Massive Intravenous Therapy as Initial Treatment in Tuberculosis

John P. Mihaly, M.D., F.C.C.P., Edward L. Mais, M.D., Samuel S. Paley, M.D., Simon Schwarz, M.D., Bennett W. Billow, M.D., and Belardino Lupini, M.D.

New York, New York

Conventional chemotherapy of tuberculosis has been adapted to the chronicity of the disease and adjusted to the provocative limitation of effective drugs. High dosage schedules pose the peril of drug toxicity, notorious with all antituberculosis therapeutic agents; low dosages bear the hazard of sublethal antimicrobial tissue concentrations and acceleration of bacillary resistance. Psychologically, the need for prolonged therapy may conflict with patient cooperation. Economically, the cost of months of therapy compounded with patient disability is a serious factor in depressed areas. Medically, adequate suppression is not optimal control. A reappraisal of the major antimicrobial approach now considered orthodox is of practical import.

The eighth cranial nerve toxicity of streptomycin and its derivatives is axiomatic. Dihydrostreptomycin has now fallen into total if not entirely deserved disrepute following the observations of Shambaugh et al. Streptomycin, however, is also not ideal from the toxicologic standpoint. This is particularly true in ambulatory patients, whose serum streptomycin levels catapult in comparison with resting subjects and are accompanied by a variety of untoward clinical symptoms, as shown by Riches.

Poised against toxicity is the question of adequacy of the so-called intermittent regime of treatment by streptomycin or its derivatives. As early as 1953 the British Medical Research Council demonstrated the superiority of daily over biweekly streptomycin injections as proper initial treatment least likely to result in bacterial resistance and clinical relapse. This thesis has been re-emphasized by Saliba et al. In the light of this, intermittent treatment as optional initial treatment is hardly tenable.

Oral PAS, whether in free form or as sodium, potassium, or calcium salts, is a notorious irritant of the upper alimentary mucosa and is automatically proscribed in patients with gastroduodenal lesions. Besides this, its tissue concentration necessarily fluctuates; after oral ingestion, therapeutic levels can be sustained no longer than four hours. Unless it can be administered around the clock, which is not practical in a chronic disease, serum PAS concentration falls to an ineffectual nadir during sleeping hours. A great stride forward in the solution of this problem has been made by the production of sustained action PAS tablets.

INH presents problems both of neurotoxicity and excessively rapid metabolic conversion to derivatives having little or no antimicrobial activity. Neurotoxicity can be in large part countered by appropriate doses of pyridoxin. Its metabolic conjugation, however, cannot be controlled in patients who are rapid inactivators by any known means, as it is presently administered.

Quite apart from the intrinsic deficiencies of the three major antituberculosis agents, there is always the lurking possibility that uninstitutionalized patients may be taking insufficient or no oral medication at all.

In a pioneering departure from established orthodox routine, Herzog and his associates were the first to introduce the concept and devise a technique to insure maximum tissue saturation by a constant intravenous drip of the three major antituberculosis agents. This method prevented undesirably high blood peaks of the streptomycin derivative used, dihydrostreptomycin tripantothenate, and produced excellent clinical results in 99 patients so treated. We adopted the original Herzog technique with some modifications.

*From the Department of Medicine, Harlem Hospital, Department of Hospitals, City of New York, Samuel S. Paley, Director of Medicine.
and have treated 42 patients in this manner since March, 1958. Our practical results have been consistent with the sound theoretical basis on which this type of therapy rests.

**METHODS**

The actual mechanics of massive intravenous therapy as the initial modality in the treatment of all forms of tuberculosis is simple and adaptable for home as well as for hospital use. The only prerequisite is the preparation of a sterile kit containing all the necessary equipment to be used.

