analysis and discussion of methods of the research, treatment and prevention of thalassemia, at least up to the mid '70s, came solely from Silvestroni and Bianco and their association through the organization of periodic lectures on the topic and articles in the scientific press.

Few controversial issues thus arose out of the obstacle-ridden action of prevention promoted by ANLMI in spite of the importance and heterogeneous nature of the problems it raised at different levels – genetic, health care, ethical and political.

1.6 Other prevention hypotheses

The sporadic action taken in those years included also other proposed preventive measures. From the early '50s on it was a commonly held idea that the migration of individual microcythemic family groups should be encouraged away from microcythemic areas to non microcythemic areas, as well as the opposite, that is migration of normal family groups to thalassemic areas[49]. However, epidemiological and social research carried out on immigrants from microcythemic zones to the industrial settlements in northern Italy had, as early as 1965, demonstrated the scanty benefits and even the detrimental effects of such measures. Inside the immigration areas there was a clear-cut trend towards selective marriages, with a prevalence of marriages between persons from the same origin which thus led to an increase in the probability of thalassemic carriers and thus to the birth of children suffering from Cooley's anemia[50]. In this sense, the thinking related to the prevention policies to be implemented in the northern regions began to include variables, factors and activities of a social, economic and town planning nature, such as the problem of the local integration of immi-

grants, their distribution over the territory and therefore the placement of the popular housing and industrial settlements[51].

1.7 The position of the Roman Catholic Church

The Roman Catholic Church took only a marginal interest in the prevention of thalassemia, even though the prophylactic campaign undertaken by Silvestroni and Bianco and the other preventive measures proposed raised a series of moral issues and were based on measures aimed at interfering with individual reproductive choices and were thus in conflict with Roman Catholic doctrine and values.

In general, the Church displayed no organic thinking or reaction to the prevention campaign. In our opinion this is clear evidence of the limited spread of the plan deployed by ANLMI in the country and in Italian society as a whole, that is, of the pragmatic response by the Church in those areas in which this action instead attained a higher level of intensity and penetration among the population, such as Ferrara. However, also in this case it would be necessary to gauge the different degree of religious feeling revealed in the customs of the different Italian regions in the implementation and effectiveness of the prevention programme attempted before the introduction of prenatal diagnosis. We mention *en passant* the limited effectiveness of prevention in the province of Rovigo, where Catholic culture had a strong hold, compared with Ferrara, an area marked by pronounced laicism and a culture often in open dispute with the Church.

A direct interest in the prevention of thalassemia was however shown by the Pope, Pius XII. On 12 September 1958, Pope Pacelli, at a special audience at Castel Gandolfo, received the participants at the VII Congress of the International Hematology Society, and gave a speech in which he presented the Church's position concerning the possible solutions *"to the problem of defective inheritance"* and in particular how to approach *"genetic counselling"*. Pius XII gave explicit answers to a series of questions that he was asked by hematologists and geneticists, four of which referred precisely to the moral dimensions of the Mediterranean anemia prevention campaigns. To the question concerning the moral legitimacy of recommending a pre-mar-

riage medical examination and blood test, the Pope replied that not only was it to be recommended but *"if the danger is truly serious [the visit and examination] could even be imposed in certain provinces and locations"*[52].

Only a thorough assessment of all the facts, such as to reveal the seriousness of the situation, would however legitimate an ethical edict. To the question whether it was *"allowed to recommend that two fiancées should not marry if a blood test revealed the presence of Mediterranean anemia"*[53], the Pope repliced that it was possible to advise against the marriage but not prevent it. Regarding the legitimacy of advising against a married couple with Mediterranean anemia having children, the Pope replied to the scientists that they could be advised against it but not forbidden. And in any case it was necessary to decide what method was to be used, since for the Church only *"perfect continence"*, *"the Ogino-Knaus method"*, or *"the adoptioon of children"* were acceptable. The Pope then reiterated that the discovery that one of the couple was affected by Mediterranean anemia could not be considered a reason for annulment of the marriage, even if the relevant information had been withheld.

In practice, - Pius XII concluded – it will often be difficult to reconcile the two points of view – eugenic and moral. But to guarantee the objectivenenss of the debate it is necessary for each to know the other's point of view and to be familiar with the arguments[54].

