The Changing Picture of Tuberculosis*

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Significant changes have developed in the treatment and control of tuberculosis during the past few years. Most of these changes are not new; they are only changes or differences in degree. Some are discouraging; others are encouraging.

The most discouraging aspect of the changing picture of tuberculosis is the gradually increasing apathy or complacency among the public, private physicians, general hospitals, and even among some public health officials. With more than 50,000 new cases and over 9,000 deaths in the United States last year from tuberculosis, this apathy is in strange contrast with the panic and pandemonium which occurred about two and one-half years ago when a teen-age boy was reported to have small pox in New York City while en route by plane from Brazil to Canada.

Tuberculosis remains the chief public health problem of all communicable diseases from the standpoint of its toll in lives and the disability it causes. Nearly five years after the Arden House Conference issued its ringing challenge for the eradication of tuberculosis, and outlined the steps necessary to attain this goal eventually, the results are disappointingly meager. We have the tools and the knowledge to progress much faster than we have. The chief problem seems to be a lack of sufficient determination to use these tools and knowledge effectively in pursuing the goal.

Consider the magnificent tool we have in chemotherapy for tuberculosis. With proper antibacterial therapy and surgery, when indicated, recovery can be anticipated, among cooperative patients, in well over 90 per cent of newly discovered, previously untreated cases, but such a splendid recovery rate can be attained only if the physician treating the case is skilled and experienced in the therapy of tuberculosis, and if the patient cooperates fully in his treatment. The high percentage of patients who require readmission to our tuberculosis hospitals is a dismal indictment of our inability to bring the disease under effective control during the first admission—and keep it under control.

Basic principles in the chemotherapy of tuberculosis have remained essentially unchanged during the past few years:

1. Patients with active tuberculosis in any form should receive antibacterial therapy.

2. The drug regimen should include at least two drugs given concurrently, and in some cases, three drugs are advisable.

3. Antibacterial therapy should be continuous and prolonged -- for at least 18 months and often for two years or more.

The “major” drugs remain the same; isoniazid, streptomycin, and para-aminosalicylic acid (Pas). Isoniazid should be included in every regimen, unless specifically contraindicated, due to undesirable side reactions. The usual dosage for adults is 100 mg. t.i.d. Streptomycin, one gram daily for the first three months, then decreased to one gram two or three times weekly for the next eight to ten months, is the dosage we favor. The generally accepted dosage for PAS is four grams t.i.d., though evidence is accumulating which suggests that six grams given daily in a single dose may be just as effective. Toxic
side reactions, which occur most frequently with PAS are anorexia, diarrhea, and abdominal distress. Allergic reactions, which are much more serious, invariably begin with symptoms of chills and fever. Maculopapular eruptions may occur followed by exfoliative dermatitis and in very severe cases of hypersensitivity, liver damage and jaundice may occur. In such instances, the PAS should be promptly discontinued when fever and chills develop. In our experience, approximately 80 per cent of patients can tolerate PAS satisfactorily.

Surgery continues to play an important role in the treatment of pulmonary tuberculosis; however, the need for surgical intervention has decreased noticeably in recent years. In the opinion of the authors, surgical resection is definitely indicated, if feasible, in the following situations: (1) the so-called destroyed lung, a lobe or lung almost completely destroyed by the disease process; (2) a cavity or nodular focus with positive cultures after four to six months of antibacterial therapy; (3) severe bronchial stenosis; and (4) bronchiectasis with significant symptoms.

The need for resection of “open negative” cavities following effective antibacterial therapy remains controversial. However, long term follow-up studies during the past ten years have shown that such patients have a very low reactivation rate if continued on antibacterial therapy indefinitely. After a few years of combined chemotherapy, isoniazid alone seems sufficient to prevent relapse.

The Drug-Resistant Infection. Treatment of the patient with drug-resistant organisms can be a difficult and trying experience for both the physician and the patient. Nearly all such cases represent treatment failures, though a small number, approximately 2 per cent, occur among newly discovered cases who have never received chemotherapy previously.

Among such patients it is imperative that pre-treatment sensitivity studies be started immediately, to determine which drugs should be used. While awaiting the results of drug susceptibility on a patient, a regimen is recommended consisting of isoniazid, 100 mg. t.i.d., streptomycin sulfate, one gram daily; and PAS, four grams t.i.d. Subsequent changes in this regimen will depend on the clinical progress of the patient and results of the susceptibility tests. It should be noted here that laboratory results indicating in vitro resistance to isoniazid do not necessarily mean clinical resistance. For this reason, we recommend that isoniazid be continued in any event until there is definite evidence of clinical resistance also. On the other hand, if in vitro, reports of the other drugs indicate moderate to severe resistance, further use of those drugs will not prove helpful.

