

THE ITALIAN CENTRES FOR THE TREATMENT OF TUBERCULOUS MENINGITIS AND MILIARY TUBERCULOSIS

PROF. PIERO FORNARA

Ospedale maggiore della Carita di Novara—Paediatric Centre—Novara, Italy

Amongst the more unpleasant consequences of the war in Italy is the increase in the mortality and morbidity due to tuberculosis: and if the mortality, after the war, has shown a clear and progressive diminution, the morbidity has again increased amongst us and, compared with 56,000 new cases of tuberculosis diagnosed in 1940, we reached 96,000 in 1949 and 85,148 in 1950.

The need to build centres for the treatment of the worst forms of tuberculosis—meningitis and miliary disease—was particularly felt in Italy. Such centres arose as a result of the initiative of individual directors of university clinics or superintendents of hospitals and were later coordinated by the High Commissioner for Hygiene and the Health Department of the Italian Government, who supplied to the centres the necessary streptomycin during the summer of 1947, when its great value in these two previously deadly forms of tubercular infection became known.

STREPTOMYCIN

Italian workers made valuable contributions to this knowledge and, following the observations made by Selman Waksman in 1944 that the streptomycin extracted from *Streptomyces griseus* is active against the microbacterium of tuberculosis, and by Hinshaw and Feldman in the same year, had shown that this antibiotic, besides being active against the Koch bacillus *in vitro*, inhibited its growth in experimental tuberculosis in the guinea-pig and the mouse and had a notable effect in the treatment of human tuberculosis, Cesare Cocchi, Director of the Paediatric Clinic in Florence, in 1946 initiated a systematic study of the different ways of applying streptomycin intramuscularly and intrathecally for the treatment of tuberculous meningitis. These researches proceeded tentatively and cautiously because, although Cocchi persistently maintained the curability of tuberculous meningitis, it is only through the combined efforts of phthisiologists, physicians, paediatricians and neurologists throughout the world that a definitive scheme of treatment has been established. In his first communications, in 1947, Cocchi advised the use of intramuscular streptomycin at the average dose of 50 mg. every 3-4 hours for 15-20 consecutive days, but stated at the same time that such intramuscular injections could—in the event of shortage of the antibiotic—be replaced by intraspinal injections, with intravenous sulphones and higher dosage of vitamin B₂ and vitamin A; for intraspinal treatment he advised daily injections (for not longer than 6-10 days) and low dosages per injection, viz. 10 mg. for infants, 20-25 mg. for children between 2 and 9 years, 30 mg. for children of 10-12 years, and 50 mg. for adolescents and adults; and eventually a

second cycle of similar treatment after an interval of a varying number of days if the meningitis showed signs of recurrence.

With this scheme of treatment, Cocchi and all of us obtained improvement in the general picture of the meningitis, but almost constantly we observed relapses, frequently fatal. Cocchi himself reported in 1948 that of 55 cases thus treated from December 1946 to July 1947 33 were fatal; 22 were apparently cured, but with frequent relapses. The same author later stated that of his previous 57 cases 45 were fatal and 12 alive, of which 11 gave normal cerebrospinal-fluid findings.

At the 1st Italian Congress on Antibiotics held in Milan in October 1948, at which I spoke on the problems of the treatment with chemotherapeutic and antibiotic substances of the various kinds of meningitis,¹ and at the 19th Italian Congress of Paediatrics and Stresa which followed,² in which the subject of tuberculous meningitis was dealt with by Pasquinucci, Cocchi's assistant, a thorough discussion followed on the subject, and on the whole it was agreed to follow the fundamental principle of the simultaneous use of intramuscular and intraspinal streptomycin in small doses but for prolonged periods.