1.8 The dysgenic effects of prevention

One of the topics of discussion was that of the dysgenic effects of prevention. It was objected that primary prophylaxis carried out by restricting marriages between carriers would ultimately increase the prevalence of microcythemia [55].

As Alicino and Fabiani wrote:

> *"It is thus possible to implement a primary prophylaxis against Cooley's anemia by restricting marriage between carriers. However, this concept lends itself to criticism from the purely genetic point of view. By so doing, we actually encourage the spread of microcythemia. Indeed, according to Mendel's laws, the mating of two individuals heterozygous for microcythemia will produce a descendance of which one quarter is homozygous. Homozygotism is however incompatible with life and reproduction: the inherited defect will in some cases be eliminated. Mating the heterozygote with a normal individual favours conservation of the defect. Consequently, in order to eradicate microcythemia it would be necessary to encourage marriages between individuals with hereditary defects. However, this concept is repugnant to our conscience as physicians as well as as men, and so it is necessary to approach the campaign against microcythemia by endeavouring to avoid the disease at the state of homozygotism"*[56].

There was concern about the high cost and the difficulty of exerting constant control over the prevalence of carriers and of a continual expansion of prevention activities. Running counter to this concern was the hypothesis of malaria as a selective factor in favour of carriers[57]. In this sense, in 1973, at V Congress on Microcythemia held at Cosenza Ida Bianco claimed:

> *"clearly the recent land reclamation and the consequent disappearance of endemic malaria must already have broken the gene equilibrium among populations, and led to a tendency towards a reduction in the genic frequency of microcythemia; consequently, the introduction of pre-marriage prophylaxis into this system, which is no longer in equilibrium but in downward movement, will not succeed in bringing about fresh increases but will at most cause a halt in the decline of gene frequencies to the present levels"*[58].

Several years later, when reflecting also about the effects of prenatal diagnosis on the human gene pool, Arno Motulski subjected the problem to detailed discussion. He claimed that the question of the dysgenic effects was exaggerated but nevertheless drew attention to the need to disseminate more information about genetics and its medical applications[59].

On the effectiveness of the Silvestroni-Bianco prevention programme

No special or specific studies have been carried out on the effectiveness of prevention implemented in Italy in the mid '50s and the two decades that followed[60]. In any case, although not directly observed, as Bianco herself admitted (personal communication) the short-medium term effects of the prevention action

that it was actually possible to carry out were scarce and in some regions completely non existent.

The small number of works in which it was attempted to evaluate the effects of the ANLMI prevention programme are however subsequent to the introduction of prenatal diagnosis and to some extent the victims of the euphoria that led people to believe that the latter method had solved the thalassemia problem[61]. The data emerging from retrospective investigations of subjects having participated in the assessments were successively adjusted. It was noted for example that the prophylactic model of Silvestroni and Bianco deployed in the ANLMI action had failed to attain its primary objective: the prevention of marriage between microcythemics[62]. However, note was taken of the positive achievements of the ANLMI approach in spreading knowledge of the genetics of microcythemia and thalassemia[63].

Barrai and Vullo showed that the work of screening, counselling, treating and informing carried out by the ANLMI-coordinated centres was later to be vital also for the purpose of introducing and spreading prenatal diagnosis[64]. The population in the areas in which the microcythemia centres had operated longest and in a systematic, root and branch manner, as in the province of Ferrara, subsequently proved ready to understand and utilize prenatal diagnosis as soon as this method was introduced[65].

The overall negative judgment on the studies described above fell somewhat acritically into line with the opinions current at the time, to which priority was given in the international literature on the topic of mass screening for carriers of recessive gene disorders and marriage counselling[66], above all when they are compared with prevention via prenatal diagnosis[67]. The negative judgment passed on mass screening expressed in these studies could however be applied only in part to the case of thalassemia prevention carried out in Italy between the '50s and the '70s. This judgment was based on the outcome of prevention plans of problematic conception or application. Stamatoyannopoulos, for example, based his conclusions on the small number of case histories that were quite peculiar in their sociocultural conditions referring to the pilot programme carried out in 1966 in a

small rural town in Greece[68]. On the other hand, the more detailed one expressed by the US Committee for Study of Inborn Error of Metabolism was based above all on the observation of the screening programme for sickle cell anemia in the US black population, a prevention plan that was serious flawed at the level of educational and information action owing to the difficulty or incapacity to establish adequate contact with the population at risk[69].

