IVth National Tuberculosis Conference

Peamount Hospital
7th & 8th May 1992
Dear Doctor,

First of all we would like to take this opportunity to welcome you to the IVth National Tuberculosis Conference to be held at Peamount Hospital. The intention of the conference is to provide a broad-based teaching experience in tuberculosis. We hope for lively discussion and exchange of views and experiences.

In this course manual there are several articles which are reproduced with permission of the Editors of the journals in which they were first published. We extend to all the Editors our thanks for their permission to reproduce these articles and to use them to further education and knowledge of tuberculosis.

We would like to take this opportunity to thank all those who contributed to producing the book and those who have agreed to speak and participate in the meeting.

Yours sincerely,

Paul Kelly, MA, DCH, MD, MRCPI

Luke Clancy, FRCPE, FRCPI, FCCP
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Recommended Reading List on Tuberculosis

1. IS BOVINE, ATYPICAL OR RESISTANT TUBERCULOSIS A PROBLEM? 
   C. Collins, P. Kelly, C. Byrne, F. Denham, L. Clancy 

2. MORTALITY FROM TUBERCULOSIS; A CAUSE FOR CONCERN 
   F. Howell, R. O’Laoide, P. Kelly, P. Salmon, L. Clancy 
   I.M.J. 1987; 80: 205-206

3. NATIONAL TUBERCULOSIS SURVEY (1986) 
   J. Stinson, P. Kelly, F. Howell, L. Clancy 
   I.M.J. 1988; 7-10

4. SHORT COURSE CHEMOTHERAPY FOR PULMONARY TUBERCULOSIS
   A RANDOMISED CONTROLLED TRIAL OF A SIX MONTH VERSUS A 
   NINE MONTH ORAL REGIMEN 
   I.M.J. 1989; 82: 11-13

5. PULMONARY TUBERCULOSIS IN THE REPUBLIC OF IRELAND: AN 
   EPIDEMIOLOGICAL PROFILE FROM A SINGLE UNIT 
   F. Howell, P. Kelly, L. Clancy 
   Respir Med 1990; 84: 111-117

6. DETECTION OF IgG AND IgA ANTIBODIES TO PDD IN TUBERCULOSIS 
   S. Browne, A. Murray, A. Whelan, P. Kelly, L. Clancy, 
   C. Feighery 

7. ISONIAZID RESISTANT TUBERCULOSIS IN A SCHOOL OUTBREAK: THE 
   PROTECTIVE EFFECT OF BCG 
   A. Shannon, P. Kelly, M. Lucey, M. Cooney, P. Corcoran, 
   L. Clancy 

8. A SCHOOL MICROEPIDEMIC OF TUBERCULOSIS 
   C.P. Reddin, M. Godfrey, J. McKiernan 
   Thorax, 1991; 46: 922-923
9. **INFECTIOUSNESS OF TUBERCULOSIS**
   L. Clancy
   Bull IUATLD, 1990; 65: 70

10. **THE PATHOGENICITY OF MYCOBACTERIUM TUBERCULOSIS DURING CHEMOTHERAPY**
    L.J. Clancy, P. Kelly, L. O'Reilly, C. Byrne, E. Costello
    Eur Respir J, 1990; 3: 399-402

11. **TUBERCULOSIS ELIMINATION IN THE COUNTRIES OF EUROPE AND OTHER INDUSTRIALIZED COUNTRIES**
    L. Clancy, H. Rieder, D.A. Enarson, S. Spinaci for International Union Against Tuberculosis and Lung Disease and World Health Organisation
    Eur Respir J, 1991; 4: 1288-1295

12. **CASE-FINDING IN THE ELIMINATION PHASE OF TUBERCULOSIS: TUBERCULOSIS IN DISPLACED PEOPLE**
    D.A. Enarson, J.S. Wang, S. Grzybowski
    Bull IUATLD, 1990; 65: 71-72

13. **BCG VACCINATION**
    Bull IUATLD, 1990; 65: 30-37
    - Human leucocyte antigens (HLA) and mycobacterial disease
      R. de Vries
    - Old BCG coming to an end - a new vaccine coming too late for Europe?
      P.E.M. Fine
    - Experience in Sweden 15 years after stopping general BCG vaccination at birth
      V. Romanus
    - Project on discontinuation of BCG vaccination in newborns in Czechoslovakia

14. **BCG VACCINATION AND HIV INFECTION**
    H.G. ten Dam
    Bull IUATLD, 1990; 65: 38-39

15. **AIDS, IV DRUG USE AND MYCOBACTERIAL DISEASE: THE DUBLIN EXPERIENCE**
    E. Healy, P. Kelly, F. Mulcahy, L. Clancy
    Respir Med - In Print
16. GLOBAL PROGRAMME ON AIDS AND TUBERCULOSIS PROGRAMME - STATEMENT ON AIDS AND TUBERCULOSIS

17. TUBERCULOSIS AND THE ACQUIRED IMMUNE DEFICIENCY SYNDROME
F. Festenstein and J.M. Grange
J Applied Bacteriology, 1991; 71: 19-30

18. TUBERCULOSIS AND HUMAN IMMUNODEFICIENCY VIRUS INFECTION IN DEVELOPING COUNTRIES
A.D. Harries
Lancet, 1990; 335: 387-390

19. AN ESTIMATE OF THE FUTURE SIZE OF THE TUBERCULOSIS PROBLEM IN SUB-SAHARAN AFRICA RESULTING FROM HIV INFECTION
M. Schulzer, J.M. Fitzgerald, D.A. Emerson, S. Grzybowski
Tubercle and Lung Disease, 1992; 73: 52-58

20. SHOULD PULMONARY TUBERCULOSIS BE AN AIDS-DEFINING DIAGNOSIS IN PATIENTS INFECTED WITH HIV
C. Perronne, A. Ghoubontni, C. Leport, D. Salmon-Ceron, F. Bricaire, J.L. Vilde
Tubercle and Lung Disease, 1992; 73: 39-44