The intramuscular treatment is carried on for an average of 8-9 months and for at least a month after the cerebrospinal-fluid findings return to normal; the dose of streptomycin is 30 mg. per kg. daily in early infancy and 25-20 mg. per kg. in later infancy, with a maximum of 1 g. of streptomycin in adolescence and adult life. Cocchi usually subdivides this dosage into 5 injections during the 24 hours, De Toni into 4 injections, and I into 2 injections according to the experimental observations of Hinshaw, Feldman and Karlson, and Corper and Cohn. Cocchi and De Toni usually leave an interval of 5 days during the intramuscular treatment, but I do not.

Cocchi's intraspinal dosage is an average of 3 mg. per kg. for infants, 2 mg. per kg. between 2 and 6 years, and 1 mg. per kg. in older patients, as a starting treatment, with maximum doses of 15 mg. up to 2 years, 20-30 mg. between 2 and 4 years, and 30-40 mg. from 4 to 10-12 years; afterwards these doses decrease by approximately 1/3rd as maintenance treatment. De Toni uses doses of 20 mg. for infants, 60-70 mg. for adolescents, and 70-80 mg. for adults. I use doses of 25 mg. for infants, 50 mg. from 3 to 4 years, and 100 mg. for adults as a starting dose for the first days, and doses of 1/3rd smaller as maintenance doses for prolonged periods.

In Cocchi's scheme, the rhythm of intraspinal injections is daily for 30-60 days, then alternate days for 20-30 doses and, after an interval of 3-4 days, injections every 2-3 days for 30-40 doses; a second interval of

3-4 days follows and then another cycle starts with injections every 2-3-4 days until the cerebrospinal-fluid becomes normal or almost so—then an interval of 7-10 days and a new control examination of the cerebrospinal fluid; following this, one injection every 7 days for 1-2 months.

In De Toni's and Bulgarelli's scheme the intraspinal injections are given daily for 5-6 months, afterwards on alternate days for 3-4 months; the dose of streptomycin injected intraspinally is progressively reduced after 2-3 months of treatment so that at the end of treatment the single dose corresponds to approximately half the starting one.

In the usual case I use 40-60 injections, a further 40 injections on alternate days, and then injections with 2-3-4 days interval for a further 3-4 months.

In Cocchi's original scheme of 1947-48 the course of streptomycin was completed with doses of intravenous sulphones daily for 20 days, followed by an interval of 6-7 days and repeated 3-4 times; to this the author added vitamin D in high doses weekly and Vitamin A in high doses (50-100U) on alternate days for 4-5 months.

The line to follow when spinal or basilar blocks and hydrocephalus appear is most important. Cocchi and Pasquinucci since 1948 have stressed the importance of surgical operations on the skull in order to bring the drug directly into the loculated zone and also to relieve hydrocephalus; for this purpose, after the cranial trepanning they used to introduce light polythene catheters into the subarachnoid space around the cerebral hemispheres, and similar catheters were introduced into the ventricles with appropriate mechanisms controlling the fluid output; but secondary septic meningitis occurred so frequently ('sovrammesse' meningitis—Cocchi) that Cocchi now uses these methods less frequently, and De Toni and ourselves not at all, apart from exceptional cases.

At the same time we all agree that it is necessary to use both the suboccipital and the lumbar routes for intrathecal injections. Since 1949,³ I have advised the systematic application of pneumo-encephalography, which I have been using normally on admission, on the 40th day of treatment and then, on an average, every 2 months, continuing as long as we have an abnormal picture of the lateral ventricles or the 3rd and 4th ventricles, or incomplete delineation of the subarachnoid space, by the cisternographic method of Belloni. These observations, together with electroencephalography, which is also used regularly in each case, are completed with the calculation of the *spinal quotient*, the *ventricular quotient*, and the *index of diffusion*. This can be estimated according to the technique of Pasquinucci, Milani and Zoli for the dose of streptomycin by the biological method on guinea-pigs, or the method of Bulgarelli and Chiossa with the succinyl-derivatives of thiosemicarbazone. In the latter method parasuccinyl-aminobenzaldehyde thiosemicarbazone is injected into the spinal canal in doses of 10-40 mg. according to age, and after 8 hours 2 c.c. of cisternal fluid and 2 c.c. of lumbar fluid are withdrawn. If after 8 hours the fluid circulation from the lower to

the upper level is free, the drug reaches the same concentration in the cisterna magna as in the lumbar fluid and the index of diffusion (suboccipital concentration divided by lumbar concentration) is one; if a partial block exists, the index will be 0.6-0.4 and if the spinal block is complete, 0.3-0.1.

