Symposium on Tuberculosis in Infancy and Childhood

National Jewish Hospital at Denver

Wednesday, November 9 to
Saturday, November 12, 1955

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ABSTRACT OF PAPERS AND PROGRAM

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ABSTRACTS*

CORRELATION OF IN VITRO SENSITIVITY OF M. TUBERCULOSIS WITH CLINICAL RESPONSE OF PATIENTS TO THERAPY

HATTIE E. ALEXANDER

Babies Hospital
and the
Columbia University College of Physicians
and Surgeons

Emergence of resistance of tubercle bacilli to streptomycin and isoniazid has been shown to be the result of selection of spontaneously occurring mutants. In pyogenic infections there is convincing evidence that emergence of resistance to antibiotics, with resultant failure of therapy, can be prevented by using initially at least two effective agents which presumably work through different mechanisms of action. Under these circumstances, the mutants resistant to one will be normally sensitive to the other. This principle has been applied for some time in the treatment of tuberculous meningitis in children. Whether emergence of resistance can thus be eliminated as a cause of failure has not yet been answered. In the Babies Hospital this problem has been studied in patients with miliary and meningeal tuberculosis during two different therapeutic regimens: 1. Simultaneous use of streptomycin and PAS, with or without promizole; 2. Simultaneous use of streptomycin, isoniazid and PAS.

The results suggest that a correlation is found between *in vitro* sensitivity tests and the clinical response of the patient; but only when a test, using an appropriate population size, media and incubation time, measures the proportion of the population which will grow at each concentration tested. When such a test is used, emergence of bacterial resistance during each therapeutic program is a rare event. Even in the unusual patient from whose spinal fluid tubercle bacilli are cultured for several weeks or during a recrudescence, the organisms are found to be sensitive, with a rare exception. These results suggest that the organisms which persist have been protected from the antimicrobial action of the antibiotics.

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* Alphabetically arranged according to authors.

DYNAMIC ASPECTS OF THE PATHOLOGY AND BACTERIOLOGY OF TUBERCULOUS LESIONS

GEORGES CANETTI

Institut Pasteur, Paris

The human tuberculous lung contains five principal types of tuberculous lesions: the exudative lesion, the tubercle, the solid caseous lesion, the soft caseous lesion, and the cavity. The exudative lesion always contains macrophages and, at times, polymorphonuclear cells and fibrin; the bacilli in such lesions are undergoing active multiplication. The tubercle contains epithelioid cells, giant cells, and lymphocytes, in various proportions: in such lesions bacilli are very rare or completely absent. The solid caseous lesion is densely necrotic: evidences of the original structure of the lung are sometimes recognizable; tubercle bacilli, very numerous during the early period of formation of such lesions, become more and more rare with time and often disappear completely. The soft caseous lesion contains no recognizable tissue structures: such lesions may contain either very few tubercle bacilli or very large numbers of these organisms in rapid multiplication. Finally, the cavity, resulting from the evacuation of liquified caseous material into the bronchi, contains large numbers of tubercle bacilli in the necrotic material which lines its internal surface.

The development of these different types of lesions may follow three different courses. If the early multiplication of the parasites is promptly interrupted, the discrete tuberculous exudative lesion develops into the tubercle: this lesion is a response to the products of destroyed bacilli. If the multiplication of the bacilli is not arrested the initial exudative lesion, now more extensive and with a more inflammatory character, becomes caseous; and it is in the solid caseous lesion that the multiplication of the bacilli is arrested, followed by their destruction. Finally, if, in spite of caseation, the multiplication of the bacilli is not interrupted, or is subsequently resumed, softening and evacuation ultimately occur. The available evidence suggests that softening precedes the resumption of bacterial multiplication.

All factors which inhibit bacterial multiplication — natural resistance, specific acquired resistance, chemotherapy, surgical collapse — tend to prevent the first and the second stages from developing. On the other hand, all factors favoring bacterial multiplication tend to lead to the third stage.

Numerous problems concerning the intimate mechanisms involved in the evolution from stage to stage remain to be

resolved. The two most important of these are the elucidation of those factors which lead to the death of the bacilli in the solid caseous lesion, and the mechanisms which lead to the resumption of bacterial multiplication in the liquified caseous lesion.