Through a 14 or 15 gauge cannula inserted into an appropriate sized superficial vein on the dorsum of the hand or anywhere in the forearm, a size 442 T polyethylene catheter is introduced as far as possible up the brachial venous system. Optimal results are obtained if the tip of the catheter reaches the deltoid area. Under no circumstances, however, should the tip of the catheter be allowed to rest permanently in the antecubital fossa, since this will inevitably cause venous irritation and thrombosis. A fluoroscopic or radiographic check may be made on the precise location of the catheter tip, but this can be accurately estimated from the length of the catheter introduced. After the catheter is in situ, it is connected to a standard infusion set by a 24 gauge needle. The infusion flask is attached to a special aluminum stand on casters. The patient is entirely ambulatory, moves the stand with himself as a full range of arm movements is retained, and poses no nursing problems.

Solutions of the following composition are prepared daily. In one liter of physiologic sodium chloride, distilled water, or 5 per cent glucose in water are dissolved: (1) one or two grams of dihydrostreptomycin panthothenate (Didrothenate); (2) 12 grams of parenteral PAS (Parasal sodium lyophilized or Pasalon); (3) 5 to 10 mg. per kg. body weight of parenteral INH; and (4) 100 mg. of heparin sodium, with such adjustments of the heparin as are necessary to keep the coagulation time below eight minutes by the Lee and White method. In cases of salt retention or where corticosteroids are used concurrently, the solvent should, of course, not be solution of sodium chloride. Parenteral watersoluble vitamins, including pyridoxin, may be incorporated in this medium if desired.

The flow rate of the drip is adjusted so that it continues for a full 24 hour period. This rate has been found to be approximately 14 drops per minute. After the infusion is completed, it is replaced by a flask of identical composition. This process is continued

**FIGURE 1**

**FIGURE 1**: J.M., 14-year-old girl. Initial roentgenogram on March 25, 1958, reveals moderately advanced bilateral pulmonary tuberculosis. Follow-up roentgenogram on July 22, 1958, about four months after therapy, shows barely perceptible lesions in the right apex and in the periphery of the left second anterior interspace.
for a target duration of six weeks, following which the patient is placed on one gram of Didrothenate intramuscularly three times weekly, 300 mg. of oral INH daily, and 12 grams of oral PAS daily, preferably the sustained action type.

As a supplementary anticoagulant measure to prevent venous thrombosis we originally administered buccal streptokinase-streptodornase (buccal Varidase) four times daily. We have since observed that better results are obtained by giving 10 mg. of warfarin (Coumadin) daily with such adjustments in dosage as are necessary to maintain the prothrombin time at about 20 seconds.

Certain hazards are inherent in and definite precautions must be taken in this form of therapy. These may be divided into (1) thrombosis of the catheterized vein, (2) PAS decomposition, and (3) hemorrhagic diathesis.

In order to minimize initial venous irritation, the catheter must not be manipulated in an excessively to and fro movement when originally introduced. This causes polyethylene fibrils to break off and produce undue intimal irritation. If an unyielding obstruction is met in introducing the catheter, it should be completely removed and reinserted into another vein.

If thrombophlebitis does begin to form during the course of treatment, this will almost always be at the catheter tip site and is usually heralded by premonitory pain at this site. In most cases thrombophlebitis can be aborted by withdrawing the catheter an inch or two and applying concentrated ichthylol over the overlying skin. If thrombosis has formed, as indicated by cessation of infusion flow, the catheter should be completely withdrawn and reinserted into another vein. In cases where thrombosis has formed more than twice, it is advisable to abandon the intravenous drip completely. It should never be started in subjects with histories of proclivity to thromboembolism.

Solutions for the infusions must be prepared daily. Parenteral solutions of PAS rapidly form toxic oxidation and reduction products. Such a decomposition is augured by a brownish discoloration of the normally transparent solution. This reaction will usually not occur within 24 hours, but if any color change of the solution is noted at any time, it should be discarded promptly and a new one prepared.

Any history of a hemorrhagic diathesis should rule out this type of therapy because of the anticoagulants used, however small the doses. Even a suspicion of such a diathesis demands careful clinical and laboratory observation.