In such cases it is wise to alternate the streptomycin injections *via* the lumbar route and the suboccipital and give them on alternate days; or, as Cocchi does in serious cases and in the acute stages, to give 2 intrathecal injections per day, one *via* the lumbar route and one *via* the suboccipital. These are the basic directions which are followed in the Italian streptomycin centres; but many problems arise from time to time, of which I can only briefly summarize a few:

Choice of antibiotic: streptomycin or dihydrostreptomycin? Dihydrostreptomycin, especially in the beginning, not only caused frequent and intense irritative meningeal reactions (called by Caronia and Ricci 'streptomycin meningism') but, after intrathecal application, a certain number of cases of impairment of hearing, which in most instances resulted in permanent and irreversible deafness. This is due to selective toxicity for the acoustic division of the VIII nerve, which when started is progressive; whilst the toxicity of streptomycin for the vestibular part of the VIII nerve, which shows itself by vertigo, can be avoided by stopping the drug. We have therefore, since 1950, abandoned the intrathecal use of dihydrostreptomycin, which we now use only intramuscularly, whilst intrathecally we use only streptomycin.

At the 'Symposium on Antibiotics in Paediatric Medicine', organized by the *Centre International de l'Enfance* at the Chateau de Longchamp in September 1952, Cocchi reported that *viomycin* is a valuable antibiotic with a streptomycin-like action, by which cases can be saved in which the organism is resistant to streptomycin up to 1000 gamma.

SULPHONES, PAS, ISONIAZID

I have already mentioned the advantages of associated treatment with *sulphone*, as reported by Cocchi, Frontali and myself after 1941-42. I was one of the first to use the 4-4' diaminodiphenyl-sulphone 1-1' dextrose sulphinate of sodium intravenously in pulmonary and infantile miliary disease; we have still not completely given up such drugs, especially in view of the experimental researches of Smith and McKlosky, who in 1945 and 1946 showed a synergic action of these preparations with streptomycin in experimental tuberculosis in the guinea-pig. This was confirmed in the same year by Feldman and Hinshaw and by Coloman, Kolmer, Rule and Pone and in 1948 by Kolmer and Rule. With the sulphones we obtained recovery in localized streptomycin-resistant tuberculous foci (which appeared during and after the streptomycin treatment of miliary tuberculosis) in bone, joint, testis, lymph-gland and subcutaneous tissue (Schiavani and Paronzi⁴). But the appearance of the new antitubercular chemotherapeutic remedies has opened new horizons. We have used PAS mostly by oral administration.

Although we followed some cases treated according to the directions of Löffler and Moschlin by intravenous drip perfusion of 5% sodium PAS, we have abandoned this method, which is badly tolerated by our patients and which frequently causes injury to veins. We have also abandoned the intrathecal administration of PAS, which was much used in 1949 by De Toni in the dosage of 40-80 c.g. daily, because in these doses it provokes a recognizable worsening of the cerebrospinal picture, whilst in the usual dose an adequate concentration for effective therapy is not obtained, as demonstrated by Bulgarelli. Thiosemicarbazone by mouth and—in De Toni's clinic—by intrathecal injections (10-20 mg. of the succinyl salt in early infancy, 20-30 mg. in later infancy, 30-40 mg. at adult age), always associated with streptomycin, gave some encouraging results but it has quickly been surpassed by the *hydrazide of the isonicotinic acid* (INH) or isoniazid.