A different case, although with the same impossibility of comparing its effectiveness with Silvestroni and Bianco's approach, is the one referring to the action carried out by Mike Kaback in the USA Tay Sachs disease in the Askenazy community, and that against beta-thalassemia on Cyprus and in Sardinia, based on prenatal diagnosis, which were characterized by technical resources, funds, organizational structures and political and social support that were unthinkable at the time Silvestroni and Bianco embarked upon their work[70].

Within this framework it is necessary to mention a study on the cost-benefit ratio of the prevention operation carried out by mass screening. One calculation for the province of Sassari made in 1973 but published only in 1976, that is, at the beginning of the prenatal diagnosis era, postulated a distinctly favourable ratio between saving and expenditure for the screening of all children, even assuming that only 30% of carriers would actually choose pre-marriage prevention and thus avoid a microcythemic partner[71].

1.9 The reasons for the lack of effectiveness

In any case the lack of effectiveness of the programme from the point of view of prevention in the narrow sense is quite evident, although this can easily be explained in historical terms. The reasons for this low prophylactic efficiency were in any case known already at the time. The report presented by Luigi Nuzzolillo, director of the Social Medicine Services of the Italian Ministry of Health on 28 September 1968 at Cagliari during the microcythemia study days organized by ANLMI and by the Istituto Italiano di Medicina Sociale, is eloquent on this subject[72].

The shortcomings are to be attributed to two groups of interacting factors: a) those related to the organization and functioning of the organizations involved in the prevention and b) those specific to the human and social environment in which the prevention was being attempted. As far as the first group of factors was concerned, it should be pointed out in the first instance that, in the field of prevention, the ANLMI microcythemia centres were working in practically complete isolation, with totally inadequate or completely nonexistent funding.

There were not enough Centres to cope with the huge areas over which they had to operate and the extent of the problem, the geographic vastness in which the prevention activity had to be carried out also because of the widespread nature of migration-produced microcythemia. Furthermore, it was impossible to coordinate the cooperation between the network of centres and the other health care bodies in the area of operations (hospitals, local GPs and obstetricians, O.N.M.I. counselling bureaus, municipal hygiene and labour offices, armed services medical corps, mutual and previdential health care institutions). In the absence of specific regulations, these relations were set up only through the initiative and determination of individuals, above all in those areas in which the administrators and health care workers were more sensitive. Lastly, the initiatives associated with mass screening or the health care education and hygiene information campaigns had to cope with obstacles of an ethical, religious, economic or local custom nature, accompanied by culture-related distrust and impediments and lack of support from the local political and health care authorities. Moreover, in this case, it was impossible to develop a common strategy as the socio-cultural contexts in the various parts of Italy in the early '60s in which the various ANLMI personnel were obliged to operate all differed too strongly.

This last point is worth stressing. The difficulties encountered during the work to raise the level of awareness and knowledge of the population were indeed too numerous and different. This was instead of central importance in the plans to prevent genetic diseases, which seem to work only when accompanied by powerful information campaigns[73].

1.10 Long-term effects

A Ministry of Health survey carried out in 1994 shows that the effects of the screening and prophylaxis work, the dissemination of knowledge – although not in a systematic, root and branch manner – may be measured by the different rates of effectiveness achieved starting in 1975, after the introduction of prenatal diagnosis. The reduction of the incidence of thalassemia measured in the periods 1970-1974 and 1988-1992 shows that the regions with the highest rates of efficiency were those, like Emilia Romagna and Lazio (in these two cases in 1992 a zero rate of birth of new sufferers of the disease was attained), where the work of screening and of the dissemination of information about the disease had been carried on longest, together with the dissemination of the idea of pre-marriage prevention[74].

The different degree of sensitivity to prevention is actually measurable inside the same region and thus theoretically under very similar socio-economic conditions, at the same levels of education, prophylactic and educational action from 1975 on. Thus, in Ferrara, with an 8% prevalence of heterozygotes, no homozygotes have been born since 1982; on the other hand, over the same period, new cases of the disease were recorded in the rest of the Emilia Romagna region, where heterozygous prevalence is only as high as 1%[75].