EFFECTS OF ISONIAZID ON ALLERGY — WITH SOME ADDITIONAL OBSERVATIONS IN CHILDREN VACCINATED WITH BCG

C. CHOREMIS

Athens University Clinic

Observations have been made after an 11-week administration of isoniazid (Dianicotyl) at a daily dose of 4-6 mg./kg. of body weight in children vaccinated with BCG. Four groups of children were studied. In the first group the administration of the drug was started a few days before vaccination, in the second on the same day, in the third one week after vaccination, while a fourth group was used as a control.

It is concluded that:

1. Treatment with isoniazid inhibits the development of allergy in 89.6 per cent of the cases. Tuberculin tests repeated in a few children four weeks after the discontinuation of isoniazid remained negative. A comparison of tuberculin test vs. BCG test was slightly in favor of the latter as far as allergy was concerned.

2. Local manifestations at the sites of vaccination were limited and less marked both macroscopically and microscopically in the isoniazid-treated children. No significant changes of electrophoretic patterns of serum proteins or of the agglutination reaction of Middlebrook-Dubos were noted on vaccinated patients regardless of whether isoniazid was administered or not. Agglutination titers were not higher than 1:8. Furthermore, isoniazid did not appear to influence quantitatively, or in relation to time, the formation of antibodies.

CORTISONE AND ACTH IN THE TREATMENT OF TUBERCULOSIS IN CHILDHOOD

CESARE COCCHI

Pediatric Clinic, University of Florence

The effects of cortisone on the course of tuberculous disease have been studied both in guinea pigs and in children.

Ragazzini, in our clinic, studied cortisone in infectious diseases — particularly, in tuberculosis — when it was considered harmful by many other investigators. He observed that it had an adjuvant effect with streptomycin in guinea pig tuberculosis, unless streptomycin-resistant tubercle bacilli were employed as the infecting agents. This result was interpreted as evidence that cortisone, by inhibiting the natural and productive processes, permits the antimicrobials to reach the germs more easily.

During subsequent years several of my associates have used cortisone, ACTH and, recently, prednisone (deltacortene) with streptomycin, isoniazid, PAS and viomycin in the treatment of the various forms of tuberculosis in childhood. Particularly in tuberculous meningitis, in tuberculosis of serous membranes and in erythema nodosum, excellent results were obtained: more speedy fall of fever, disappearance of clinical signs and improvement in the general clinical condition.

It is concluded that antimicrobial agents and cortisone (or ACTH) have synergistic therapeutic effects in tuberculosis.

SYSTEMATIC TREATMENT OF PRIMARY TUBERCULOSIS

ROBERT DEBRE

Hopital des Enfants Malades,
and the
University of Paris

When tuberculous infection is encountered in a child, treatment must be initiated. Hygiene, good air and rest are not sufficiently reliable defensive measures. Simultaneously with the development of a primary tuberculous complex, diffuse pulmonary and systemic dissemination occurs (choroidal nodules are found in 6% of children with primary tuberculosis). The subsequent course of primary infection cannot be predicted in any individual case. Epidemiological studies show that 12% of school children infected at age 7 have manifest tuberculosis before age 20. What about the future? One does not know in what proportion of cases adolescent and adult tuberculosis is the ultimate stage of childhood infection.

The younger the child, the greater the risk of serious tuberculosis; no doubt may therefore be raised regarding the necessity of treating infants. The outlook is also bad when infection first occurs in puberty. It is worse when infection is the result

of prolonged, intimate contact with a contagious subject. In any case, even in school children, and even if tuberculin allergy is the only sign of infection, we believe in the necessity of treatment. In order to be effective, treatment should always be long (no less than 6 months). It should consist of isoniazid (20 mg/kg/day in 2 divided doses) with para-aminosalicylic acid added (300 mg/kg/day in 2 divided doses) in order to avoid resistance. Streptomycin should be resorted to only in case of subsequent need. The Institut National d'Hygiène in France is investigating the effects of this treatment in a large number of children with latent primary tuberculosis, comparatively, with an adequate number of controls.