Minor or secondary drugs presently available which may be helpful in the management of drug resistant cases are cycloserine, pyrazinamide, ethionamide, viomycin sulfate, and kanamycin sulfate. There is no cross resistance among these or with the major drugs. Though less effective and used less often than the major drugs, they play an important role in the treatment of drug resistant cases.

Cycloserine is a potent drug for tuberculosis, but may have undesirable side effects on the central nervous system when used in doses of one gram or more per day. Tremor, “nervousness,” convulsions, and even psychotic reactions may occur. Because of the potential toxic side reactions, it is usually best to use it in a dosage of ¼ gram three to four times daily, depending on the patient’s tolerance. However, in “salvage” cases when heroic measures are called for, it can sometimes be used to good advantage when given in large dosages, 25 to 30 mg. per kg. body weight, i.e., 1 to 2 gm. daily in three divided doses for the average adult. The toxicity, which is usually proportionate to the dosage, can often be controlled by the use of vitamin B6 in a high dosage (300 mg. daily). Tranquilizers and phenobarbital are also helpful. In our experience, the side reactions have been reversed by discontinuing the
cycloserine. This drug should be administered in the hospital.

Pyrazinamide (PZA), has a potent, though short-term effect in tuberculosis when used alone. The usual dosage for adults is 2 to 3 grams per day, divided into three doses. It should be used in combination with at least one other drug, and preferably two in most cases.

Ethionamide is the most recent addition to the antibacterial therapy of tuberculosis. It has a definite place in the treatment of patients with drug-resistant organisms. It, too, should be combined with one or two other drugs to which the organisms are sensitive. The longer the combined regimen can be continued, the higher the rate of sputum conversion to negative. Dosage varies from 0.5 to 1 gram daily, depending on the patient's tolerance. The most common toxic effects are anorexia and nausea. Mental depression and skin rash may also occur.

Viomycin is useful in some cases. The usual recommended dosage is 1 to 2 grams given twice weekly. When given daily, electrolyte imbalance, nephrotoxicity, and injury to the eighth cranial nerve may occur.

Kanamycin tends to cause ototoxicity and nephrotoxicity when given daily, hence the dosage should be limited to two or three times weekly to decrease this hazard. It should not be given to patients with renal insufficiency.

In the use of the secondary drugs, it is important to employ, concurrently, two or more drugs to which the organisms are sensitive. To use them one at a time is to dissipate their potential therapeutic effect. An aggressive approach is essential for best results. The dosage of each drug should be increased to patient's tolerance. Timid, halfway measures often end in failure. In many cases, surgical intervention is essential to recovery and the optimal time for surgery must be carefully determined. In truly "salvage" cases, heroic measures are not only justified; they are essential.

Adrenocorticosteroids, employed as a supplement to antibacterial therapy in the treatment of tuberculosis, remain controversial and not well defined. A perusal of the literature on this subject is apt to leave the inexperienced clinician in a state of confusion. Some reports advise the use of steroids frequently; other investigators believe they are seldom indicated. There is also difference of opinion regarding the optimal dosage and duration of the use of steroids.

However, in the desperately ill patient with acute, fulminating pulmonary tuberculosis, steroids used concurrently with adequate antibacterial therapy may be lifesaving. A daily dosage of prednisone, 20 to 30 mg. for three to four weeks, with gradual reduction in dosage for the next two to three weeks, before discontinuing, is the regimen we recommend for such cases. Steroids can also be helpful in avoiding or reducing complications in selected cases of tuberculous meningitis. In Addison's disease, due to tuberculosis, steroids are indicated. Steroids should be employed only in initial treatment cases in which the organisms can be presumed to be sensitive.

Perhaps the most encouraging trend in the tuberculosis picture is the increased emphasis on chemoprophylaxis.

The use of isoniazid among patients at "high risk" of developing active tuberculosis is gaining favor among public health officials and tuberculosis physicians. These high risk groups include the following: (1) infants and children under three years of age who have a positive tuberculin test without demonstrable evidence of active tuberculosis; (2) other persons, regardless of age, whose tuberculin test has become positive during the previous six months — the so called "recent converter;" (3) unstable or severe diabetics who are positive tuberculin reactors, since it is well known that tuberculosis develops three to four times as often among diabetics as in the general population; (4) patients with silicosis who have a positive tuberculin test; (5) patients with a positive tuberculin test who are receiving long-term steroid therapy for other diseases; and (6) patients
with a positive tuberculin reaction whose chest roentgenograms show evidence of latent or inactive tuberculosis.

