Chapter

Specific Bacterial Immunotherapy in Treating Chronic Osteomyelitis

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Abstract

The immunological experience is treating osteomyelitis chronic forms at the Istituto Putti in Cortina starts in 1963 by introducing immunotherapy, applied by the progressive administration in growing doses of a staphylococci pool, that had been collected from some patients with bone infections by the same germ and then inactivated in an aqueous solution suspension. This therapy is coadjutant of antibiotics, surgical and hyperbaric therapy and not substitutive of these. This study ascertained indeed a reduction of the phagocytic activity as a whole, and especially the opsonisation activity It has been thought therefore that in immunotherapy more factors are involved; their principal property is to reduce the allergising effect and therefore to desensitise vs. the germ proteins and to increase the phagocytic activity. This condition, neither whose entity nor its lasting may be defined, does not appear to be unlimited. Obviously this desensitisation can be obtained also by the right antibiotic choice that, as already said mainly in acute forms, may develop their bactericidal properties and sterilise the focus. In the chronic forms it is possible to provoke this mechanism by carrying out a surgical toilette that restores the vascularization and stimulation conditions needed for a correct antibiotic action. Checks upon immuno-stimulation treatment termination clearly showed corresponding results between laboratory deficit corrected and clinical conditions bettering. The casuistry is based on 50 patients with hematogenic osteomyelitis, all under the age of 16, age at which the growth plate is still active, and 117 post-traumatic septic non-union, where this term was adopted for cases that showed a lack of non-solidification at 6 months after trauma. We have expressly made a distinction between hematogenic and post-traumatic forms, since the relationships between bacterial counts vs. host response do differ.

Keywords: immunotherapy, osteomyelitis, non union, psudoarthritis, vaccine

1. Introduction

The Codivilla-Putti Institutes has been a strong will of Prof. Vittorio Putti, especially for treating chronic infections; it started its activity in 1930 and had been located in a famous winter sport resort, as it was the case for almost all sanatoriums build in those years to treat septical diseases with “good air” and sun (UV rays), that were then the only therapeutic treatments available to the medical science.

We are now facing in modern therapeutic treatment of chronic osteomyelitis some growing obstacles in using antibiotics, as we find often resistance, principally concerning staphylococcus, which are the major responsible concerning bone infections. The clinician therefore has to dispose not only of surgical knowledge, but

1884	Leucotoxin	Van de Velde
1901	Anti-Staphylolysin	Neisser, Wechsberg
1925	Anti-Staphylococcus-Sera	Baker, Shands
1936	Anatoxin-Therapy	Ramon
1938	Exp. Allergic Osteomyelitis	Derizanov
1939	Autovaccination	Schoolfield
1953	Sensitisation and Osteomyelitis	Grundmann
1968	Opsonin Activity	Williams
1971	Prophylactic Immunisation	Weber
1972	Anti-Staphylolysin-titre	Queneau, Bertoye
1973	Anti-Nuclear Factors	Hierholzer
1973	Wound-Specific Antibodies	Ring, Seifert
1976	The Staphylococci	Cohen

Table 1.
Historical list of work on immunotherapy in osteomyelitis.

he has to be also acquainted with all most recent advances in the field of antibiotic therapies. Moreover, he has to be acquainted with the immunoresponses offered by the body in special circumstances. As a matter of fact the lack of success in such cases induced many scientists to re-evaluate the immunological system by considering its possible deficit.

An immunodeficiency may also show itself in the clinical picture as an increased tendency to chronicize, a reduced phlogistic reaction and an increased frequency of multifocal processes [1].

The use of the so-called "immunotherapy" started at the beginning of the 20th century and is still a field of investigation (**Table 1**) [1–3].

2. Definition of chronic

Chronic osteomyelitis as all forms of bone inflammatory lesions, sustained by pyogenic germs, who selectively involved from the start bone marrow and intratrabecular spaces and therefore are not healing anyhow, as they brought about a suppuration process, but engender foci in the internal part of bones, who maintain themselves active or more or less weakened [4].

Chronicizing may be:

1. The consequence of initially acute osteomyelitis (hematogenous, post-traumatic, iatrogenous), that passes gradually into the chronic phase (reduced reaction by the patient owing to the symbiosis guest-host through a progressive reduction in acuteness;

2. Induced by rapid evolution from the acute form into the chronical form (it happens sometimes as an effect of the antibiotic's administration);

3. A chronic form "ab initio" without any initial acuteness or a generalisation of the process.

3. Characteristics of the Staphylococcus

Staphylococci are the most important micro-organisms in the Microccaceae family: they have been denominated by Ogston, as in microscopic slides their elements dispose themselves in clusters. They have a spherical form and are asporigenic and normally non-capsulated, gram-positive, aerobic and optionally anaerobic. It is easy to grow them on common culture media; optimal temperature is 37°C. They are among the most resistant germs to heating and disinfectants. With reference to the colony colours they are classed in aureus, albus, citreus and aurantiacus.

More recently they have been divided in aureus and epidermidis, as the former produces coagulasis and is able to ferment mannitol in anaerobic conditions. By phagic typisation 4 groups have been ascertained, whose major representatives in chronic bone pathologies are type 5 and type 8 [5].

Staphylococcus produces many extracellular substances that show almost all antigenic properties. The most interesting is coagulase that fosters a fibrin barrier around the staphylococcus that might oppose the action of phagocytes and opsonins [6].

It can also induce in the host a form of "allergy" that further reduces his defences [2–4]. It seems moreover that the bacterial resistance develops proportionally to its capacity to produce para-aminobenzoic acid, necessary to its metabolism, or producing its precursor folic acid. It is supposed that para-aminobenzensulfonamide displaces para-aminobenzoic acid from the bacterial body, i.e. owing to the antibiotic action the bacterial bodies may lose their strong cellular wall transforming themselves in sferoblasts with a weakened antigenic function or without any antigenic function, who are responsible for some infections with a chronic evolution.