**Results of Study**

For the 30-month period from March, 1958 to September, 1960, we started treatment on a total of 54 patients by the type of therapy outlined above. In three, therapy was abandoned because of repeated thrombosis and in nine because of failure to obtain complete patient cooperation. In the remaining 42 patients treatment was continued to a successful conclusion. Ages of successfully treated patients ranged from 13 months (one case) to 70 years (one case), the majority of patients being in their fourth and fifth decades. There were 32 men and ten women. There were five cases of miliary and meningeal tuberculosis, one of renal tuberculosis, and 36 of pulmonary tuberculosis. Of the latter, 32 were far advanced, two moderately advanced, and two minimal cases. One case of meningitis was complicated by and evidently originated from tuberculosis of the right greater trochanter with a cold abscess of the hip. Three cases of pulmonary tuberculosis were complicated by diabetes, two by hypertensive arteriosclerotic heart disease, and one by idiopathic epilepsy. The diagnosis in all 42 patients was proved by the recovery of tubercle bacilli from sputum, gastric washings, spinal fluid, or urine. The duration of treatment ranged from five weeks (in three cases) to nine weeks (in one case), the median being 46 days.

Originally, only cases with apparently hopeless prognoses were chosen. This consideration did not stem from any fear of the hazards of this type of therapy but from a desire to test it under a real baptism of fire.
Once the results became apparent, the indications were extended to include less severe cases.

Without exception, there was complete clinical remission with defervescence within 14 days after the start of therapy. Sputum, spinal fluid, and urine conversion was achieved within the same period, and with the exception of two pulmonary cases, these body fluids have remained negative on smear and culture ever since. One of the two patients was a poorly controlled diabetic subjected to intense physical and emotional strain. She was eventually controlled by retreatment and resectional surgery. The other patient showed only one bacteriologic escape of three colonies on gastric culture, which has never recurred.

The rapidity of radiologic clearing in the pulmonary cases was directly proportional to the nature and extent of the involvement. Miliary cases cleared in an average of two months. One case of minimal tuberculosis resolved so completely that no pulmonary lesion whatsoever was discernible at the end of the six week period. The other minimal case and the two cases of moderately advanced tuberculosis regressed to the point of faintly detectable residua (Fig. 1). In the far advanced cases there was astounding radiographic clearing of the exudative elements within a few weeks after the start of therapy (Fig. 2).

In about 25 per cent of far advanced pulmonary cases a curious phenomenon was observed. Within two or three weeks after the start of massive intravenous therapy the radiologic picture distinctly worsened. Originally our impression was that this could represent pulmonary infarction secondary to emboli from the catheterized vein, but continued experience vitiated this assumption. We therefore elaborated and still entertain the hypothesis that this manifestation indicated either a Herxheimer-type of reaction or an allergic tissue response to massive amounts of proteins released by the lysis of bacterial myriads. In consonance with this thought, we treated these patients with prednisone and corticotropin with very beneficial local and systemic effects. The former was given in doses of 10 mg. three times daily for five days, then 5 mg. twice daily for two weeks longer. Thereafter, 40 units of corticotropin were administered daily for three days. With this regime the strange new shadows cleared within four weeks and never reappeared.

In the meningeal cases, spinal fluid glucose and chlorides rose to normal levels in three weeks, and spinal fluid proteins declined to a normal titer in an average of six weeks. In the case of meningitis complicated by bone and soft tissue tuberculosis, there was complete healing with full preservation.

**Figure 2**

C.G., 36-year-old man. Initial roentgenogram on June 22, 1958, discloses almost complete opacity of the upper half of the left lung field. Scattered lesions are also present throughout the right lung field. Second roentgenogram on July 3, 1958, 11 days after intravenous therapy was begun, reveals marked resolution in the left upper lung field. The right lung field appears entirely clear.
of hip function. The case of renal tuberculosis manifested a moderate hematuria during the course of therapy. This subsided when treatment was temporarily discontinued. It was not clear whether it was due to his renal lesion or to anticoagulants. It did not recur after the resumption of treatment, however, and his course was otherwise satisfactory. Follow-up studies revealed a deformity of the right renal pelvis, spotty calcification in the renal parenchyma, and partial stenosis of the right ureter due to granulations.