21. AN OUTBREAK OF TUBERCULOSIS WITH ACCELERATED PROGRESSION AMONG PERSONS INFECTED WITH THE HUMAN IMMUNODEFICIENCY VIRUS
C. L. Daley, P. M. Small, G.F. Schecter, G. K. Schoolnik, R.A. McAdam, W.R. Jacobs, P. C. Hopewell
N.E.J.M., 1992; 326: 231-235

22. NOSOCOMIAL EPIDEMIC OF ACTIVE TUBERCULOSIS AMONG HIV-INFECTED PATIENTS
G. Di Perri, M.C. Danzi, G. De Checchi, S. Pizzighella, M. Solbiati, M. Cruciani, R. Luzzati, M. Malena, R. Mazzì, E. Concia, D. Bassetti
TUBERCULOSIS - A HISTORICAL NOTE

Dr. Paul Kelly
Dr. Fenton Howell
It has been estimated by the World Health Organisation that almost one half of the world's population has been infected with the tubercle bacillus. Some 3.5 million new cases are registered a year and one third of these patients will die. An active (smear positive) case of tuberculosis would infect up to 40% of susceptible contacts and 10% of contacts will develop active disease.

So how old is this disease known as tuberculosis (the white death or in Irish "Noirin Ban")? The earliest reference is in the Chinese medical work Huang Ti Nei-Ching which was written almost 5000 years ago. Analysis and study of archaeological remains shows evidence of bone tuberculosis in the Chang Dynasty in China (1650-1027 BC), in 3000 year old mummies from Egypt and in neolithic remains in Europe.

Without definitive diagnosis we rely on historical descriptions compatible with tuberculosis. Herodotus (485-425 BC) describes symptom complexes consistent with tuberculosis and Pliny The Elder who died in the eruption of Vesuvius at Pompeii in 79 AD had sought a cure for tuberculosis in Egypt. While it was in relatively modern times that the transmission of TB by expectoration was proven Hippocrates (460-377 BC) suggested this mode of transmission. The term "tubercula" was coined by Sylvius Deleho (1614-1672) to describe nodular formations seen during an autopsy examination; and Richard Morton (1637-1698) described 16 different forms of TB but it was not until 1832 that Shonlein coined the term tuberculosis.
In March, 1882 at a Saturday night meeting of the Berlin Physiological Institute Robert Koch demonstrated Koch's bacillus and showed for the first time that it was the cause of the disease known as tuberculosis. According to eye witness accounts of the meeting after Dr. Koch's finished his paper it was greeted with a shocked, stunned silence. To understand the impact of his findings on tuberculosis and medical science one could imagine the impact of announcing the definitive solution to AIDS or cancer at a weekend seminar in one of the Royal Colleges. Koch was awarded the Nobel Prize in 1905 for his work.

Armed with classical and contemporary descriptions and categorisation of tuberculosis, Koch's demonstration of the aetiological role of the tubercle bacillus in the disease, medical science set out to look for a scientific cure for TB. Prior to the development of effective chemotherapy in the early 1950s many other modalities of therapy were tried. Sanatorium treatment, high altitude sanatorium treatment, rest cures, occupational therapy, artificial pneumothorax and pneumoperitoneum, all had their advocates. Infusions of various roots and herbs (ginseng, caraway, cardamon, violets, opium, arsenic) were advocated in China whereas in ancient Greece physicians advocated baths with luke warm water and hot ablutions. Treatments based on red wine, white wine, honey, milk, figs, mint, lily seeds, turpentine, sodium carbonate, copper, all had their advocates in classical and later times. An ancient Jewish remedy was to "take six handfuls of chopped mangold, seven handfuls of chopped leek, five handfuls of jujubes, three handfuls
of lentils, a handful of carroway, a handful of chabla and stuff it in a sausage skin taken from a first horn animal, eat and then wash down with strong beer". Inhalations of antiseptic substances such as creosote, trypan red and trypan blue and even gold and copper compounds were tried unsuccessfully. The modern era of chemotherapy can be dated from the development of Streptomycin, first used by Waksman in the University of New Brunswick in 1943. Isoniazid was introduced a few years later, even though the chemical Isoniazid had been isolated as early as 1912 but had never been used in medicine.

In the context of Ireland there is evidence to suggest that tuberculosis was not a widespread problem until perhaps the middle ages, i.e. some 3000 years after its appearance in classical civilisations. It has been suggested that this late advent of tuberculosis, in historical terms, in Ireland is one reason why there is a relatively high rate of tuberculosis in Ireland and why many believe that as a nation we are more susceptible to disease. The suggestion is that if a population is exposed to an illness which is fatal that the population, through natural selection, will develop a degree of immunity to that disease. The best example of this is the relationship between sickle cell anaemia and malaria in Africa. The suggestion is that as we are relative late-comers to the world pandemic of TB that we had not time to develop any herd or population resistance, through natural selection and hence had a relatively high
degree of susceptibility to this disease with the development of
urbanisation during the Industrial Revolution and other social changes
which took place in the late 18th and 19th centuries. In effect we
had a "virgin population" in terms of tuberculosis, with little or no
inherited protection against this disease, suddenly moved off the land
into crowded disadvantaged poor urban conditions and this led to the
explosive epidemic of TB seen in Ireland in the 19th and 20th
centuries.

We still have a relatively high incidence of tuberculosis and a high
mortality but the reasons are unclear. It cannot be explained by
large numbers of immigrants from Third World countries, as is the case
in most of our European neighbours.
TREATMENT FOR TUBERCULOSIS - AN OUTLINE

Dr. P. Kelly

Dr. L. Clancy
It is over three decades since it was shown conclusively that an appropriate combination of drugs would give complete cure of the disease provided treatment was continued for long enough and that there was good patient compliance. Examples of these early regimes are shown in Figure 1.