4. Some immunological information

Before discussing this point some general knowledge concerning immunology is required. We do not refer to immunology as a whole (as the matter covers very wide aspects), but only to infection resistance.

The host defence to bacterial infections happens through two classical mechanisms, i.e.:

a. natural **non-specific** immunoresistance (humoral and cellular factors mainly related to phagocyte reactions) [7].

b. acquired **specific** immunity (specific antibodies production and Ag-Ab reaction).

We shall mainly focus on the **former** mechanism, as its deficiency is considered as the major cause of chronic septical forms; it is the fastest and it arises through humoral and cellular factors (in order to summarise we shall treat the matter in very schematic terms).

Humoral factors may be divided principally in three species.

- **The complement (C)** (a biological entity showing itself through the concomitant action of several constituents, some of which are thermolabile) comprehends a group of known substances, that are present in fresh serum and able to interact, in clearly defined sequence, with all possible kind of Ag-Ab combination.

The **C** does not show any antibody activity and there is no evidence that its blood levels increase as a consequence of immunisation processes. It has been however evidenced (Lopow, Beker) that at least some C components have enzymatic activity against the bacterial cellular walls, that therefore are opsonised and become weaker to the phagocyte action.

- **The bacteriocidines** are produced mainly by leukocytes and in their majority thermostable. They are principally active against Gram+.

- **Lysozime** is an enzyme discovered by Fleming in 1922 and it has been confirmed in many body fluids and tissues and in the internal parts of neutrophile granulocytes. It is constituted by a protein that should be able to depolymerise some polysaccharides contained in many bacterial species. Moreover it should stimulate: phagocytosis, bacterial suspensions agglutinations (Ferrina), phlogistic processes inhibition (Matracia).

- **Opsonins** [8] act on micro-organisms by making them easier to be phagocitated. Generally neutrophyles are able to phagocytate aggressive micro-organisms only after a specific Opsonin has covered (opsonisation) the micro-organisms. Their action fosters also the elimination of micro-organisms from blood by means of the reticuloendothelial system.
  As far as the non-specific cellular immunity is concerned, it is mainly related to phagocytosis, i.e. the capacity showed by some cells to take up corpuscular matter of different nature and origin; the cells are part of the so-called reticulohistocytic system (R.H.S).
  Metchnikoff considers that cells with the capability to phagocitate are essentially:

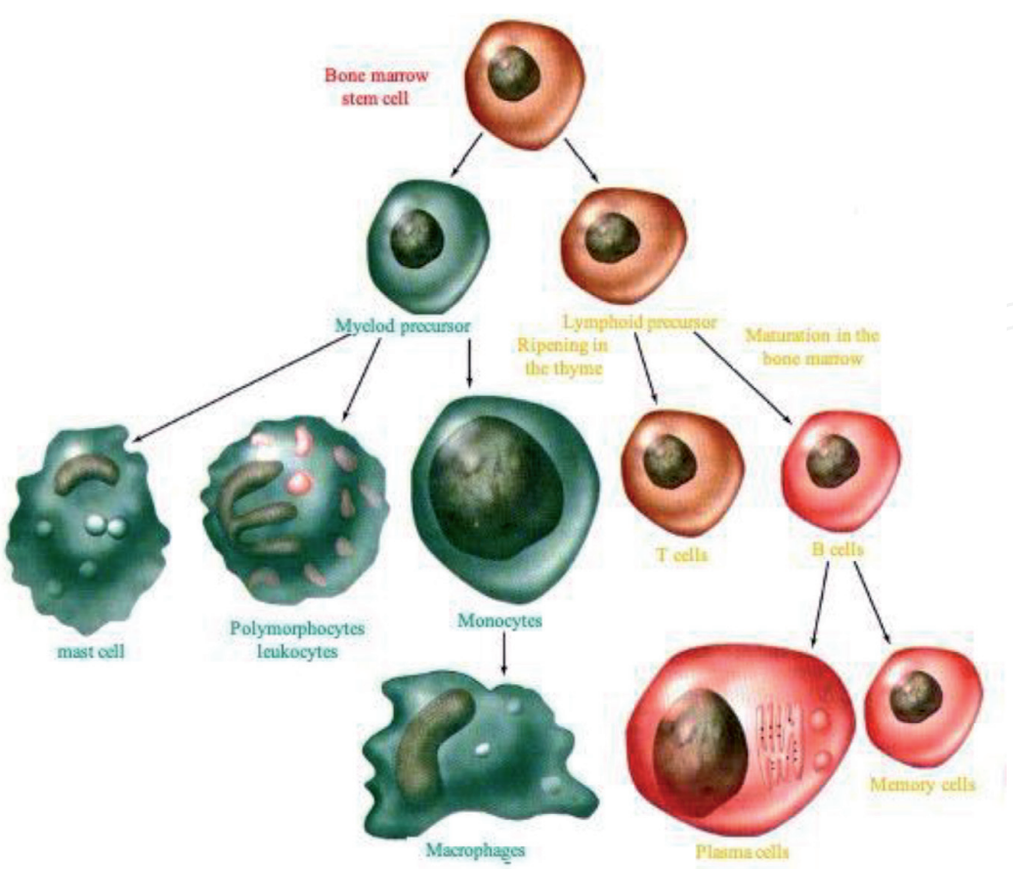


Figure 1.
Genesis of the immunolgical cells.

- **The macrophages** [9], classed in fixed and mobile, are the reticular cells in the spleen and in the lymphonodules and the Küpfer cells in the liver, the fixed osteoclasts and the histiocytes, which pass from the tissues into circulation (mobile) (see macrophages origin in **Figure 1**).