And this is not all. Over the same period of time, with the same level of care and therapy, the regions with a more consolidated prevention experience and a more widely disseminated knowledge of the problem at the population level - again Emilia Romagna and Lazio – boast a greater extension of the average life of the patients, up to five years longer than in the other regions with high thalassemia incidence[76].

Other studies on Mediterranean anemia mortality studies in Italy during the period 1951-1976 recorded by the Istituto Centrale di Statistica (ISTAT), reveal a clear-cut reduction in thalassemia mortality starting from 1965, with an incidence of 0.60 out of 100,000 inhabitants, to 0.26 in 1976, is probably a reflection on the improvement in the diagnostic systems, the treatment and the care of Cooley's anemia patients[77].

The Mediterranean anemia mortality figures for the first year of life presented in the study seem to be particularly significant for the purpose of making a positive assessment of eugenic and preventive action, of the refresher training of healthcare personnel and of the raising of the level of awareness of the population priort to the introduction of prenatal diagnosis. From 1965 to 1976 this mortality rate dropped from 6.26 to 1.02. The decrease, the equivalent of a 7.4 fold reduction, was distinctly higher than that recorded over the same period of time of infantile mortality as a whole, which corresponded to 1.9 times[78].

Some indication of the preventive efficiency of Silvestroni and Bianco's approach also comes from the data referring to the mortality trends of Mediterranean anemia broken down by province. In the provinces of Ferrara and Rome the decline in the mortality rate began in the late '50s, nearly ten years earlier than in the rest of Italy, and progressed very rapidly. Within 5-10 years, constant minimum levels were reached[79].

Conclusions

The work of Silvestroni and Bianco, the mass screening and the premarriage prevention carried out by ANLMI took place in a period in which genetic medical knowledge was at a low level, to say the least, also among physicians; a period in which the average educational level of the Italian population was low, and their cultural, moral and ethical resistance to the use of the already fragmentary notions of prevention obtained by means of genetic counselling much higher than they are today. The diversity of cultures and customs among the various Italian regions was, in a word, very pronounced.

In some ways, the low level of health care education attained, the slowness of the penetration of the messages conveyed by the prevention campaigns, the partial adjustment over time of the level of education and thus of the understanding of the content of the information campaign, made the eugenic appeals and the use of the prevention centres less traumatic and fraught with conflict. This differed from the case of Cyprus where the widespread information, repeated and intensive, at root and branch level, where the combined coordination efforts of the lay and religious organizations and of the health care authorities directed towards a massive appeal to prevention, created a dominant opinion and such strong social pressures that the desired behaviour was actually imposed, and non directive genetic counselling was rendered unlikely[80].

Although unable to modify the behaviour of individuals in the short term, this disseminated knowledge, metabolised by several generations of Italians through the ANLMI prevention plan, rendered the prevention choices more conscious and thus freer when prenatal diagnosis became available. It also made it possible to tackle with a higher degree of maturity the inevitable tension between the quest for individual wellbeing, the realization of personal values and health care policies addressed to the community and to the State's needs: this tension increases when prevention campaigns are run.

For all these reasons, probably, the assessment of the experience of the ANLMI prevention plan must be expressed in a broader time span, considered over a longer period of time. It is thus necessary rather to interpret the prevention plan coordinated by Silvestroni and Bianco as marking a beginning, the beginning of one of the most complex preventive medicine operations ever carried out in Italy and to some extent in the world, preparing the way for the later action.