**FIGURE 1**

<table>
<thead>
<tr>
<th>(a)</th>
<th>Streptomycin (S)</th>
<th>P : H daily</th>
<th>P.A.S. (P)</th>
<th>For 12 weeks</th>
<th>or</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Isoniazid (H)</td>
<td></td>
<td></td>
<td>S : H twice weekly</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(b)</th>
<th>Streptomycin (S)</th>
<th>T : H daily</th>
<th>Thiacetzone (T)</th>
<th>For 12 weeks</th>
<th>or</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Isoniazid (H)</td>
<td></td>
<td></td>
<td>S : H twice weekly</td>
<td></td>
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</table>

In these earlier "standard" regimes treatment needed to continue for up to 18 months to eradicate the organism. Later on it was shown that Ethambutol could be used instead of P.A.S. or Thiacetzone as a companion drug to Streptomycin and Isoniazid in both phases of treatment, and with the availability of Rifampicin an entirely oral regime of shorter duration became possible.
In the early prolonged chemotherapeutic regimens drug combinations were selected with a view to preventing emergence of drug resistance. However, in "short course chemotherapy" the object is to select drug combinations that are rapidly sterilising. It is essential, especially in patients with large bacterial population, to stop bacterial multiplication and thus to bring the disease under control rapidly. The drugs most commonly used in short course chemotherapy are:- Isoniazid (H), Rifampicin (R), Streptomycin (S), Ethambutol (E), and Pyrazinamide (Z). Ethambutol probably contributes little to the efficacy of these regimes, and its principle role is probably to prevent the emergence of drug resistance.

It has been shown that mycobacteria exist in four sub-populations within a patient and that different drugs are optimally effective against different sub populations.
FIGURE 3

SUB-POPULATIONS OF MYCOBACTERIA

High rate of bacterial growth:

A. Continuous Growth:
   e.g. cavity walls
   (Alkaline environment)
   Isoniazid
   Rifampicin
   Streptomycin

B. Acid Environment:
   e.g. within cells/phagocytes
   Pyrazinamide

C. Spurts of Metabolism:
   Rifampicin

D. Dormant:
   ? die off gradually
   Low rate of bacterial growth
Isoniazid is a less effective sterilising agent than Rifampicin or Pyrazinamide, but because of its low toxicity, efficacy, and low cost, it remains the sheet anchor of therapy. Because relapse may occur from bacteria in sub populations A & C, Rifampicin and Pyrazinamide emerge as the most effective sterilising agents.

It should be pointed out that anti-tuberculosis drugs, like all antimicrobial agents, are most effective when the organism is actively metabolising and dividing. When inactive the organism may persist even in the presence of effective drugs. These "persisters" can produce relapse when they do eventually begin to divide and metabolise.

Thus, there are two parts to the eradication of mycobacteria, as follows:

1. **Initial Phase:**
   Early killing of actively metabolising and dividing organisms.

2. **Continuation Phase:**
   Sterilisation of all slowly metabolising organisms.
The standard short course chemotherapy regimen of Rifampicin and Isoniazid with either Ethambutol or Streptomycin for two months, followed by Rifampicin and Isoniazid alone for a total of nine months, has been shown to be "100% effective" with almost no relapses. However, it has now been shown that an initial four drug regimen of Rifampicin, Isoniazid, Ethambutol and Pyrazinamide for two months, followed by Rifampicin and Isoniazid for a total of six months, is equally effective.

Recently the International Union Against Tuberculosis and Lung Disease recommended a standard treatment regimen of Rifampicin, Isoniazid and Pyrazinamide for two months followed by Rifampicin and Isoniazid for four months as standard treatment for all forms of tuberculosis. In studies at Peamount we have shown that this regimen is equally effective with the standard four drug, six month regimen and that patients become consistently culture negative earlier than with the four drug regimen.
FIGURE 4

Short Course Regimen  
(Bacteriological relapse rate 2%)

<table>
<thead>
<tr>
<th>Initial Phase</th>
<th>Continuation Phase</th>
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<tr>
<td>+ 2 E H R Z</td>
<td>4 H.R.</td>
</tr>
<tr>
<td>+ 2 S H R Z</td>
<td>4 H.R.</td>
</tr>
<tr>
<td>+ 2 S H R Z</td>
<td>4 H.R.Z.</td>
</tr>
<tr>
<td>+ 2 S H R Z</td>
<td>H R</td>
</tr>
<tr>
<td>+ 2 H Z R</td>
<td>2 2 H R</td>
</tr>
<tr>
<td></td>
<td>3 3</td>
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</tbody>
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Nine Months

| * 2 E H R   | 7 H.R. |
| 2 S H R     | 7 H.R. |
| 2 - 4 E H R | 7 H.E. |

Figures preceding symbols e.g. 2 E H R indicate duration in months of initial phase.

Small figures below line e.g. H R indicate that H and R are given twice weekly.

R = Rifampicin  
H = Isoniazid  
S = Streptomycin  
Z = Pyrazinamide

* Standard nine months regimen
+ Six months regimen.
THE ADVANTAGES OF SHORT COURSE CHEMOTHERAPY ARE

1. Reduced total quantity of drugs which may reduce cost.

2. Perhaps better compliance and less patients defaulting.

3. Shortened period of supervision and thus savings in terms of money, personnel, etc.

4. Because of the initial killing phase patients are less likely to relapse if they default later in treatment.

5. Relapse due to default tends to be with sensitive organisms.

6. Perhaps reduced toxicity because of shorter duration of treatment but this may be balanced by increased toxicity in the early part of treatment because of the number of drugs used.

FIGURE 5
ALL DRUGS GIVEN ONCE DAILY

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Weight ≤ 50kg</th>
<th>&gt; 50kg</th>
</tr>
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<tbody>
<tr>
<td>Rifampicin</td>
<td>450mg</td>
<td>600mg</td>
<td></td>
</tr>
<tr>
<td>Isoniazid</td>
<td>200/300mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethambutol</td>
<td>15-25mg/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptomycin</td>
<td>0.75 gram i.m. daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1 gram thrice weekly</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>if older than 45 yrs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>20/30 mg/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>or</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.5-2.5 gram</td>
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<td></td>
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DRUGS USED IN CHEMOTHERAPY OF TUBERCULOSIS  (See Figure 5 for dosage)

A. 1st Line Drugs/Commonly Used

Rifampicin  Oral (Capsule or syrup): Vials for i.v. injection
Isoniazid  Oral (Tablet or Elixir): ampoule for parenteral use.
Ethambutol  Oral (Tablet)
Streptomycin  i.m. only
Pyrazinamide  Oral (Tablet)

N.B. Rifampicin and Isoniazid available in combined formulation
Isoniazid and Ethambutol available in combined formulation
Rifampicin, Isoniazid, Pyrazinamide available in combined formulation.