- **Microphages** are represented by the blood polymorphonucleic leukocytes, essentially by neutrophyles.

With reference to **specific activity** brought about by the production of most often Permanent Ab, it does not seem that staphylococci infections have such characteristics. A study by Ring shows indeed that only 26 cases on 112 have an increased antistaphylolysinic level.

It has been observed that the staphylococci pathogenicity appears on one side as an increased resistance to the defensive powers of the patient and on the other side as a capacity to establish a kind of allergy that further reduces body defences. The production of toxins might have only a minor role in the pathogenicity (Zironi) [2]; as a matter of fact there is no parallelism between germ virulence and the seriousness of the illness. It has been observed that the two factors provoking allergy (hypersensitivity against the germ or its products and increased reaction capacity) do not always evolve in parallel but may show different evolution.

Sensitivity to the micro-organism and its antigens, without variation of the host reactivity may beobserved and such a mechanism induces a very dangerous condition, called by immunologists "specific hyperreceptivity". Such a mechanism could account as an explication how this state may grow by inappropriate use of antibiotics.

Insufficient immunitary system predisposition to the entrance of the germ inadequate microbial sterilisation (inappropriate antibiotics – dosage – choice) bacterial persistence, even only latent stimulation repeated in the time hyper-receptivity (**Figure 2**).

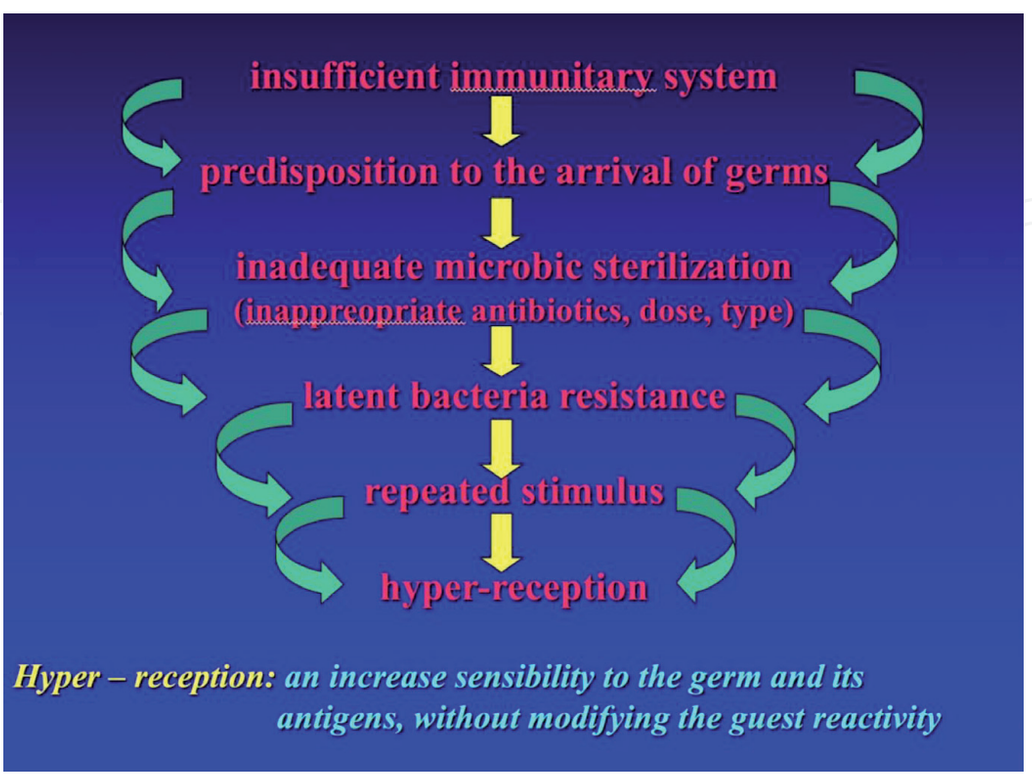


Figure 2.
The cascade for arrive to the hyper-receptivity.