The works of De Toni and Ricci have made known the contribution of Italian workers in this field. In all Italian centres since February 1952, INH by mouth or intrathecal injection is associated with streptomycin with really encouraging results, shown by a more rapid return of the cerebrospinal fluid to normal and a reduced mortality during the danger period (especially for patients admitted late), viz. the first 8-10 days of treatment. But only subsequent observation will show the real effects of this therapeutic combination, which we consider far superior to all the others mentioned above, and will indicate in which cases we can use only INH intrathecally in association with oral INH and intramuscular streptomycin—treatment which up to now, in Italy, has been performed in very few cases, by Tacconi, Caronia and De Toni. For my part, I prefer to continue associated treatment on the following lines advised by Bulgarelli:

	<i>Intra- muscular Strept daily</i>	<i>Oral INH daily</i>	<i>Intrathecal Strept. daily</i>	<i>Intrathecal INH daily</i>
Infants	25 mg. per kg.	10 mg. per kg.	2 mg. per kg.	1.5 mg. per kg.
Children	20-15 mg. per kg.	8 mg. per kg.	1.5 mg. per kg.	1 mg. per kg.
Adolescents and adults	15-10 mg. per kg.*	4-6 mg. per kg.	60-70 mg.	50-55 mg.

* For adults a daily average of 1g.

The dose of oral INH is subdivided into 5 equal portions—one after each of the 4 meals and one in the middle of the night. We use the lumbar injection rather than the suboccipital, both for streptomycin and INH; half a dose is injected.

With this scheme of treatment, which we use nowadays in all Italian centres—with slight variations—*, the results obtained in tuberculous meningitis are really remarkable.

* Professor Salvioi⁵ of Bologna, for instance, prefers the use of alternate cycles of streptomycin and INH, starting with streptomycin intramuscularly and intravenously, and adding in the 2nd month INH by mouth and alternating, after the first 3-4 months, streptomycin and INH intrathecally, generally in cycles of 20 days.

RESULTS OF TREATMENT

At the Congress of the Tuscan Section of the Italian Paediatric Society held in June 1952 at Arezzo, the problem of the treatment of tuberculous meningitis was dealt with and Drs. Masi and Moggi⁶ presented the statistical results of 635 cases treated in the Paediatric Clinic at Florence under Professor Cocchi. The number of deaths was 245, with a percentage mortality of 38.5% and 61.5% of recoveries, as follows:

<i>Year</i>	<i>No. of Cases</i>	<i>% Recovery</i>	<i>% Mortality</i>
1947	123	34.1	65.9
1948	111	68.5	31.5
1949	125	68.8	31.2
1950	130	64.7	35.3
1951	146	69.9	30.1

At the same Congress, Nicolai, Orlandelli and Degli Esposti⁷ presented the results obtained in the Paediatric Clinic Centre of Bologna in 211 cases of all ages admitted between 1947 and 1951. Of these 119 were discharged recovered (56.4%), 89 died (42.2%), and 3 (1.4%) were still under treatment. Eliminating the patients who died during the first 5 days of admission and those admitted in desperate condition from other institutes, 166 patients remain, of whom 119 (71.7%) were discharged recovered, 44 (26.5%) died, and 3 (1.8%) were still under treatment.

Professor De Toni through his co-worker Bulgarelli⁸ in 1952 presented the results obtained in 226 cases treated in the Paediatric Clinic at Genoa; the percentage of survivors was 61.4% (12 had neuropsychiatric defects more or less serious and 8 had sensorial lesions) and the mortality rate 38.6%. But they divided their cases into 2 groups: the first of 22 cases treated with the inadequate method of the 1st period, of which 20 died and 2 recovered (one, after 2 relapses, left with permanent deafness); the second of 204 cases, from October 1947 to July 1952, treated with an adequate method, of which 32.8% died and 67.2% survived.

The Paediatric Clinic at Milan, under Professor Masso and Drs. Quarti and Verga,⁸ in 1952 presented the results obtained in 123 infantile cases; of these 84 resulted in death and 39 survived. These authors distinguish 2 periods: in the first, in which the patients were treated with discontinuous cycles of treatment as originally advised by Cocchi, of 33 cases, 32 resulted in death; in the second, of 90 cases treated by the adequate method, 52 died and 38 recovered. Subsequently, a year later, from the same institution, Brusa and Carletti¹⁰ referred to a further 19 cases in which INH was added to the streptomycin treatment; in these there were only 2 deaths, 10 recoveries, 5 cases improved after 3-7 months of treatment, and 2 cases unchanged.