This program of chemoprophylaxis, if vigorously pursued, may well have a significant effect in reducing the number of new active cases in the years to come. Further long term studies in this area should be encouraged.

Another facet in the changing picture of tuberculosis is the problem of pulmonary disease caused by the "unclassified" mycobacteria. This problem is attracting an increasing interest and concern among clinicians, bacteriologists, and epidemiologists.\(^\text{10,11}\) Such cases are being reported with greater frequency in the United States and elsewhere in the world, as clinicians have become more aware of the problem and hospital laboratories have become more alert and accurate in identifying these organisms.

Runyon has divided these unclassified mycobacteria into four groups: (1) Group I—the photochromogens (\(M. kansasii\)); (2) Group II—the scotochromogens; (3) Group III—the non-photochromogens (Battey bacillus); and (4) Group IV—the rapid growers.\(^\text{12}\) These groups are identical by cultural characteristics, biochemical tests, and animal inoculation.

Group II and Group IV organisms rarely cause disease in humans so do not constitute a public health problem. The Group I—photochromogens, and the Group III—Battey bacilli, account for the vast majority of cases due to the unclassified mycobacteria.

The epidemiology of these infections remains thus far obscure; nor have the natural sources of these organisms been determined. Person-to-person transmission of the disease has not been established. To our knowledge, no more than one case has been reported from the same family.

Group I infections are distributed rather widely throughout the United States, though most prevalent in Texas and the central states. Group III infections are found chiefly in the southeastern states.

Men are affected more often than women, in a ratio of about three to one. Middle-aged and elderly men with emphysema seem to be especially susceptible.

Pulmonary disease due to these organisms resembles true pulmonary tuberculosis in its roentgenography and pathology.\(^\text{13,14}\) Symptoms are also similar though less severe.

Accurate diagnosis of these cases is important if the best results with treatment are to be obtained. Due to drug resistance, chemotherapy is much less effective in the treatment of these infections than it is for true tuberculosis. The photochromogens, though somewhat drug-resistant, are nevertheless much more susceptible to antibacterial therapy than the Battey bacillus. In more than 160 cases of photochromogenic infection treated at our hospital during the past ten years, sputum conversion to negative status by culture occurred in approximately 80 per cent of the cases. This is more than three times the conversion rate obtained with chemotherapy among patients with disease due to Group III (Battey) strains.\(^\text{15}\)

Due to the relatively poor results obtained with chemotherapy, surgical resection is indicated much more frequently among these patients than among similar cases of true tuberculosis. At our hospital, during the past ten years, nearly one-third of the patients with Group I infections have received surgery in addition to antibacterial therapy. This is more than three times the rate of surgical intervention among our patients with true pulmonary tuberculosis during the same period.

Residual cavitary disease is the chief indication for surgery among these patients. In most cases, resection is the procedure of choice, though occasionally collapse by extrapleurosternal wax pack thoracoplasty is preferable among middle-aged and elderly patients with limited respiratory reserve. Despite the problem of drug-resistance among patients, the recovery rate with Group I infections who received surgery at
our hospital has been more than 90 per cent.

Public Health Aspects. Cases of pulmonary disease due to unclassified mycobacteria should be reported to the public health authorities, indicating the group or strain which is involved. With better reporting and improved investigative techniques, it is hoped that a better understanding of the epidemiology of these infections can be achieved.

In conclusion, it should be emphasized that the skill and understanding of the physician and full cooperation on the part of the patient are essential for recovery. Despite the wonder drugs and the marvels of modern surgery, tuberculosis remains a dangerous disease.

SUMMARY

Significant changes have developed in the treatment and control of tuberculosis during the past few years. This paper deals with these changes, including: (1) current concepts of proper management of newly discovered active cases; (2) management of the patient with drug-resistant organisms; (3) the role of adrenocortico-steroids in the treatment of tuberculosis; (4) the increasing emphasis and importance of chemoprophylaxis among patients at “high risk” of developing tuberculosis as a public health measure; and (5) the increasing problem of diagnosis and treatment of pulmonary disease caused by the “unclassified” mycobacteria.