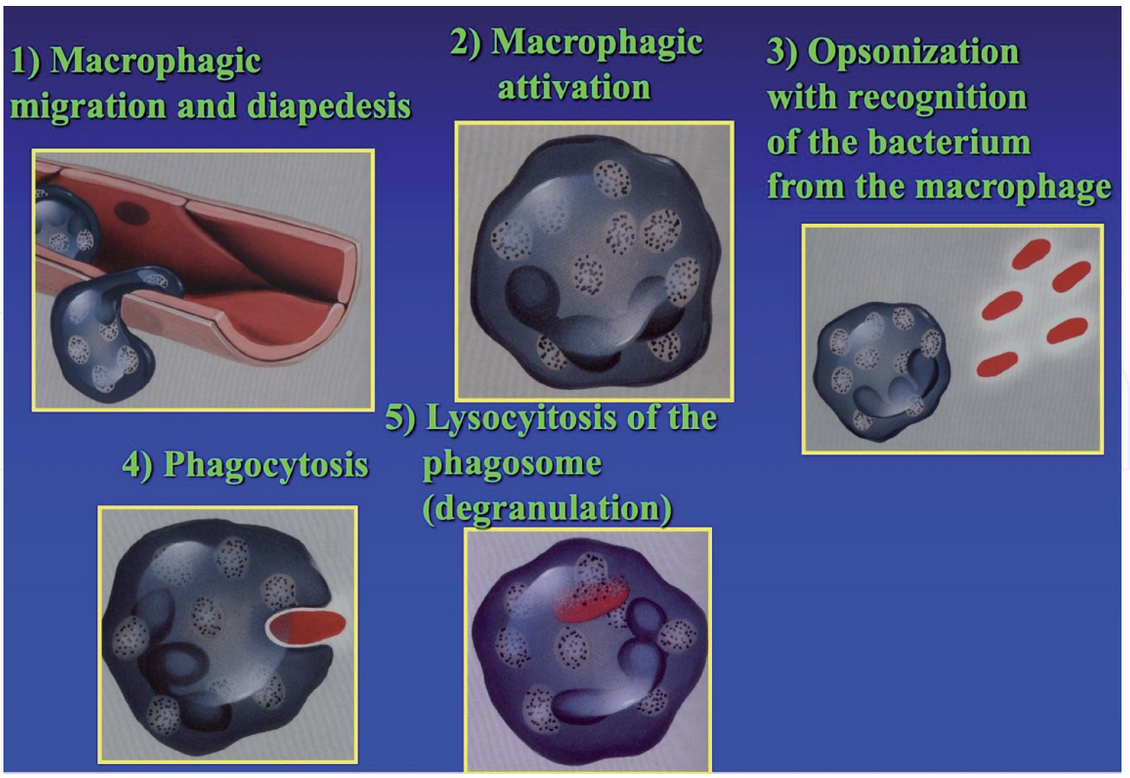


Figure 3.
Summary opsonization-phagocytosis of the "macrophages".

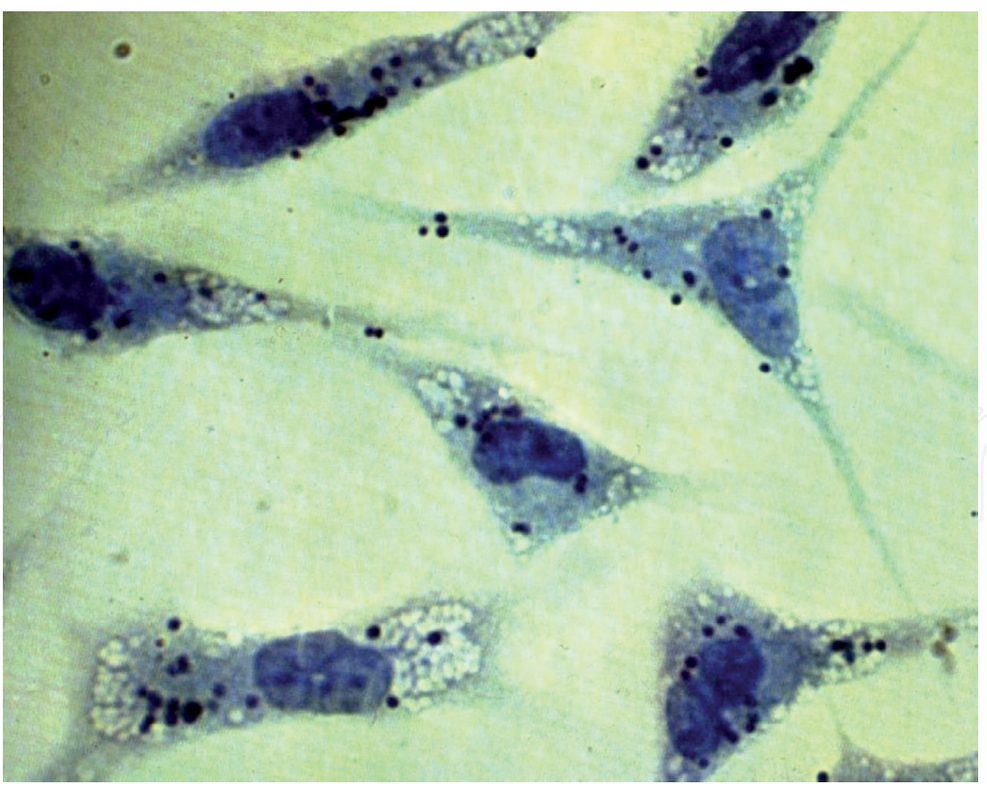


Figure 4.
Phagocytosis of the staphylococci from "macrophagis".

We have many actions in the aspecific immunological activity but one of the most important action is the activity of the Macrofages to fight staphylococcus and the action is the opsonization (**Figures 3** and **4**) [10].

5. Specific bacterial immunotherapy (S.B.I.T)

The immunological experience is treating osteomyelitis chronic forms at the Istituto Putti in Cortina starts in 1963 [11–13] by introducing immunotherapy, applied by the progressive administration in growing doses of a staphylococci pool, that had been collected from some patients with bone infections by the same germ and then inactivated in an aqueous solution suspension. At that time also autologous immunostimulation was carried out, i.e. a therapy prepared by isolating the responsible bacterial agent directly in the patient's exudate.

Also experiences with a *Pseudomonas aeruginosa* autologous immunotherapy have been carried out, but we abandoned it, as we saw that this bacterium wasn't the principal pathogenic agent, which provoked bone infections.

Nowadays only the isolation of Staphylococcus strains 5 and 8 is carried out, as only these strains are responsible for 98% of the bone infections. This aspect has been showed by a joint research with Institut Pasteur in Paris. We are working now only with these kinds of staphylococci and were able to better the general characteristics.

As already mentioned, administration is performed at growing dosages according to patterns adopted since long avoiding that too approached stimulation may exhaust the capacity responses as a consequence of a too prolonged stress.

The preparation is inoculated subcutaneously, and the therapy lasts about three months. After at least one month stop treatment may be repeated (**Figure 5**).

With reference to the above said we tried, together with "Immuno" in Vienna, to find out whether among chronic osteomyelitis patients there was some immunological deficit. We did not consider this evaluation had to be made on acute forms, as they show different characteristics while the host reactivity is still within the norm.