EXPERIENCES WITH INTRA- AND EXTRA-LUMINAL BRONCHIAL TUBERCULOUS LESIONS

ROBERT H. HIGH AND WALDO E. NELSON

St. Christopher's Hospital for Children
and the
Temple University School of Medicine

This report will review the clinical, roentgenographic and bronchoscopic findings in a group of infants and children with tuberculosis of the hilar and paratracheal lymph nodes. Such tuberculous lesions very commonly cause reactions in the adjacent tracheobronchial tree. These reactions vary in severity from increased mucoid secretions as a result of local irritation to bronchial obstruction resulting in interference to the normal movement of air.

Special attention will be directed to obstructive lesions produced by extraluminal compression from enlarged lymph nodes or intraluminal obstruction produced by endobronchial granulomas. The bronchoscopic findings in such patients will be reviewed.

Serial bronchoscopic observations in these patients will be correlated with roentgenographic findings and with the ultimate outcome of such lesions.

RESULTS OF VOLE AND BCG VACCINATIONS

K. NEVILLE IRVINE

Oxford Regional Hospital Board

This paper falls into two parts. The first deals with the

development of BCG vaccination in Great Britain since its inception in 1949. Vaccination was originally restricted to nurses, medical students, and the contacts of tuberculous persons; the speaker, who has supervised vaccination in the Oxford Region — an area with a population of one and a half million — will give details of the available results. In 1954 vaccination was extended to 13-year-old school children and preliminary figures from this group will be given; the new Heaf multiple-puncture tuberculin test, which is a major simplification of tuberculin testing, will be demonstrated.

The second part deals with vaccination with Wells' vole bacillus. The speaker, who has worked with Dr. A. Q. Wells over the last five years, will explain the development of this vaccine and give details of the present position.

A comparison of BCG with the vole vaccine will be made as far as the present position allows. It is hoped that the preliminary report of the Medical Research Council on the BCG and vole vaccination trial will be available in time for the Symposium.

NUTRITIONAL STUDIES IN TUBERCULOSIS IN ADOLESCENCE

J. A. JOHNSTON

Henry Ford Hospital

In a 25-year follow-up of 1100 reactors removed from contact, the development of reinfections, presumably endogenous, in adolescence led to a study of the metabolism and nutritional requirements of that age group.

It is felt that a correlation can be shown between the development and the subsequent course of reinfection tuberculosis and the maintenance of an adequate nitrogen balance. Studies will be presented on the factors influencing the storage of nitrogen and calcium: these include age, the intake of protein, calcium and vitamins, the effect of various endocrine glands, focal non-tuberculous infection, as well as comparisons of the metabolism of prolonged bed rest with various levels of physical activity.

Stress will be laid on the distinction between diets offered and actually consumed and on the importance of assessing all factors influencing the utilization of the ingested diet.

COMPLICATIONS OF SKELETAL TUBERCULOSIS AND ITS TREATMENT

CHARLES H. LACK

Royal National Orthopedic Hospital, London

Unsuspected tuberculosis has appeared after injury and after the giving of cortisone and ACTH. Clinical and experimental data are put forward to support the theory that both trauma and cortisone may so alter local conditions as to allow multiplication of bacilli long resident in tissue not showing disease.

The part played by secondary infection, especially by staphylococci, is exemplified in case histories. While morbidity and mortality are increased by secondary infection, it is noteworthy that it may bring about bony union in a tuberculous joint that might otherwise end up with an unstable fibrous ankylosis.

Osteoporosis due to immobilization leads to flattening of the chest, fractures following minor falls, and to renal calculi. An awareness of these effects coincided with the discovery of antibiotics, so that any change in progress of the disease resulting from measures taken to reduce immobilization osteoporosis is masked by the use of drugs. It is pertinent, nevertheless, to consider whether venous stasis which has this adverse effect on bone is not also disadvantageous to the tubercle bacilli themselves.

Renal tuberculosis occurs in fifteen to thirty per cent of cases of skeletal disease; usually it does not become clinically manifest until several years later. Systematic examination and guinea pig inoculation reveal tubercle bacilli in the urine of some who would otherwise not be suspected of having renal involvement. The bacilli of these early renal lesions may become resistant to the drugs used for treating the skeletal tuberculosis before the clinician is aware of renal disease.

Complications of antibiotic treatment *per se* require no special mention in regard to skeletal tuberculosis.