B. 2nd Line Drugs/Used for resistant organisms

Cycloserine
Prothionamide
Ethionamide
Capreomycin
Viomycin
Kanamycin
**Rifampicin:** (Bacteriocidal)

Activity against TB demonstrated in 1967.
Effective against Staphylococci, Streptococci, Clostrides and coliforms as well as on Pseudomonas, Proteus, bacteroiides.
Absorbed from G.I.T. and excreted in bile.
Half life is not significantly affected by poor renal function.
Penetrates into C.S.F. (20% of serum concentration).
Penetration into C.S.F. is best if meninges are inflamed.

Administered once daily while fasting.
May need to reduce dose in liver disease.
May turn urine, tears, etc a reddish colour.

**Adverse Reactions:**

C.I.T. upset more common in elderly.
Flushing of skin.
Risk of hepatitis is small and addition of Isoniazid and Pyrazinamide does not seem to increase the risk.
A transient rise in liver transaminases seen early in treatment Thromobytopenia, osteomalacia, pseudomembranous colitis and pseudoadrenal crisis, have been described. The "flu syndrome" (fever, shivers, malaise, headache, dizziness seen in third to sixth month of treatment) occurs more often with higher dose and with intermittent regimes.
Care should be taken with those with liver disease. Because it induces liver enzymes it may increase the metabolism of steroids, oestrogens, the "pill", Warfarin, digitalis and oral antidiabetic agents. Patients should be advised to use alternative forms of contraceptives and not to rely on the "pill" if taking Rifampicin.

(2) Isoniazid: (Bacteriocidal)

First synthesised in 1917 but not used in T.B. therapy until 1950s. Absorbed from G.I.T., penetrates well into C.S.F. and all body tissues. Some drug excreted unchanged in urine but some is acetylated in liver by acetyl transfer to an inactive metabolite. The degree of conversion is genetically determined. Peripheral neuropathy may occur. It can be prevented by administration of Vitamin B6. (Pyridoxine - Benadon).

Adverse Reactions:

- Hepatitis (not common)
- Peripheral neuropathy
- Haemolytic anaemia (rare)
- Lupus syndrome.
(3) Ethambutol:

Bacteriostatic.
Main use is in the prevention of the emergence of resistance

Adverse Reactions:

Retrobulbar neuritis. Can cause optic atrophy and blindness if not stopped early after onset of visual symptoms.

May need reduction of dose in renal failure (keep serum level below 5 ug/ml).

Is probably best to avoid Ethambutol in young children, mentally handicapped and confused or demented elderly patients as they may be unable to report early visual disturbance.

(4) Streptomycin:

Bacteriocidal.
Active against organisms other than T.B.
Must be given by i.m. injection
Can be given intrathecally (50-100mg).
**Adverse Reactions:**

- Ototoxicity with deafness, vestibular damage or nystagmus.
- Renal toxicity
- Potentiation of neuromuscular blocking agents. (Curare).

(5) **Pyrazinamide:**

- Bacteriocidal
- *M. Bovis* and most atypical mycobacteria are resistant.

**Adverse Reactions:**

- Hepatotoxicity, hyperuricaemia
- Occasionally precipitates Gout.

**TREATMENT FOR NON PULMONARY TUBERCULOSIS**

(1) **Primary Tuberculosis:**

This is frequently diagnosed by finding a strongly positive Mantoux reaction to 1 T.U. in a contact or in the presence of erythema nodosum. If a primary lesion is demonstrable e.g. on X-ray, a standard drug regime should be employed. However, isoniazid prophylaxis (see below) is sufficient if chest X-ray is normal.
(2) **Pleural Effusion and Serous Effusion:**

A standard regime with the addition of steroids for about six weeks (20mg daily). Effusions should be tapped.

(3) **Bone and Joint Tuberculosis:**

Best results obtained by early surgery to remove abscesses and caseous debris, followed by a short period of immobilisation (3-6 weeks) and standard chemotherapy.

(4) **Genito-Urinary Disease:**

Prednisolone (20mg daily) for ureteric obstruction. Repeat I.V.P. after about six weeks treatment. If obstruction persists, surgery will probably be required.

(5) **Miliary Tuberculosis:**

Standard drug chemotherapy.
(6) Tuberculous Meningitis:

Probably a five drug regime as follows:

Isoniazid 15mg/kg. (Can also be given intrathecally 50-100mg)

Rifampicin 20mg/kg

Ethambutol up to 25mg/kg

Streptomycin can be given i.m. and intrathecally.

Pyrazinamide 1,500-2,000mg

The above five drug regime for up to three months followed by Rifampicin and Isoniazid for at least a total of 12 months.

The role of corticosteroids remains somewhat unclear but they are usually given to try to reduce cerebral oedema. May need assessment by Neurosurgeon with view to decompressive surgery.

DRUGS IN SPECIAL SITUATIONS

(1) Renal Impairment:

Rifampicin is the safest drug as it is excreted in bile. The maximum dose of Isoniazid should be 200mg daily if the G.F.R. is less than 10ml/min.

The dose of Streptomycin should be reduced and serum levels monitored if G.F.R. is less than 50ml/min.

Ethambutol is best avoided because it accumulates in renal failure and should have serum levels monitored.
(2) **Liver Impairment:**

Nearly all of the anti-tuberculosis drugs can cause hepatitis but it is rare with Ethambutol and Streptomycin. Rifampicin may need dose adjustment in the presence of cirrhosis or impaired biliary excretion.