We evaluated therefore about 150 cases, with different ages and causes (hematogenic, post-traumatical and iatrogenous) and referred to following parameters:

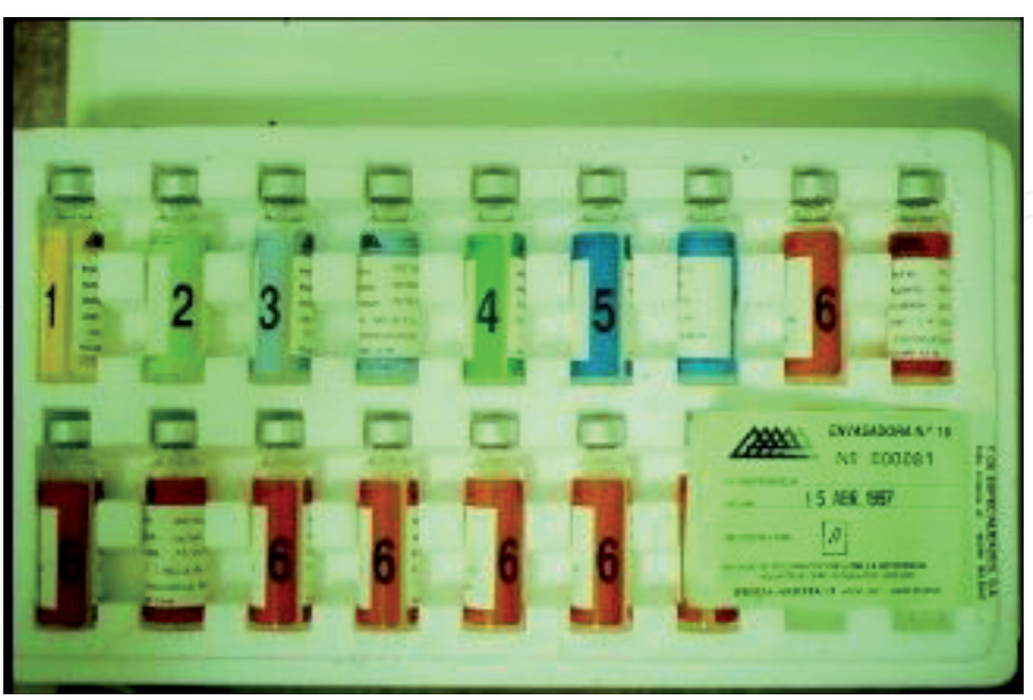


Figure 5.
Increasing subcutaneous injections of doses, according to a widely scheme (since 1963) of an inactivated staphylococci pool of type 5 and 8.

- Antibody titre
- Complement (fraction 3)
- Phagocytic activity
- Opsonisation capacity
- Bactericidal reaction
- Bacterial agglutinins
- "T" lymphocyte count

This study ascertained indeed a reduction of the phagocytic activity as a whole, and especially the opsonisation activity.

• Opsonisation capacity deficit	62%
• Antibody activity deficit	34%
• "T" lymphocytes decrease	4%

It has been thought therefore that in immunotherapy more factors are involved; their principal property is to reduce the allergising effect and therefore to desensitise vs. the germ proteins and to increase the phagocytic activity.

This condition, neither whose entity nor its lasting may be defined, does not appear to be unlimited.

Obviously, this desensitisation can be obtained also by the right antibiotic choice that, as already said mainly in acute forms, may develop their bactericidal properties and sterilise the focus.

In the chronic forms it is possible to provoke this mechanism by carrying out a surgical toilette that restores the vascularization and stimulation conditions needed for a correct antibiotic action.

Checks upon immuno-stimulation treatment termination clearly showed corresponding results between laboratory deficit clinical conditions bettering laboratory bettering.

6. Laboratory

Parameters normalisation	35%
Minor increases	34%
No variations	25%

7. Clinical

Good	50%
Reduced	28%
Bad	22%

Patients	Phagocytosis*		LIF**
	PMN	Monocyte	
19 Non-responders	60.6 ± 19.1^	52.6 ± 11.7^	30.5 ± 9.3^
3 responders	87.0 ± 3.2	87.6 ± 5.3	54.3 ± 12.4
40 (controllo)	86.9 ± 4.45	87.1 ± 4.2	48.3 ± 6.9

Table 2.
*The phagocytosis: Is valued as percentage of cells that englobe the specific Bacterias. *Description of the study.*

Patients	Phagocytosis*					
	PMN		Monocyte		LIF**	
	Before	After	Before	After	Before	After
19 Non-responders	65.7 ± 19.1	72.4 ± 12.4	30.6 ± 8.9	70.4 ± 8.9	25.8 ± 8.1	30.6 ± 8.9
3 Responders	87.0 ± 3.1	85.3 ± 6.1	87.3 ± 5.3	85.2 ± 4.7	54.3 ± 12.4	60.3 ± 11.2

Table 3.
*The valuation was repeated after the sominstration of S.B.I.T and the results were significant, as you can see on the table, between the beginning and the end of treatment. *The results.*

8. Another immunological evaluation in the use of S.B.I.T

Dr. G. Mastrorillo Work Bari's School (**Tables 2** and **3**) [14].

- LIF: inhibition of the leucocytic migration in percentage
- ^: Relevant statistic values

This work considers the immunological effects of S.B.I.T.

In 22 patients with chronic osteomyelitis with a follow up of 20 months the Authors valued:

- The phagocytosis of polymorphonucleate and monocytes versus some bacteria that were identified in at least two samples on three.
- The dosage of LIF (inhibition of the leukocytes migration in percentage).

The patients were divided in two categories and compared with 40 volunteers.

The responders (3) who had almost normal parameters.

The non responders (19) who were immuno-compromised.

From this valuation, we understand that in chronic osteomyelitis there is unimportant immunological compromise.