BRONCHOSCOPY IN PRIMARY TUBERCULOSIS OF CHILDHOOD

HERMAN I. LAFF

National Jewish Hospital at Denver
and the
University of Colorado School of Medicine

Bronchial involvement is an important and increasingly

recognized factor in the pathogenesis of parenchymal pulmonary tuberculosis in children. Bronchoscopy is the indispensable diagnostic method for visualization of the inflammatory or obstructive phenomena resulting from mediastinal lymph node involvement. Bronchoscopy in tuberculous children is not dangerous and is best performed with adequate general anesthesia. Indications are similar to those associated with foreign bodies aspirated into the tracheobronchial system. Frequently complications of bronchial involvement may require bronchoscopic treatment, which may also avert other undesirable pulmonary sequelae. The difference between bronchial involvement in children and adults is discussed.

THE COURSE AND PROGNOSIS OF ENDOBRONCHIAL DISEASE IN CHILDREN

EDITH M. LINCOLN

Bellevue Hospital
and
New York University College of Medicine

Endobronchial disease in children is usually due to encroachment of tuberculous nodes on a bronchus. The clinical pictures and the evolution of the disease as seen through the bronchoscope will be reviewed. The prognosis of endobronchial disease in the pre-chemotherapy era on the children's chest service at Bellevue Hospital will be evaluated.

About 150 children with endobronchial disease, proven by bronchoscopy and seen in the years 1947 through 1953, will be reported. Some of these patients were not treated with any form of chemotherapy and others were treated with various antimicrobial agents. The course of the endobronchial disease in these patients will be analyzed with particular emphasis on the clinical course, occurrence and duration of evidence of pulmonary obstruction, the duration of evidence of endobronchial disease and the incidence and extent of permanent bronchial and pulmonary damage as shown by bronchoscopy and bronchography.

Abstracts continued on page 9 following program

PROGRAM*

SYMPOSIUM ON TUBERCULOSIS IN INFANCY AND CHILDHOOD

November 9-12, 1955

Session I
Morning, November 9

Registration		8:30 to 9:30
Welcome		9:30 to 10:00
Emanuel Friedman, *Honorary Chairman* René J. Dubos, *Moderator*		
"The Problem"	René J. Dubos	10:00 to 10:30
Coffee		10:30 to 11:00
"Morphological Analysis of Fatal Tuberculosis in Children with Some Comments on Endogenous Exacerbation and Tuberculous Meningitis"	Kornel L. Terplan	11:00 to 11:30
"Dynamic Aspects of the Pathology and Bacteriology of Tuberculous Lesions"	Georges Canetti	11:30 to 12:10
Discussion		12:10 to 12:45
Lunch		12:55 to 1:45

Session II
Afternoon, November 9

Edgar Mayer, *Honorary Chairman*
James J. Waring, *Moderator*

"Vaccination Against Tuberculosis — Clinical Aspects"	Lars Ström	2:00 to 2:30
"Usual and Unusual Reactions to BCG Inoculation in Children"	Hans J. Ustvedt	2:30 to 3:00
Tea		3:00 to 3:20
"Results of BCG and Vole Vaccinations"	K. Neville Irvine	3:20 to 3:50
Discussion		3:50 to 4:30
Dinner		

* *Tentative, as of Oct. 1, 1955*

Session III
Morning, November 10

Esmond Long, *Honorary Chairman*
G. Middlebrook, *Moderator*

"Immunopathology of Tuberculosis"	9:00 to 9:30
Sidney Raffel	
"Pathogenicity of the Isoniazid-resistant Tubercle Bacilli and Prophylaxis of Tuberculosis in Childhood"	9:30 to 9:50
Noël Rist	
Discussion	9:50 to 10:20
Coffee	10:20 to 10:40
"Dynamics of Antituberculous Chemotherapy"	10:40 to 11:10
Walsh McDermott	
"The Bactericidal Activity of Antituberculous Drugs"	11:10 to 11:30
D. A. Mitchison	
Discussion	11:30 to 12:00
"Complications of Skeletal Tuberculosis and Its Treatment" C. H. Lack	12:00 to 12:20
Discussion	12:20 to 12:45
Lunch	12:55 to 1:45