Hospitalization in this series of patients ranged from two to six, with an average of three months. Only two patients required institutional care longer than six months, but for reasons other than tuberculosis. Similarly, the infant in this series was rehospitalized for custodial care because of extremely adverse home conditions. After discharge from the hospital, the patients were referred to the outpatient department for a regimen of treatment already described. In all these patients the total therapy time, including treatment received in the hospital, did not exceed one year.

Of the 42 patients successfully treated, five died of unrelated causes and three are being followed by facilities other than our own, from where continued stability of the tuberculous lesions is reported. Nine patients have been lost to follow-up after the first year, and 25 are being observed by our outpatient department, all having been returned to gainful employment or the full responsibilities of homemaking and being in no further need of any antimicrobial therapy.

**DISCUSSION**

The phenomenal efficacy of massive intravenous antituberculosis therapy as initial treatment probably depends primarily on sustained optimal serum and tissue levels of the three antituberculosis agents used. Bathed in an unfluctuating lethal milieu, the tubercle bacillus evidently has little respite to develop any degree of resistance. On the other hand, the blood levels of the three agents used never rise to peaks toxic to the host.

Didrothenate, the streptomycin derivative employed in this series, is not yet available for commercial use in the United States. There is ample evidence that pantothenic acid acts as a detoxifying moiety with the basic streptomycines antibiotics. Keller et al, have done much excellent investigative work. confirmed by others, in this field. They conclude that the pantothenates of the basic streptomycines antibiotics are less toxic than the sulfates in acute experiments since they reduce the calcium-binding ability of the antibiotics, and less toxic in chronic experiments by becoming a protective factor to the ectoderm, especially the vestibule and cochlea. In this hospital we have demonstrated in a previous study that didrothenate is superior to both streptomycin and dihydrostreptomycin sulfate in the treatment of pulmonary tuberculosis. La Caille and Prigot also showed that there was lesser toxicity, lower morbidity, and greater micro-organism susceptibility to Didrothenate than to streptomycin sulfate in soft tissue infections.

Sustained blood levels of PAS and INH are no less urgent than those of streptomycin. The constant intravenous drip of administration obviously insures an adequate 24-hour level of the former. Moreover, distressing gastroduodenal symptoms are circumvented, which is especially important in the malnourished, cachectic, and critically ill patients so commonly admitted to this hospital. Finally, PAS administered by the intravenous route mobilizes the pituitary-adrenal axis. Favez et al. have clearly demonstrated the marked corticotropin-releasing effects of intravenous perfusions of PAS as compared with slight or absent amounts liberated by oral administration. The anti-inflammatory action of this effect in the presence of adequate antimicrobial coverage is approbatory.

While the metabolic destruction of INH is unpredictable in any given subject and unremediable in some patients even with neurotoxic doses orally, it has never, to our knowledge, been established how rapidly this conjugation occurs in man according to different routes of administration. It is reasonable to assume, however, that if tissues are constantly saturated by INH as they are in this form of therapy, this therapeutically unde-
sirable chemical conjugation must be decelerated because of a constant supply of substrate. A stabilizing chemical interaction also occurs between INH and the streptomycins. Berczeller and Frank have demonstrated that INH is a potent stabilizer of both streptomycin and dihydrostreptomycin.14

A bactericidally augmenting reaction occurs also between streptomycin and heparin. Dolowitz has described remarkable results upon combining heparin with several antibiotics, including streptomycin.15 He postulates that heparin acts as a biologic repository diminishing drug toxicity and allowing sufficiently high blood levels of the several antibiotics he studied for long enough periods to control infection. Although we employ heparin for its anticoagulant properties and its solvent concentration is only 0.1 per cent as compared with the concentration of 1 per cent used by Dolowitz, it nevertheless may be exerting a significant antimicrobial effect in our mode of therapy.