9. Clinical effect with the S.B.I.T. treatment

We clinically evaluated the results obtained by using immunotherapy and we observed different facts recorded on about 7,500 cases treated since 1963 till 2016.

- Spontaneous elimination of sequestra,
- Demarcation or resorption,
- Output colour change,
- Trend to fistula healing,
- Reduction of congestive facts,
- Less frequent reacutisation,
- Reduced articular rigidity,
- Stimulation of bone reparation,
- Reduction of soft tissues calcification.

Some of these effects (sequestrum resorption or demarcation, reduced articular rigidity, increased repairing capacity) may be explained only by hypothesising a stimulating action on the reticuloendothelial cells that are able to differentiate themselves in different tissues [9].

We studied also possible differences between children, known for their evolutive receptive potentiality, and adults leaving the kind pf suffered infection out of consideration.

10. Result

The results on 100 adults and 100 children have been compared by referring to following parameters:

100 adults	♂:90	♀:10
100 children	♂:80	♀:20

11. Form

	Children	**Adults**
Hematogen	66	19
Post-traumatic	30	40
Iatrogenic	4	4

12. Stabilisation

Time	**Children**	**Adults**
1–6 months	36	15
6–12 months	30	26

Time	Children	Adults
> 1 year	31	37
Non attained	3	22

13. Healing

	Children	Adults
Obtained	90	73
Not obtained	10	27

Whereas healed are the patients who do not show any restart at least after 1 year from stabilisation, stabilised are those, who do not show any clinical, radiographic or bio-humoral sign of inflammation. As however chronic infections may show restarts, even after more than 1 year from stabilisation, the word "healing" has been adopted by us only to quantitize the research results and we have to evidence that it is more a language term than a truth, as it is well known to our colleagues who deal with these pathologies [15].

Another study has been made by us in order to define the Immunotherapy potentiality concerning both hematogenic and post-traumatic forms.

14. The casuistry

The casuistic is based on 50 patients with hematogenous osteomyelitis, all less than 16 years old, age at which the growth cartilage knit, and 117 post-traumatic infective pseudoarthroses, where this term has been adopted for cases who showed a lack of non-solidification at 6 months after trauma.

We expressly made a distinction between hematogenic and post-traumatic forms, as the relations bacterial count vs. host response do differ. Let us first consider the hematogenic form with all patients infected by coagulase positive *Staphylococcus aureus*.

Males were infected most often (78%); the prevailing age were between 10 and 16 years old.

Lower limbs were involved three times more than arms, while there was no difference between proximal diaphyseal and distal diaphyseal localisation. In 30% of cases the lesion involved the whole bone segment (panostytis), while the remaining 70% showed a localisation at the diaphysis half (42%) or at the diaphysis (28%).

In males diffused forms are more frequent, while in females the same applies to localised forms.

Patients have been checked with a following-up lasting from 1 till 10 years after healing (where healing has already been defined).

With the depicted criteria we obtained 86% of healing (88.5% when considering localisation), of which 74% already from the first treatment, and only 12% after possible recurrences. Of these relapses only the half involved a bone, while in the other cases they were the periodical opening of abscesses and fistulae, without any bone involvement. 50% of the patients healed by adopting only immunotherapy; in 38% immunotherapy complemented a surgical intervention, and remaining 11.5% did not heal.

As far as time elapsed from treatment beginning till healing is concerned, we observed 46% healing within 6 months, 30% between 6 months and 1 year, and 24% between 1 and 5 years with an average duration of 9.6 months.

With reference to radiographic belated evidences 20 patients showed the damaged bone segments fully leaked, whereas in later checks 33 patients showed a bone rearrangement (residual osteosclerosis without periostal reaction or osteolytic area).

In 7 cases there were still traces of active infection.

In 3 cases the later checks showed growth disturbs higher than 2.5 cm (in 2 cases there had been a contraction owing to growth cartilage lesions and in 1 case there was a lengthening). In 5 further cases, that initially showed limb lengthening, such dysmetrias disappeared afterwards.

In 5 cases the later checks showed a limitation in movements concerning the articulation near the focus; in 4 cases such limitation was already ascertained at the first control and imputable to the treatment with plaster. The joint limitation has never been imputable to joint involvement by the inflammation process (osteoarthritis).

In 3 cases there were deformities of the bone segments (coxa varia, femur procurvation).

We discuss now the data concerning the 147 cases of post-traumatic infective pseudoarthrosis.

The higher percentage of 75.5% concerns pseudoarthrosis subsequent to osteosynthesis.

In this percentage there were 118 males (83.3%) and 29 female patients (19.7%). Mean age has been 32 years and 5 months; the youngest patient was 18 years old, whereas the oldest was 68 years old. The most frequently interested bone has been the shinbone with 99 cases and secondarily the femur with 35 cases.

25 cases were a two bone fractures and there were exactly 19 tibia and fibula and 6 radius and ulna fractures.

We had 7 cases concerning radius and ulna, 3 cases collar bone, 1 case humerus and 1 case hand. The time elapsed between trauma and infection beginning has been in the male 30 days with 7 days in the shortest case and 5 months in the most belated.

The tome between infection initial and our therapy start has been on an average 8 months, varying from minimal 6 months till maximal 4 years. Our treatment allowed almost always precocious weight bearing; as a matter of fact only the most serious cases had to wait 6 months before being in condition to use the sick limb.

At first hospitalisation already 89.1% of the patients showed a fistula.

In all cases therapy has been immunotherapy+antibioticotherapy. In 11 cases immunotherapy has been repeated and in 5 cases it has been administered 3 times.

We carried out 98 surgical toilets and sequestrectomies, of which 22 cases were more than once. In 4 cases we carried out Paltrinieri parafocal osteotomy (all tibial). In 45 cases the Ilizarof system has been adopted with resection of the focus and compactotomy. We had to amputate only in 1 case. Solidification rimes vary according to the involved bone. On the tibiae they vary from at least 3 till maximal 36 months, on average 9.9 months.