(3) **Pregnancy:**

Nobody can guarantee that any of the anti-tuberculosis drugs are safe in pregnancy. It is, however, rarely possible to postpone treatment of tuberculosis, and indeed treatment may already have been started before pregnancy is recognised. Isoniazid has not been demonstrated to be teratogenic in man. Isolated cases of psychomotor retardation and convulsion have been described in infants exposed during gestation but the link is very tenuous. Rifampicin in very high dosage has been shown to be teratogenic in rodents. However, Girling and Witze stated that "there is no evidence that the dosage of Rifampicin used in clinical practice has a teratogenic effect". Again it should be noted that the "pill" may not be effective while taking Rifampicin.

Ethambutol and Pyrazinamide are probably safe in pregnancy, while Streptomycin is potentially ototoxic to the developing foetus.
AIDS AND TUBERCULOSIS

Tuberculosis has been recognised as one of the commonest bacterial infections in patients with AIDS. Up to 20% of patients with the Acquired Immunity Deficiency Syndrome will have the disease due to Mycobacterium tuberculosis hominis (MTB). The importance of tuberculosis in patients with AIDS is that it is potentially preventable, is treatable and curable and it is the only infection to which AIDS patients are susceptible that is easily transmitted to the non-immunosuppressed people. There seems to be two presentations of tuberculosis in patients who are infected with HIV -

1. Classical appearance with upper lobe disease and cavititation

2. An atypical radiological appearance with involvement of lower lobes, absence of cavititation, a glandular component similar to that seen in primary tuberculosis and frequently extrapulmonary disease.

In patients with AIDS extrapulmonary tuberculosis seems to be common. In our experience we have seen patients with combined pulmonary, genito-urinary, gastrointestinal and meningeal TB. Experience to date suggests that tuberculosis in AIDS patients responds well to standard chemotherapy.
Recently (annual meeting IUATLD Paris, November 1991) the International Union Against Tuberculosis and Lung Disease Committee on Treatment of Tuberculosis has recommended the standard anti-tuberculous regimens for patients with HIV infection/AIDS and tuberculosis. There is no evidence that a prolonged duration of therapy is required. Opinion is divided and there is yet insufficient data to decide whether longterm prophylaxis with Isoniazid should be continued in these patients following treatment.

Infection with atypical mycobacteria (MOTT: mycobacteria other than tuberculosis) particularly Mycobacterium avium intracellulare is common in AIDS in countries with low incidence of TB. These organisms are ubiquitous within the environment and the mode of acquiring the infection is unclear. They are relatively non-infectious organisms and transmission from patient to patient is not documented. Treatment of atypical mycobacterial infection is difficult and the best treatment regimen has not yet been identified.

There have been several recent outbreaks (Hopewell et al) of hospital based mini-epidemics of tuberculosis in which there has been demonstrated both inpatient and out-patient spread of disease and spread to patients and staff who are HIV negative and HIV positive in the hospital situation. The disturbing feature of some of these outbreaks has been that transmission seems to have occurred after the initiation of treatment. Compliance with therapy for patients involved however cannot be assured.
BOVINE TB

Mycobacterium Bovis which causes bovine TB can cause disease in man. It is always resistant to Pyrazinamide. Standard three drug (Rifampicin, Isoniazid, Ethambutol) nine months regimen is effective. Bovine TB comprises less than 1% of all bacteriologically positive TB in man in Ireland.
IS A THREE DRUG REGIMEN THE BEST TREATMENT FOR TUBERCULOSIS?

Drs. G. Cunnane, P. Kelly, P. Corcoran, L. Clancy

We present the data on 218 consecutive patients with TB treated with Rifater (combination RHZ and who have been followed for up to 2 years post completion of treatment. Comparison with previous series (IMJ, 1989; 8 2: 11-13) shows: that patients had fewer visible cavities on X-ray (p = 0.0004); more patients negative direct/positive culture (p = 0.02); no difference in terms of radiological extent of disease, pleural effusion, extrapulmonary TB, drug toxicity, mortality, other reasons for withdrawal from therapy. More patients are consistently culture negative when treated with Rifater at one month and two months compared to the other regimens - RHEZ x 6 months, RHF x 9 months.

RELAPSE RATE

To date of the 98 patients who have completed treatment, 39 have one year or more post treatment follow up. Two patients have relapsed with fully sensitive B. Both patients, one HIV positive, admit non-compliance with treatment.

CONCLUSION

The three drug regimen of Rif, Inah, Pyrazinamide (Rifater) produces significantly faster consistent sputum culture conversion than other regimens. These results support a policy of ongoing treatment with Rif, Inah, Pyrazinamide without Ethambutol or Streptomycin in the management of TB.
THE TUBERCULIN SKIN TEST

Paul Kelly, MA, DCH, MD, MRCPI
The tuberculin skin examines the ability to mount a cell mediated reaction in response to tubercular protein (purified protein derivative). It is not a diagnostic test. A "positive" tuberculin test does not definitively diagnose tuberculosis and a "negative" tuberculin test does not definitively exclude a diagnosis of active TB.

Following initial exposure to TB (this includes an iatrogenic primary infection in the form of BCG vaccination) it may take up to 10 weeks for the tuberculin test to become positive. The degree of positivity of the post vaccination or post primary infection skin test will wane with time.

A negative skin test occurs in people who have never had vaccination or a primary infection; people who have depressed cell mediated immunity as occurs following viral infection and in patients with AIDS; and may occur in elderly people. It must be stressed however that the skin test may still be negative soon after the initial exposure (up to 10 weeks) and occasionally in patients with active tuberculosis. In our experience some 4% of patients with proven active tuberculosis have a negative skin test to all strengths of tuberculin.