In the Novara Centre, from 1947 to the end of 1951 (as I reported at the Congress of French-speaking Paediatricians held in May 1955 at Brussels), we have cured 30 cases of *miliary tuberculosis* with a single death of a child of 6 months. In 110 cases of tuberculous meningitis (72 children and 38 adolescents) there were 53 deaths (48.17%) and 57 survivals (51.83%). Of these 110 cases 72 were children and 38 adolescents and

adults. In the 72 infantile cases we had 31 deaths (43.1%) and 41 survivals (56.9%). Of these 25 were patients in the first 2 years of life, of whom 15 died and 10 survived (40%), but 6 with sensorial or cerebropathic sequelae: in 10 children in the first year of life, 7 died and 3 were alive (30%), 2 after 2 years and 1 after 6 months of treatment, but all 3 were cerebropathics.

Of the 47 cases between 2 and 12 years of age 16 died and 31 survived (65.9%). Of the survivors 17 completed treatment more than 2 years ago, 6 1-2 years ago, and 8 6-12 months ago; 28 are normal and regularly attending school, 1 is deaf, 1 is hemiplegic and 1 is seriously cerebropathic.

Of 38 adolescent and adult cases, 22 died and 16 survived (42.1%), of which 10 are normal and 6 have sequelae, viz. 1 with right hemiplegia and aphasia which is slowly improving, 1 with blindness from chiasmatic arachnoiditis, 1 with slight cerebropathy from porencephaly shown by pneumo-encephalography and electro-encephalography, 2 with complete deafness, and 1 with persistent vertigo.

In our 110 cases meningitis was associated with miliary disease in 26, and in these the survival rate is 34.6% (17 dead) subdivided into 6 deaths out of the 8 cases in the first 2 years of life, 3 deaths out of the 7 cases aged 2-12 years, and 8 deaths out of the 11 adult cases.

We noted only 4 relapses—3 in adults and 1 in a girl of 9 years. Two of these resulted in death (1 adult 8 days after the start of the relapse, and the girl of 9 after 3½ months) and 2 are alive, one completely normal and one with deafness.

I shall not waste time on the details of the technique followed in our centre, which are not different from others, nor on the results obtained with cisternography, encephalography (which we always perform on admission, on the 40th day, on the 90th day, and at the end of the treatment, unless it is also necessary for anomalies), electro-encephalography which we perform regularly and find most useful for the early diagnosis of tuberculous meningitis, as shown in our centre by Schiavini, Martelli and Pisani,¹¹ and the mental tests and re-education method which the doctors and instructors of our Medical Paediatric Centre carry out on all patients.

I shall only point out in conclusion that since April 1952, a period during which to streptomycin we added isoniazid intrathecally, orally and intramuscularly, we treated 22 cases of tuberculous meningitis with 6 deaths and 16 survivals (72.7%).

VALUE OF SPECIAL CENTRES FOR TUBERCULOUS MENINGITIS

These are the results, published up to the present, obtained in the more important Italian centres for the treatment of tuberculous meningitis and miliary tuberculosis. These diseases are treated also in phthisiological, neurological and paediatric clinics, and in hospital wards for general medicine, paediatrics, neurology and phthisiology. We stress the advantage of our centres, in which patients are brought together, in tranquil surroundings, separated from the busy general hospital ward; they acquire an intelligent idea of their condition, thus avoiding imprudences and the wish for premature discharge so likely to lead to eventual relapses; and they become more disciplined and follow with interest their treatment; all of which makes useful propaganda for the necessary improvement of the hygienic conscience of the public and the general practitioner and enable us to make an instructive study by comparison of the various patients.

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