Session IV
Afternoon, November 10

Albert Guggenheim, *Honorary Chairman*
Lee Forrest Hill, *Moderator*

"Some Observations on the Utility of Simian Tuberculosis in Defining the Therapeutic Potentialities of Isoniazid"	2:00 to 2:30
L. H. Schmidt	
Discussion	2:30 to 2:50
"Cutaneous Tuberculous Complexes"	2:50 to 3:10
R. V. Platou	
Discussion	3:10 to 3:25
Tea	3:25 to 3:50
"Nutritional Studies in Tuberculosis in Adolescence"	3:50 to 4:20
Joseph A. Johnston	
Discussion	4:20 to 4:45
Dinner	

Session V
Morning, November 11

J. Arthur Myers, *Honorary Chairman*
Sidney H. Dressler, *Moderator*

"Systematic Treatment of Primary Tuberculosis" Robert Debré	9:00 to 9:30
"Effect of Isoniazid on Allergy — With Some Additional Observations in Children Vaccinated with BCG" C. Choremis	9:30 to 10:00
"Cortisone and ACTH in the Treatment of Tuberculosis in Childhood" C. Cocchi	10:00 to 10:30
Discussion	10:30 to 11:00
Coffee	11:00 to 11:20
"The Management of Special Problems in the Chemotherapy of Tuberculosis in Infants and Children" José Sifontes	11:20 to 11:50
"Correlation of *In Vitro* Sensitivity of *M. Tuberculosis* with Clinical Response of Patient to Therapy" Hattie Alexander	11:50 to 12:15
Discussion	12:15 to 12:45
Lunch	12:55 to 1:45

Session VI
Afternoon, November 11

Honorary Chairman (to be announced)
Arthur Robinson, *Moderator*

"The Course and Prognosis of Endobronchial Disease in Children" Edith Lincoln	2:00 to 2:30
"Experiences with Intra- and Extra-Luminal Bronchial Tuberculous Lesions" Robert High and Waldo K. Nelson	2:30 to 3:00
"Bronchoscopy in Primary Tuberculosis of Childhood" Herman I. Laff	3:00 to 3:20
Discussion	3:20 to 4:00
"Views in Perspective" Bela Schick	4:00 to 4:30
Dinner	
An Evening Lecture: "Some Problems in the Prevention of Infectious Diseases" Robert Debré	8:30

Session VII
Morning, November 12

Honorary Chairman (to be announced)
Robert H. Alway, *Moderator*

Introduction of Participants in the Summary Session	9:30 to 9:45
Participants: Distinguished Public Health Workers, and Others to be Announced	
Discussion	9:45 to 10:45
Coffee	10:45 to 11:05
Discussion (resumed)	11:05 to 12:30
Lunch	12:55

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In addition to the above seven sessions, a banquet will be given by the Hospital on the evening of Thursday, November 10.

All sessions will take place in the Schoenberg Auditorium at the National Jewish Hospital at Denver. Attendance will be strictly limited in order to obtain a free manner of discussion. The smallness of the group means the exclusion of many workers active and interested in the subject discussed. Therefore, the proceedings of this Symposium will be published and made available throughout the world.

The special lecture by Professor Debré will be held in the Dennison Auditorium at the University of Colorado School of Medicine, and will be open to the public.

DYNAMICS OF ANTITUBERCULOUS CHEMOTHERAPY

WALSH McDERMOTT

New York Hospital
and the
Cornell University Medical College

The state of "physiologic insusceptibility" of dormant tubercle bacilli to the available antimicrobial agents is a prime obstacle to "eradicative" chemotherapy in tuberculosis. An approach to the experimental study of this phenomenon *in vivo* has been provided by a microbial enumeration technique applied to the lungs and spleens of infected mice, untreated, or treated with different antimicrobial agents, alone or in combination.

Important differences in the drug-parasite relationships have been established in different organs of the same species of host: while true latency (absence of demonstrable bacilli) can be effected with regularity in the lungs of mice treated with the combination isoniazid-pyrazinamide, in particular, it cannot so readily be achieved in the spleen. This is attributed to distinct differences in the fashion in which tubercle bacilli are handled by the host in these organs.

The effects of other combinations of antimicrobial agents under similar experimental conditions will also be described. And, the implications of these observations for chemotherapy of tuberculosis in man will be discussed.