**MANTOUX TESTING**

This is performed by the injection of 0.1mls of purified protein derivative (PPD) intradermally using a thin (25 gauge) needle. The PPD used in Ireland comes from the Staten Serum Institute in Copenhagen.
and the commonly used strengths are - 1 TU, 2 TU, 10 TU and 100 TU. The strength of the reagent is a biologic potency rather than a concentration. Thus 0.05 ml of the 10 TU reagent does not equal 5 TU. The purified protein derivative in this product is known as PPD-RT 23. It contains Tween 80 which is a chemical which prevents the adherence of PPD to glass.

There are other purified protein derivatives available such as PPD-Weybridge available in the United Kingdom and PPD-S (PPD-Seibert) which is the standard in the United States of America.

The term purified protein derivative (PPD) was coined in 1934 by Florence Seibert for a product she made from heat concentrated synthetic medium of old tuberculin by precipitating the protein with trichloro-acetic acid. Later precipitation was accomplished with ammonium sulphate to obtain a preparation with less nucleic acid and polysaccharide. A large batch of this purified protein derivative was produced in 1940 to be used as the standard tuberculin preparation. This product (Lot. 49608) was designated PPD-S and became the international standard as well as the United States of America reference standard for all tuberculins. A purified protein derivative made to this standard is one with a biologic potency which produces the same degree of induration as PPD-S + 20%. Again it must be stressed that purified protein derivative, irrespective of source of manufacturer, represents a biologic potency and not a chemical concentration.
Administering the Mantoux Test

Using a 25 gauge needle 0.1 ml of the Mantoux reagent is injected intradermally just below the skin surface so as to produce a wheal (elevation) of 6-10 mms in diameter. The test result is read 48 - 72 hours later. The result should be recorded as the diameter of induration in mms (measured transversely to the long axis of the forearm). Little further change in the size of the reaction will occur before the fifth day and large reactions may still be evident 7-10 days later. Readings should be made in good light with the forearm slightly flexed at the elbow.

In subjects who have received BCG vaccination, at any time in their lives, it is not possible to distinguish between a response due to BCG vaccination and a response due to infection. A clinical decision has to be made in the context of the patient as to whether the skin test response supports the diagnosis of infection or is what would be regarded as "compatible with BCG vaccination".

In the United States of America it is recommended that an area of induration 5-6 mms in diameter in response to 5 TU PPD-S should be regarded as indicative of prior infection with tuberculosis. BCG vaccination is not widely used in the United States and these recommendations are based on population studies where they are confident that using this cut-off level (5-6 mms induration) they detect greater than 90% of people who are likely to have been infected. They regard a negative response to 250 tuberculin units as indicative of never having been infected with tuberculosis.
There are two problems with this contention. Patients with the Acquired Immunodeficiency Syndrome and tuberculosis are commonly tuberculin negative; some 4% of patients in our experience with active tuberculosis are negative to all strengths of Mantoux; the tuberculin skin response wanes and in old age a person who was previously positive may become skin test negative. In these latter patients a boosting phenomenon may be seen wherein repeated Mantoux testing will eventually produce a positive response. Certain disease processes e.g. sarcoidosis and viral diseases can also interfere with the Mantoux test.

The World Health Organisation suggest that 10 mms of induration to 2 tuberculin units PPD-RT 23 indicates infection whereas in the United Kingdom 5 mms of induration or greater in response to 10 tuberculin units has been accepted as an indication of previous infection. The main problem with intradermal skin testing with purified protein derivative is that it is a biological test and the response of an individual will depend on:-

(a) Current integrity of their immune system
(b) Have they ever had primary infection or BCG vaccination
(c) How long ago was that primary infection/BCG vaccination
(d) Have they, having had a previous infection or vaccination, come in contact with tuberculosis (as in health care workers) and been subject to a boosting phenomenon giving them a strongly positive response.
Efforts have been made in Ireland and Great Britain to use 5 tuberculin units Mantoux (RT 23) on the basis of North American recommendations and criteria. The main difficulty with this is that because of the addition of Tween 80 to PPD RT 23 the biologic potency of the reagent is raised 2-3 fold and hence 5 TU of RT 23 represents the equivalent of 10-15 TU of PPD-S (the North American standard). This phenomenon whereby the biologic potency of purified protein derivative in PPD-RT 23 is raised up to three fold by the addition of Tween reagent has created considerable difficulties in extrapolating American recommendations to the European context.

The significance attached to the tuberculin response will depend on why the test was performed. If the test is performed to determine the necessity of BCG vaccination in a health care worker we would recommend vaccination if there is no response to 10 TU Mantoux (RT-23). There is however no evidence that re-vaccinating a subject who has previously been successfully vaccinated (positive skin test or presence of scars) because they have a negative Mantoux test confers any further advantage.

The suggested interpretation of the tuberculin response in the context of contact tracing is discussed in the "Protocol for Managing Tuberculosis: The Community" produced by the Eastern Health Board Tuberculosis Advisory Committee.
SKIN ANERGY AND TUBERCULOSIS

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P. Kelly, MA, DCH, MD, MRCP
P. Hughes, MB, BCH
L. Clancy, FRCP, FRCP, FCCP

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In our experience tuberculin skin anergy (negative response to 10 TU Mantoux) occurs in 8% of patients with tuberculosis. In this study we compare 81 patients with skin anergy and proven tuberculosis with a background reactive population of patients with tuberculosis. Patients with skin anergy and tuberculosis were older and had fewer symptoms—less cough, less sputum production, less haemoptysis, less malaise, less chest pain—than patients without skin anergy. There was no difference with respect to male/female ratio, martial status, smoking habits, coexistent major illness, prescribed medications at diagnosis, nor the proportion of patients with extrapulmonary tuberculosis, previous history of BCG vaccination or past history of tuberculosis. Comparison of chest radiographs showed more advanced, more bilateral and more miliary disease in the anergic patients. Pyrexia and elevated ESR at diagnosis were also more common in this group. Fewer of the anergic group of patients were consistently culture negative after one months treatment compared to the background population. Mortality was higher in the anergic group, but this excess mortality occurred from causes other than tuberculosis. Repeat Mantoux testing was performed in 20 of the 81 anergic patients, after a minimum of 3 months of anti-tuberculous chemotherapy, and 14 had become tuberculin positive, suggesting that tuberculin skin anergy may be a temporary phenomenon.
INTRODUCTION

Tuberculin skin testing, while clinically useful in evaluating a patient with suspected tuberculosis, is not a diagnostic test for active disease. A negative tuberculin reaction is also compatible with a diagnosis of active disease and we decided to investigate its clinical significance.