Turning from biochemical foundations to practical clinical results, initial intravenous therapy of tuberculosis has reduced hospitalization to an average of three months and the total therapy time to one year, even in patients with far advanced, fulminating, miliary, and meningal tuberculosis. There is little doubt that it has been life-saving. Considering the type of case constituting the majority of patients in this series, the relapse rate has been remarkably low. In an average of six months, most patients were returned to employment or homemaking, and in 12 months: all were. Not unimportant has been zealous patient acceptance of this type of therapy. Seeing the dramatic clinical results and early discharge of patients receiving intravenous therapy, patients on conventional therapy often clamored for the "bottle treatment."

Aside from the complication of thrombophlebitis, there have been no others, such as secondary infection due to intravenous catheterization, nor was any clinical manifestation of eighth cranial nerve damage observed. This was confirmed in five patients by audiometric studies.

Projecting our statistically limited experience to other forms of tuberculosis, intravenous therapy may be reasonably expected to be of great value in renal and orthopedic foci. In early minimal pulmonary cases there is every reason to believe that clearing will be so complete that not only will permanent cure be obtained, but the stigma of residual pulmonary scars in subsequent radiograms throughout life will be avoided. The sociologic implications of this possibility hardly need emphasis.

In regions of the world where tuberculosis still finds little therapeutic challenge, initial intravenous therapy for six weeks and a total treatment time of one year should be able to suppress infectiousness rapidly and be more likely acceptable to shifting and displaced peoples than more prolonged courses of treatment. Closely related is the fact that in such areas extirpative surgery of residual cavitary lesions will fail to make any great quantitative impression for decades to come. Under such conditions, pneumothorax and pneumoperitonium, though now considered obsolete, can probably serve a useful interim purpose. It obviously requires far less skill and equipment to initiate and maintain effectual therapeutic pulmonary collapse than to perform resectional surgery. Moreover, collapse therapy in conjunction with the rapid sterilization of pulmonary cavities attainable by initial massive intravenous therapy can be anticipated to be signally effective. If thick-walled, infected, and necrotic cavities were in so many instances effectively closed by collapse therapy in the pre-antimicrobial era, certainly much better results can be expected with thin-walled sterilized cavities. We hope to test this hypothesis in the very near future in studies outside the United States.

**Summary**

To solve the many problems of conventional antituberculosis therapy, we adopted, after Herzog's method, a technique of initial intravenous treatment. Through a catheter in a brachial vein we administer a constant intravenous drip of a dihydrostreptomycin pantothenate-PAS-INH-heparin mixture for
a six-week period. Precautions are taken against thrombosis, PAS decomposition, and hemorrhagic diathesis. There are no other hazards. Forty-two patients have been successfully treated by this method since 1958 with clinical and bacteriologic remission within two weeks. Hospitalization was reduced to three months and total therapy time to one year. The efficacy of this treatment depends on sustained optimal tissue levels of the three antimicrobials used and probably on a stabilizing interplay among the antimicrobials and heparin. This type of treatment should be especially suitable in high incidence tuberculosis areas and could possibly be combined with collapse therapy in cavity disease where resectional facilities are limited.

**ZUSAMMENFASSUNG**


**REFERENCES**

MASSIVE INTRAVENOUS THERAPY IN TUBERCULOSIS


BRONCHIAL ANOMALIES IN CHILDREN

Out of 1159 bronchographies made simultaneously with bronchoscopies in children, bronchial anomalies were found in 24 cases. Most frequent were separate branching of the subsegmental branchus of the segment 3 branching from the upper wall of the right medial lobe was the rarest encountered anomaly.


IMMUNOPATHOLOGIC STUDIES IN DIVERSE CARDIOPATHIES

Kozma and Drayer studied 80 instances with different inflammatory and degenerative cardiopathies using the reaction of diffusion-precipitation-gel, with a purified antigen of a normal human heart extract, for investigation on the presence of cardiac circulatory antibodies. Positive reactions vs. heart extract were demonstrated in all cases with clinical evidence of an active myocardial process, infarcts, chronic myocarditis, cardioangiosclerosis and rheumatic cardiopathies. With these results, they advance the hypothesis that antibodies are a factor in the pathogenesis of chronic inflammatory process.