THE BACTERICIDAL ACTIVITIES OF ANTITUBERCULOUS DRUGS

D. A. MITCHISON

Postgraduate Medical School of London

Streptomycin, isoniazid and viomycin have bactericidal activities against log phase cultures of tubercle bacilli, which are usually greater when two or more of these agents are employed together than when one is used alone (bactericidal synergism). On the other hand, any agent or condition which inhibits bacterial growth diminishes their bactericidal activity (bactericidal antagonism). Thus the bactericidal activity of

streptomycin and isoniazid is abolished or greatly diminished at the end of the log phase and in the stationary growth period, under anaerobic conditions and in the presence of bacteriostatic concentrations of terramycin. In experimental tuberculosis in animals, the defense mechanisms may be considered either as principally bactericidal or principally bacteriostatic. In the former case, there should be synergism between the immune processes and a bactericidal chemotherapeutic agent, while in the latter case antagonism would be expected. Previous BCG immunization increased the bactericidal activity of isoniazid in the spleens of guinea pigs infected intravenously with either virulent or attenuated tubercle bacilli.

CUTANEOUS TUBERCULOUS COMPLEXES

R. V. PLATOU and R. H. LENOX

Charity Hospital of Louisiana
and the
Tulane University Medical School

Employing kodachrome slides, this brief review will be concerned with a number of typical tuberculous lesions of the skin in infants and children. Particular reference will be made to the peculiarities and characteristic diagnostic criteria for several of these, their general prognostic significance, and our current feelings about therapy for each.

IMMUNOPATHOLOGY OF TUBERCULOSIS

SIDNEY RAFFEL

Stanford University Medical School

If the conventional, simplified version of the evolution of tuberculosis is accepted — and there are uncertainties about this — one can attempt to describe in some detail certain of its more important events. This is analogous to mapping the geologic structure of a mountain range by digging a few shallow observation pits in what are considered to be the more important peaks. The resulting description may be appealingly rational but entirely false, depending upon the digger's judg-

ment in selecting his peaks and the quality of the imagination applied to interpretation.

At the beginning of the tuberculous process, the event to be accounted for is the ability of the bacillus to initiate reproduction in normal tissues. We have observed certain differences between virulent and avirulent bacilli in addition to those previously described. These include variations in the lag phase of growth when adapting to new cultural environments, sensitivities to penicillin, and the degrees to which growth is influenced by the pO_2 of the milieu, *in vivo* and *in vitro*.

Once infection is under way, an early event is the formation of the granuloma, and concomitantly the development of hypersensitivity. The relation of bacillary lipids to granuloma induction, on the one hand, and to tuberculin reactivity and antibodies, on the other, will be discussed.

The acquisition of immunity comes at about the same time. The question of the relationship of this phenomenon to antibodies or to macrophages is an old one in which interest has been recently revived. Experiments with systemically derived macrophages as well as those obtained from lymph nodes regional to sites of vaccination will be compared.

PATHOGENICITY OF THE ISONIAZID-RESISTANT TUBERCLE BACILLI AND PROPHYLAXIS OF TUBERCULOSIS IN CHILDHOOD

NOEL RIST

Institut Pasteur, Paris

I. Among the isolated, pure isoniazid-resistant strains, most have a reduced pathogenicity for the guinea-pig: in that host they provoke a generalized but regressive tuberculosis. Nevertheless, the pathogenicity of these strains is still much greater than that of typically avirulent strains, BCG or H37Ra. This can be demonstrated with guinea-pigs and with mice. Moreover, a small number of pure isoniazid-resistant strains are definitely virulent for the guinea-pig, causing a progressive and lethal tuberculosis.

II. As for the bacillary populations actually excreted by isoniazid-treated patients, the *in vitro* resistance tests do not allow one to assert that a given population, when inoculated into the guinea-pig, will not reveal some virulent bacilli (either

isoniazid-sensitive, or isoniazid-resistant). Only after the inoculation of a very great number of bacilli and the observation of the guinea-pig for 8 to 12 months can this be proved.

These facts do not solve the problem of the pathogenicity of isoniazid-resistant bacilli for the child. But they should incline the clinician to the greatest caution before discharging sputum-positive isoniazid-treated patients from hospital environments.