More frequently (76.8% of cases) healing was attained within 1 year from therapy start, 26 cases (equalling 26%) did not attain solidification, of which 18 cases are still under treatment.

Very similar times have been observed on femurs, from 3 till 35 months with 9.2 months average duration.

Also for the femur the 84% of cases heals after 12 months therapy, whereas the non consolidated cases are 10 equalling 28.6%, of which 6 cases are still under treatment.

The forearm does not show substantial differences concerning ulna and radius; the same results indeed have been obtained for both bone segments; in 2 cases on 7 we observed a lack of solidification with bone material loss/this happened in the pre-microsurgical period of our experience).

Fistulae closed fairly fast 6 months in 53.48 of cases. The main check control has been 15 months, varying from 4 months at least up to 7 years.

Belated consequences have been:

Articular rigidity. Patients who have been treated with immunotherapy and submitted to plaster casts, both cylinder or valve casts, and precocious walking showed significant articular functional limitations only in 26 cases, equalling 17.6%. 14 cases concerned the talocrural articulation, 8 cases the knee and 4 cases on 7 concerned the elbow.

Shortenings have been significant (more than 4 cm) only in 2% of cases, whereas there have been 30.5% with less than 4 cm. In the whole 102 cases showed shortenings, that were compatible with a good functionality of the sick limb with good walking.

Axial deviations appeared in 18.3% of cases: 15 cases in varus dislocation, 12 in valgus dislocation, 17 in recordation and 10 in procurvation. Calcification of soft parts have been only 3.4%, whereas they were very frequent before systematically introducing immunotherapy.

Relapses concern 26.5% of our patients, i.e. about 39 cases. In 15 cases (10.2%) it was a simple reopening of the fistula that healed soon, in 13 cases the restart of the infective focus was associated with a new relaxation of the fracture. Afterwards 9 cases healed and these have been the precocious relapses (within 1 year from healing), the belated ones have been 11 cases (7.5%) with 10 healings.

15. Final considerations of the results

The efficacy of immunotherapy is certainly higher in children, as it is confirmed by a lower number of surgical interventions and by the stabilisation and healing results. *We analysed 50 cases of hematogenous osteomyelitis in order to consider which factors might have influenced the prognoses.*

1. No negative influences have been brought about by age.

2. The same applied to sex, though males showed major lesions. Daoud and Martin consider the female sex a favourable prognostic factor.

3. Prognoses are more difficult in cases with lesions, that are localised on the femur (21% without healing, whereas these reduce themselves to 5–6% in other localisation).

4. Also the extension (pandiaphysis) and the deep localisation (diaphysis) of the infection adversely influence the illness evolution.

5. Finally the prognoses is very sensible to the lesion chronicity. As a matter of fact the healing frequency is adversely proportional to the lesion duration (94%, 77%, 36%, 5%). The failures have been observed only with symptoms

that has been lasted more than 1 year. Immunotherapy has to be started as soon as possible.

Another analysis with similar considerations has been made by us on 147 cases of infected pseudoarthrose:

1. Healing is significantly influenced by the fistula healing. As a matter of fact we found 86% healing when fistula closes within 6 months. Healing frequency is lower when fistula has staid open for longer times.

2. the contrary recovery is not influenced by time elapsed from trauma till infection beginning.

3. Presence of a fistula upon hospitalisation did not affect healing.

4. Very important has been time elapsed from infection beginning and immunological treatment. With times less than 6 months recoveries show satisfactory percentages that reduce themselves to 50.6% when elapsed times are more than 1 year.

5. Localisation influences results. Whereas hands recover soon, times are on an average when tibiae are involved to become long lasting on femurs.

6. Male patients are more frequent than women (118 cases vs. 29 cases).

16. Conclusions

By comparing the results obtained in chronic osteomyelitis (both hematogenous and post-traumatic) before introducing immunotherapy and reconsidered afterwards, after having acquired a long experience in its administration, we feel following conclusions have to be drawn.

1. Immunotherapy (eventually associated to surgical therapy) ensures high recovery percentages (among the lightest mentioned in the scientific literature) [16–22].

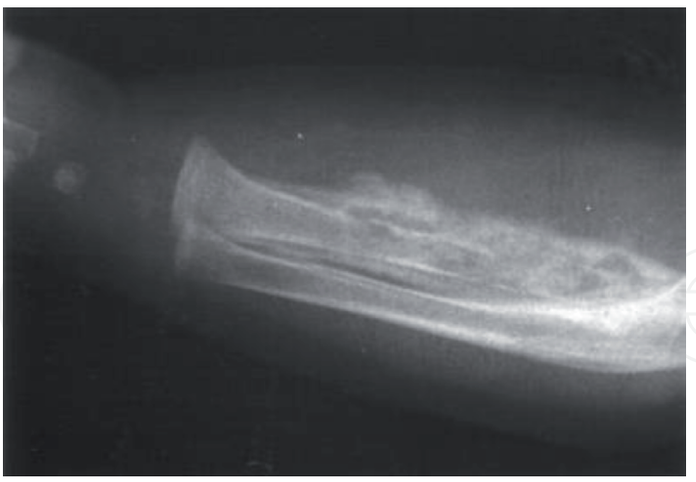
2. Such therapy notably reduces recurrences (12% instead of 40% mentioned in the literature), as it fosters natural defences.

3. Immunological therapy is somewhat more efficacious (and certainly less toxic) than antibioticotherapy. The two approaches have to be associated, as immunotherapy does not substitute antibioticotherapy (only 15% of patients affected by chronic osteomyelitis fully recover by administering only antibiotics).