We profiled patients with a first time proven diagnosis of pulmonary tuberculosis who displayed tuberculin skin anergy. We also sought to determine if skin anergy had any prognostic significance and if it was a temporary reversible phenomenon.

PATIENTS AND METHODS

All patients with a proven (bacteriological or histological) diagnosis of tuberculosis between 1st January, 1980 and 30th June, 1989 with TSA were studied retrospectively. Patients with a known immunodeficiency state or a concurrent or previous diagnosis of sarcoidosis were excluded. In the analysis we exclude patients who have extrapulmonary disease; a previous history of diagnosis and treatment for tuberculosis; disease due to atypical mycobacteria. We routinely use the Mantoux technique and PPD-RT23 (Staten Serum Institute, Copenhagen). At presentation we sequentially test with 1 TU, followed by 10 TU if
less than 5 mm induration, followed by 100 TU if less than 5 mm
induration to 10 TU. For the purposes of this paper we define tuberculin
skin anergy (TSA) as the absence of any induration in response to 10 TU
Mantoux testing after 72 hours. This strict definition of TSA is to
avoid dispute over the significance of minor degrees of induration to 10
TU. Mantoux testing is routinely performed at the time of diagnosis.

We compared these patients with the background tuberculin reactive
patients with tuberculosis who have been studied in detail. Patients
who died were compared with previously described group of patients who
died from tuberculosis. The radiological staging of pulmonary TB was
assessed in the standard manner. Statistical comparisons were
performed using the X² test.

RESULTS

A total of 93 patients with proven tuberculosis and tuberculin skin
anergy were identified. Twelve patients (5 with extrapulmonary
tuberculosis; 7 with previous treatment for tuberculosis) were excluded
from analysis leaving a study population of 81 patients.

Comparison with background tuberculin reactive population (1011) showed
no difference in terms of ratio of male to female patients (68% males in
the reactive population and 76% of males in the TSA group). There were
slightly fewer (31%) single compared to (45%) married people with TSA
but this may reflect an older age group with slightly more widowed patients. The differences were not statistically significant. Patients with TSA were older than reactive population with significantly more patients older than 50 years and older than 75 years (See Table 1). Significantly more patients with TSA had fever \( \leq 38^\circ \text{C} \) at diagnosis \( p < 0.0001, X^2 = 28.87 \) and an elevated ESR \( p = 0.008, X^2 = 7.004 \).

Significantly more patients with TSA had peptic ulcer disease \( p = 0.026, X^2 = 4.88 \); malignant disease \( p = 0.006, X^2 = 7.37 \); proven major psychiatric illness \( p = 0.008, X^2 = 11.59 \); or a history of cardiovascular/cerebrovascular disease \( p = 0.003, X^2 = 13.47 \). There were no differences in incidence of chronic bronchitis and emphysema, asthma, fibrotic lung disease, or diabetes mellitus. Only 3 patients had diabetes mellitus (1 insulin dependent) and this is not different from the incidence of diabetes in the reactive population.

Patients with TSA had a longer duration of symptoms prior to diagnosis but with significantly fewer patients having cough, sputum production, malaise, chest pain or haemoptysis (See Table 2).

At diagnosis patients with TSA had more widespread disease on X-ray with significantly more bilateral disease and significantly more advanced disease (See Table 3). Seventy-eight percent of TSA patients were positive on direct staining (S+) and on culture (C+); 20% were S-,C+ and 2% were culture negative but histologically positive. This is not significantly different from the reactive population. Patients with TSA
however took longer to become consistently culture negative with significantly fewer patients culture negative at one month, two months and three months treatment (See Table 3).

Twenty two of the 81 patients died before completion of anti-tuberculous therapy and this was significantly more \( (p = 0.0016) \) than in the reactive population. Comparison with our previously described pattern of mortality from tuberculosis showed that the excess mortality in TSA patients could not be explained on the basis of more advanced age or radiological extent of disease. The immediate causes of death in TSA patients were: tuberculosis (4); COAD/CCF (7); malignancy (7); pulmonary fibrosis (1); acute renal failure (1); GIT bleed (1); pulmonary embolus (1); pneumonia (2); CVA (2). One patient was reported to have died of acute myocardial infarction, 18 months following completion of his anti-tuberculous treatment.

TSA was not a permanent phenomenon and in 20 patients who had a repeat Mantoux test performed after a minimum of three months, 14 had become reactive to 1 TU or 10 TU.

Analysis of drugs prescribed prior to diagnosis did not reveal a pattern of drug prescription that would indicate possible suppression of skin reactivity by these drugs e.g. corticosteroids, immunosuppressant drugs.
Disturbances of serum biochemistry were common in the TSA group. Fifty-eight patients had urea and electrolyte estimation at diagnosis prior to any therapy. Of these patients 41 had hyponatraemia (sodium <135 mmol/litre) of whom 15 were receiving concurrent therapy with diuretics or oral corticosteroid drugs. Elevated blood urea occurred in 19 patients; hyperkalaemia in 5 patients and hypokalaemia in 8 patients. Hypoalbuminaemia (<30 grms/litres) occurred in 7 of 27 patients tested. Similar data for the background reactive population has not been tabulated.