III. Once the laboratory behavior of pure isoniazid-resistant strains and of the bacillary populations excreted by isoniazid-treated patients is known, the next step will be the obstinate searching for contact cases, possibly infected by isoniazid-treated patients. To be fruitful, the analysis of the bacillary population found in the lesions of the infected child should involve a quantitative *in vitro* evaluation of the resistant fractions, a long term evaluation of the pathogenicity in the guinea-pig, and the testing of the resistance of the bacilli recultivated from the guinea-pig. Owing to the usual lack of these tests, among about twenty published cases claimed to have been infected by isoniazid-resistant strains, only one (published by G. Meissner) probably justifies this claim. The question is now to know whether this case will remain an exception or will be followed by many others.

SOME OBSERVATIONS ON THE UTILITY OF SIMIAN PULMONARY TUBERCULOSIS IN DEFINING THE THERAPEUTIC POTENTIALITIES OF ISONIAZID

L. H. SCHMIDT

The Christ Hospital Institute of Medical Research
and the
University of Cincinnati College of Medicine

The work to be described in this report stemmed from an investigation of the effectiveness of isoniazid in modifying the otherwise fatal course of naturally acquired pulmonary tuberculosis in the rhesus monkey and in preventing dissemination of the disease from infected to non-infected animals housed in close proximity. Groups of 157 infected and 50 non-infected monkeys were housed together for periods up to one year, during which time they received isoniazid at a daily dose of 5 mg. per kg. for the first six weeks and 20 mg. per kg. thereafter. The progress of established disease and development of infection among the non-immunes was followed in serial radiologi-

cal studies. Representative animals from the infected group were sacrificed at intervals for purposes of bacteriological and histopathological study. At the termination of treatment, the remaining previously infected monkeys were separated from the non-infected; these groups were then held for an additional 10-month period to observe the incidence of recrudescences and new infections. Summarized briefly, these studies showed that administration of isoniazid had a profoundly favorable effect on the course of established pulmonary tuberculosis. From histopathological and bacteriological viewpoints, the effects of such treatment were significantly different from those of other antituberculous drugs. No active infections developed among the non-immune animals during the period of isoniazid administration. However, pulmonary tuberculosis developed in 50 per cent of such animals in the post-treatment period. The general significance of these findings will be discussed.

THE MANAGEMENT OF SPECIAL PROBLEMS IN THE CHEMOTHERAPY OF TUBERCULOSIS IN INFANTS AND CHILDREN

JOSE E. SIFONTES

Sanatorium A. R. Soler
and the
University of Puerto Rico School of Medicine

The problems of chemotherapy among 555 infants and children admitted with all forms of tuberculosis since the advent of isoniazid are analyzed.

Our observations have taught us the following: 1. The proper management of complications in the seriously ill patient is just as important as the chemotherapy of tuberculosis. 2. All forms of progressive tuberculosis should receive chemotherapy. 3. Active primary tuberculosis should probably be treated with isoniazid, but the final answer is not available yet. 4. Drug dosage should be based on body surface in markedly undernourished children. 5. Chemotherapy should be administered for a year or longer. 6. Deafness due to intrathecal streptomycin (57 per cent of cases) is the most serious and unnecessary manifestation of drug toxicity. 7. Resistance to isoniazid and streptomycin occurs mainly in reinfection tuberculosis (10 per cent of cases) and indicates a change to iproniazid, viomycin or other drugs. 8. Tuberculous absecesses may develop during

chemotherapy, but, once drainage is established, healing is rapid. 9. Block in tuberculous meningitis usually clears spontaneously. 10. Bed rest is usually not essential after the initial toxic phase. 11. Therapy of tuberculous otitis is often unsuccessful because of a changing drug-resistant flora. 12. Permanent tissue damage is encountered: atelectasis, bronchiectasis, neurological sequelae, deformities, etc., should receive individual attention in order to rehabilitate the patient as completely as possible.

VACCINATION AGAINST TUBERCULOSIS — CLINICAL ASPECTS

LARS STROM

Karolinska Sjukhuset

In combating tuberculosis one has to lay the greatest stress on prophylaxis. We have to realize that BCG-vaccination is only one of several measures that can be applied in order to protect children against tuberculous disease. In judging the value of the BCG-vaccination we must remember that about 25 years ago, when BCG was introduced in several countries, the situation of the tuberculous disease was quite different from today. No doubt BCG-vaccination became a welcome and important means in the struggle against tuberculosis, especially for the pediatricians. At this time the mortality among the children, with tuberculous infection during their first year of age was 35% (in Sweden) — now we know that these vaccinated children generally are free of clinical tuberculosis and that we never see among them a case of clinical post-primary tuberculosis. A review of the follow-up investigations of larger groups of vaccinated individuals will be given.