Resumen

Durante los últimos años ha habido cambios de significación en el tratamiento y control de la tuberculosis. Este trabajo se refiere a ellos, incluyendo: (1) conceptos actuales del tratamiento adecuado de los nuevos casos descubiertos; (2) tratamiento del enfermo con bacilos drogaringentes; (3) el papel de los adrenocorticoides en el tratamiento de la tuberculosis; (4) el aumento de la importancia de la quimioprofilaxis entre los enfermos de “riesgo elevado” para desarrollar tuberculosis, como una medida de salubridad pública; (5) el creciente aumento del problema del diagnóstico y tratamiento de la enfermedad pulmonar causada por las micobacterias no clasificadas.

ZUSAMMENFASSUNG

Entscheidende Veränderungen in der Behandlung und Bekämpfung der Tuberkulose haben sich innerhalb der letztervergangenen Jahre entwickelt. Die vorgelegte Untersuchung beschäftigt sich mit diesen Veränderungen und umfaßt: (1) Die gegenwärtigen Auffassungen einer entsprechenden Behandlung neuentdeckter aktiver Fälle; (2) Behandlung der Patienten mit resistenten Keimen; (3) Die Rolle der Nebennieren-Hormone bei der Behandlung der Tuberkulose; (4) Die zunehmende Bedeutung und das Gewicht der Chemoprophylaxe bei Patienten, die als stark tuberkulosegefährdet angesehen werden müssen im Sinne einer Maßnahme des öffentlichen Gesundheitsdienstes; (5) Das zunehmende Problem der Erkennung und Behandlung von durch die unklassifizierten Mycobakterien verursachten Lungenkrankung.

REFERENCES

16 Unpublished data.

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PRIMARY PULMONARY CRYPTOCOCCOSIS

A case is presented of isolated pulmonary crypto-

coccosis in a 28-year-old man who was successfully treated by means of lobectomy. It is believed this is

the first case successfully treated by surgical inter-

vention in Japan.


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RADIOLOGIC FOLLOW UP OF ESOPHAGEAL HIATAL HERNIA

A series of 70 patients operated upon for hiatal hernia is presented; 55 were followed up an average of 7.6 years after the operation. Fifty-two were subjected to radiography which showed a satisfactory result in 31, while 18 had a recurrence of the hernia; in most of the latter, the hernia was smaller than before operation. Thirty-one patients were symptom-free at follow-up. These were not the same patients, as the correlation between subjective and objective findings was poor. It is concluded that the Allison operation for esophageal hiatal hernia is not the ideal treatment, but more than half the patients were symptom-free an average of 7.6 years after the operation.


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ACQUIRED ESOPHAGOBRONCHIAL FISTULA

Three cases of acquired esophagobronchial fistulas of infectious origin are reported. The etiologic agent was tuberculosis in one case and histoplasmosis probably in the other two cases. The pathogenesis of the esophagorespiratory tract communication in both tuberculosis and histoplasmosis is related to hilar lymph node involvement by the disease process. A carefully detailed history, roentgenologic examination of the esophagus and upper air passages, and endoscopy are most important in making a diagnosis and in planning therapy. Specific organisms may not be found at operation as the infection has usually passed its active stage. Diagnosis must, therefore, remain presumptive. Surgical treatment consists of isolation, division and closure of the fistulous tract and removal of any irreversibly damaged portion of the lung. The site of closure should be reinforced with a fascial or pleural flap.

Hutchin, P. and Lindskog, G. E.: "Acquired Esophago-


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TEN YEARS OF VACCINATION WITH BCG IN NAPLES

The results of ten years of work conducted by the Centre of Vaccination of the Tuberculosis Clinic of Naples covering kindergarten and elementary schools of Naples, as well as the children of bedridden consumptives at the Istituto Principi di Piemonte are presented. On the whole, approximately 20,000 subjects have been vaccinated with BCG from 1953 to 1962.

In 17,090 children vaccinated from 1953 to 1961, in a little less than 60 per cent of the cases, some direct followup has been carried on through photo-

fluorography, while in 26.9 per cent of the cases, the subjects have been controlled indirectly through domiciliary visits; only 14.5 per cent of the vac-
cinated group has not been followed.

In the vaccinated, eight cases of tuberculosis have been found, of which only one was of evolutive type in a young girl who had refused the revaccination.

The research carried out at the General Register Office of the Commune of Naples has permitted us to establish that in the ten years, among the vac-
cinated, 21 children have died, but none of them of tuberculosis. Of the unvaccinated subjects, three died of tuberculous meningitis.