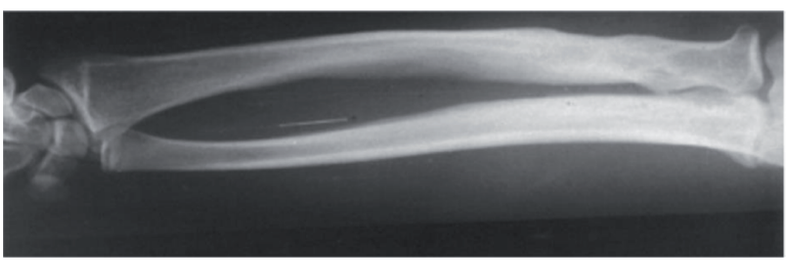
4. Immunotherapy remarkably reduced surgical interventions.

We may conclude that Specific Bacterial Immunotherapy (S.B.I.T.) has to be considered an important defence, that does not exclude, but has to be associated to antibiotico therapy and even more to surgery. The obtained positive results shall be studied with complex research methods, as the concept "immunity messenger" opens therapeutical approaches, still difficult to evaluate.

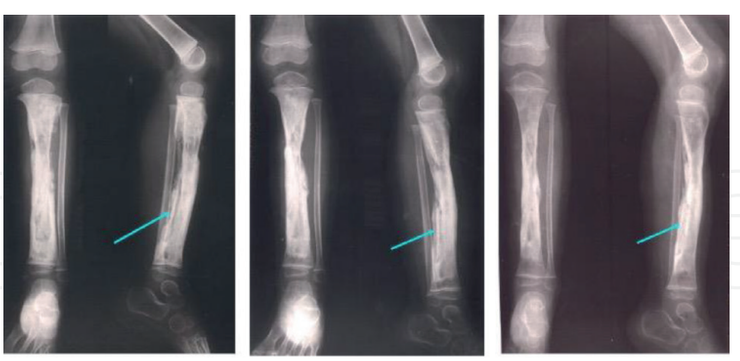
17. Some cases



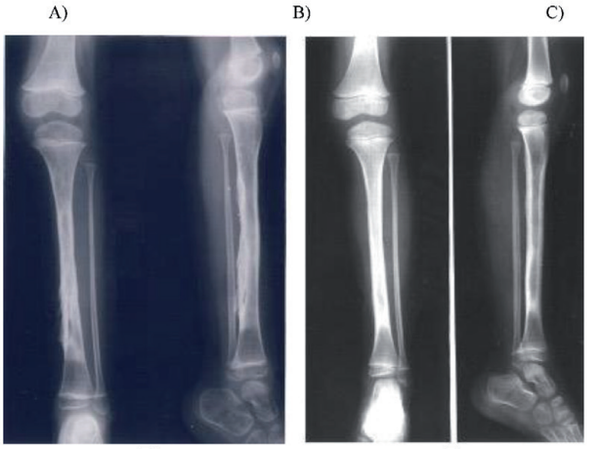
A case of hemathogenous osteomyelitis of radio in the young patient, 3 year old treated with only S.B.I.T (doses reduction) and antibiotics of course.



X-ray control after 13 years. Completed reconstruction of the bone. The infection health after 6 months of treatement with immunotherapy and antibiotics.



A) B) C)



D) E)

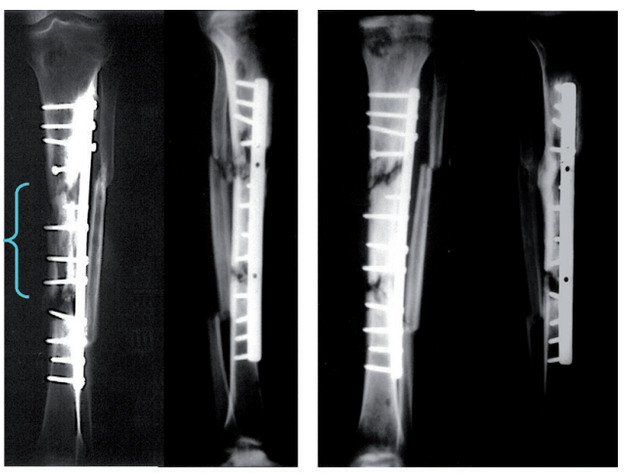
a. Heavy hematogenic pandiaphysitis in a 10 years old child, who has been treated only with S.B.I.T. according to a reduced therapeutical scheme.

b. After 2 months of treatment the whole diaphysis partially recovers there are still sequestrum of wich one is postero cortical. Fistulae closed.

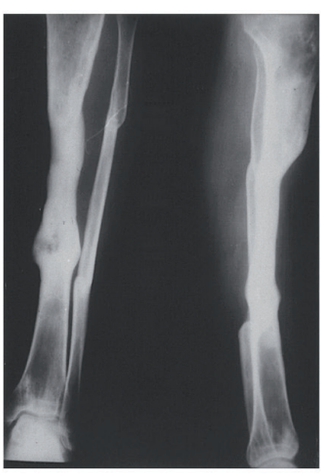
c. After 2 months reabitation of big sequestrum. (The arrow indicates bone sequestrum and its revitalization)

d. Rx control after 15 months after the beginning of the treatment

e. Rx control one year after the previous one, please note the complete reconstruction of the bones of the leg, absence of flogosi markers (clinical and laboratory)



A) B)



C)

a. 45 years old man after an open fracture of the leg. Arrived to our hospital after 12 months; he had two fistulae and two focuses of non union and a wide sequestrum was presented.

b. Rx control after 3 months of treatment with S.B.I.T. and you can see the reabitation of the central sequestrum and the beginning of callification on the two focuses (of non union

c. Rx control after removal plate, screw e a debridment and 3 months in plaster.

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