Different methods of vaccination against tuberculosis are discussed. The experiences of vaccination with BCG and of vaccination according to Salvioli-Petragnani are compared. A review of the various methods of injection of the vaccine and points of view about the peroral application according to our own experimental studies are given.

On the basis of experiments with BCG-vaccine, labeled with radio-active phosphorus, the reaction of the host organism after the injection of the vaccine is discussed. Almost immediately after the injection a hematogenous dissemination of the BCG-bacilli seems to take place. Finally there will be a discussion of the following points: 1. What BCG-vaccination may

accomplish at best; 2. the importance of BCG in explaining the present low tuberculous morbidity and mortality; 3. the problems of the future.

MORPHOLOGICAL ANALYSIS OF FATAL TUBERCULOSIS IN CHILDREN WITH SOME COMMENTS ON ENDOGENOUS EXACERBATION AND TUBERCULOUS MENINGITIS

KORNEL L. TERPLAN

Buffalo General Hospital
and the
University of Buffalo School of Medicine

The paper is based on experience gained during the past 15 years and includes 50 cases with tuberculosis as the cause of death and 28 in which tuberculous lesions were an incidental finding.

In line with the classic experience obtained nearly half a century ago, it is still the hematogenous dissemination of the primary tuberculous infection which is responsible for death from tuberculosis in children. It is not the destruction of lung tissue. In all, but one, fatal cases of childhood tuberculosis studied during the past 15 years, death was caused by tuberculous meningitis. Attention is focused on the selective role which the soft membranes of the brain seem to play in the localization of the spreading tuberculous infection in the child. Material is presented to prove that in spite of the chalky or even firmly calcified state of the original lesions of first infection, large numbers of tubercle bacilli remain active in these old lesions. The ways by which an apparently reactivated infection reaches, in such a selective manner, the membranes of the brain, causing tuberculous meningitis, are not at all clear. In contrast to the usual type of miliary tuberculosis, there are few or no miliary tubercles in organs other than the soft membranes of the brain. The problem of the fatal form of tuberculosis in children, as seen from the experience gained in Buffalo, is primarily that of prevention of tuberculous meningitis, or its successful treatment.

The comparison of the recent experience with a similar study from the preceding 10 years shows that the incidence of fatal tuberculosis has dropped from 4 per cent of all deaths from various causes to 0.5 per cent in the last 5 years. Also, findings of minimal tuberculous infection as incidentally dis-

closed in children who had died from causes other than tuberculosis have considerably diminished. However, the relative incidence of those minimal tuberculous lesions which remain restricted to a small area in the lung, without any further spread to the lymph nodes, has increased. 42 per cent of all such minimal primary lesions in the lung tissue belong to this group.

USUAL AND UNUSUAL REACTIONS TO BCG INOCULATION IN CHILDREN

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The BCG variant of the *Mycobact. tub.* usually produces a typical primary complex, with cutaneous primary focus and regional adenitis, when inoculated intra- or per-cutaneously in non-allergic human beings.

Various parasite and host factors influence the extent, duration and character of the local lesion and the regional adenitis. Of particular importance is the size of the infecting dose and the age of the host.

An unusual type of late reaction at the site of inoculation is represented by lupus nodules.

In the allergic human being, BCG vaccination usually gives rise to accelerated nodule formation at the site of inoculation (Koch phenomenon), often accompanied by early regional adenitis — contrary to commonly accepted views.

An early hematogenous spread, with formation of minute, non-progressive foci in different organs, probably takes place after BCG vaccination. Usually this dissemination is not clinically detectable. In recent years, however, a small number of cases of atypical, generalized tuberculosis attributed to BCG organism has been described. Four of these cases have been fatal. The lymph nodes, the skeleton and the lungs have been mainly affected, and thorough bacteriological and pathological investigations seem to demonstrate that a dissemination of BCG after vaccination has been involved.

In this paper the main emphasis is to be put on a discussion of these cases, particularly with regard to their relation to BCG-inoculation and their explanation.

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