It will be the subject of a later work to compare, as far as possible, the results obtained at the quantitative and qualitative level (the latter defined as the degree of cultural awareness of the population regarding the problem and effectiveness of counseling) by Silvestroni and Bianco through the screening work and campaigns carried out in Sardinia by Antonio Cao exclusively by means of prenatal diagnosis. We can already advance some conclusions by pointing out that after the initial acritical enthusiasm, the prospective prevention programme using prenatal diagnosis begun in Cagliari in September 1977, after a few years showed some signs of weakness and the indubitably high efficiency of the action did not come up to initial expectations. On the one hand, the approach sometimes actually failed to prevent unidentified couples at risk from giving birth to new cases of the disease; on the other, precisely the behaviour of the couples at

risk, after the introduction of prenatal diagnosis, tended partially to clash with the preventive effects of the method. The phenomenon of *"compensatory reproduction"*, that is, the observed fact that couples with children suffering from the disease gave birth to twice as many other children as carrier couples with healthy children, is indicative of the need in prevention programmes to proceed along the path of screening so as to be able to carry out true prospective prevention[81]. In pratice, precisely by working on the idea that prenatal diagnosis is sufficient to prevent the birth of homozygotes, Cao's group discovered – although it failed to assign to it the importance it deserved – that the birth of a child with the disease seems to have deterrent effect, above all on adequately informed couples. Both in prevention achieved by voluntary limitation of births and in that attained via prenatal diagnosis, information is of fundamental importance. Just as Silvestroni and Bianco always maintained.

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4. Italy is the European country with the greatest increase in the number of genetic tests and with the largest number of molecular diagnosis laboratories. A recent study by the Società Italiana di Genetica Umana (Italian Society for Human Genetics) voiced its concern that this increase has not corresponded to an improvement in the quality of information given to users or in the training of physicians; in other words, "the inadequacy, or more frequently, the total lack of counselling, which must, or rather should, be part and parcel of genetic tests ". See DALLAPICCOLA B., TORRENTE I., MARI A., MINGARELLI R., *Censimento dei test genetici in Italia. Anno 2001*. Società Italiana di Genetica Umana, 2001, Roma.

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19. In a moving autobiography soon to be published (*Storia della Microcitemia in Italia. Pagine di Scienza e di Vita*, Fioriti Editore, Roma, forthcoming), Ida Bianco gives a detailed description of the humiliations endured as the result of a conception of academic power interpreted as the absolute and unflinching domination by directors of the university institutes.
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22. SILVESTRONI E., BIANCO I., *Ricerche sull'eziopatogenesi del morbo di Cooley*, ref. 14. Actually, it was the Greek hematologist, Jean Caminopetros, who first claimed it was possible to prevent thalassemia, or rather, as it was called at that time, erythroblastic anemia, by forbidding procreation by carriers. In 1937 he wrote: "L'examen de la résistance des globules rouges constitue une méthode sure pour trouver parmi les membres des familles des malades, les porteurs apparemment sains de la maladie, et par ce fait permet la prise de mesures de prophylaxie sociale. L'interdiction de la procréation, le seul moyen de prophylaxie indiqué contre la maladie, devient applicable, parce qu'elle peut se limiter à quelques personnes seulement de la famille des malades." CAMINOPETROS J., ref. 8., p. 139.
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27. In an interview published in *Avanti* on 19 November 1949, Silvestroni declared: "How is it possible to prevent a disease for which no cure has yet been discovered? There are two ways, according to us. One, which involves the State taking on the task of continuing research without burdening doctors; the other, which impresses upon the people the importance of a feasible eugenics by avoiding marriages between microcythemics, is thus capable of reducing the cases of the disease to an insignificant number".
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60. One reason for this lies in the fact that there are no available data on the number of those suffering from the disease when the difficult undertaking began. Another reason is probably to be sought in the relative lack of interest shown by the scientific community in the activity of a private association completely separate from the academic world. Furthermore, the progress of the ANLMI programme must have been so atypical due to the degree and the mainly low intensity of its implementation, the involvement and coordination of the institutions and the population in the various provinces in which it was activated in Italy as not to give at the time the impression of a univocal and comprehensive plan, a precise preventive action, which could be characterized as a whole and thus its effectiveness measured. This was due also to the lack of funds and the absence of involvement of the central health institutions. The lack of support from the health care policies must however be judged against the background of the general historical context in which it was situated, in which the preventive approach to genetic diseases had yet to be fully introduced and in which medical circles themselves did not have a clear understanding of the pathology and mechanisms of hereditary transmission. See SANSONE G., ref. 38. Another factor was Silvestroni and Bianco's isolation in the scientific community and consequently their greater difficulty in establishing contact with and in influencing the centres of control, orientation and funding of health care policy and research.

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