DISCUSSION

The mechanisms underlying TSA are not as yet fully clear. Tuberculosis is known to be associated with lymphocytopenia, a phenomenon slightly more pronounced in that population of patients with tuberculin skin anergy (TSA). This quantitative deficit in T cell function is further exaggerated by the reduced T helper (Th) to T suppressor (Ts) cell ratio accompanying untreated TB. Ellner has suggested that anergy may result from the presence of a suppressor mononuclear cell population comprising both Ts cells and monocytes. Impaired monocyte function has also been demonstrated in these anergic patients and Wieczorek et al have provided evidence for the role of serum factors in suppression of tuberculin hypersensitivity. Rook has suggested that the problem is one of compartmentalisation with the demonstration that antigen specific lymphocytes may become trapped in the lymph nodes of tuberculin anergic individuals. Genetic factors may be of importance and an association with HLA B7 has been described.
This study has demonstrated that advanced pulmonary tuberculosis is significantly more common in patients with TSA, as evidenced by the longer duration of symptoms and greater degree of radiological disease.

Pyrexia and an elevated ESR were more frequently observed in patients with TSA. They also had fewer symptoms. They took longer to become consistently culture negative. In relation to these findings it is of note that states of antigen excess are known to have the potential to mediate immunosuppression. Support for a key role for "antigen overload" in the cause of the anergic state is given by the observation that many defects in cell mediated immunity tend to recover as chemotherapy for TB progresses. Nevertheless, as in this study not all cases of tuberculin anergy can be attributed to extensive disease and some may represent examples of specific tuberculin anergic state as described by Mascher.

As reported in previous studies tuberculin anergic patients are older, and frequently hypoalbuminaemic.

Certain drugs such as corticosteroids may act to modulate tuberculin hypersensitivity, but we found no evidence to suggest that steroid medication was more commonly prescribed to TSA patients. Rifampicin is capable of suppressing certain aspects of humoral and cellular immunity and Isoniazid has been shown to increase the magnitude of skin reaction to tuberculosis. Our skin testing however was performed at diagnosis before either of these drugs could have had an effect on skin hypersensitivity.
Tuberculin anergy is associated with higher mortality and this is not explained by either more advanced disease, or advanced age. The mortality may however reflect differences in background pathology other than tuberculosis.

Tuberculin anergy is not a permanent phenomenon in many patients and the majority of patients retested at least three months after starting treatment had become tuberculin reactive. While repeat Mantoux testing, especially in the elderly, is known to be associated with up to 30% conversion rates, we considered this "booster phenomenon" not to be relevant in our situation as the tiny tuberculin supplement provided by Mantoux testing would not be expected to significantly augment tuberculin in a patient already suffering from active tuberculosis.

CONCLUSIONS

In the study we have demonstrated that tuberculin anergy is associated with advanced age, more extensive radiological disease and increased mortality. The anergic state is usually transient with recovery of tuberculin hypersensitivity in the majority of patients.
TABLE 1: COMPARISON OF AGE DISTRIBUTION BETWEEN TSA POPULATION AND TUBERCULIN REACTIVE POPULATION

<table>
<thead>
<tr>
<th>Age</th>
<th>Tuberculin Reactive Population (%)</th>
<th>TSA Population (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 1011</td>
<td>n = 81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 75 yrs</td>
<td>172 (17%)</td>
<td>6 (7%)</td>
<td>.034</td>
</tr>
<tr>
<td>26 - 50 yrs</td>
<td>330 (33%)</td>
<td>6 (7%)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>51 - 75 yrs</td>
<td>400 (40%)</td>
<td>54 (67%)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>&gt; 75 yrs</td>
<td>103 (10%)</td>
<td>15 (19%)</td>
<td>.031</td>
</tr>
</tbody>
</table>
## Table 2: A Comparison Between Reactive and Anergic Patients

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Tuberculin Reactive Patients (%)</th>
<th>TSA Patients (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 1011</td>
<td>n = 81</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>904 (89%)</td>
<td>42 (52%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Sputum</td>
<td>847 (84%)</td>
<td>51 (63%)</td>
<td>0.067</td>
</tr>
<tr>
<td>Malaise</td>
<td>745 (74%)</td>
<td>17 (21%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>568 (56%)</td>
<td>49 (61%)</td>
<td>0.53</td>
</tr>
<tr>
<td>Anorexia</td>
<td>517 (51%)</td>
<td>42 (52%)</td>
<td>0.986</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>409 (40%)</td>
<td>31 (38%)</td>
<td>0.811</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>365 (36%)</td>
<td>13 (16%)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Sweating</td>
<td>322 (32%)</td>
<td>22 (26%)</td>
<td>0.672</td>
</tr>
<tr>
<td>Fever</td>
<td>233 (23%)</td>
<td>41 (51%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>184 (18%)</td>
<td>3 (4%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Wheeze</td>
<td>83 (8%)</td>
<td>6 (7%)</td>
<td>0.922</td>
</tr>
</tbody>
</table>

### Duration of Symptoms

<table>
<thead>
<tr>
<th>Duration</th>
<th>Tuberculin Reactive Patients</th>
<th>TSA Patients</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms</td>
<td>9</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1 month</td>
<td>22</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>1 - 3 months</td>
<td>42</td>
<td>28</td>
<td>0.0507</td>
</tr>
<tr>
<td>3 - 6 months</td>
<td>17</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>6 - 12 months</td>
<td>11</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>
TABLE 3:
RADIOLOGICAL EXTENT OF DISEASE AND TIME TAKEN TO BECOME CONSISTENTLY CULTURE NEGATIVE IN TB PATIENTS

<table>
<thead>
<tr>
<th>Tuberculin Reactive Population (%)</th>
<th>TSA Population (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 1011</td>
<td>n = 81</td>
<td></td>
</tr>
</tbody>
</table>

CHEST X-RAY

<table>
<thead>
<tr>
<th>Extent</th>
<th>Population (%)</th>
<th>TSA Population (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral</td>
<td>458 (45%)</td>
<td>14 (17%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Bilateral</td>
<td>553 (55%)</td>
<td>67 (83%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Minimal</td>
<td>130 (13%)</td>
<td>8 (10%)</td>
<td>0.55</td>
</tr>
<tr>
<td>Moderate</td>
<td>432 (43%)</td>
<td>11 (14%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Advanced</td>
<td>449 (44%)</td>
<td>62 (77%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Cavities</td>
<td>591 (58%)</td>
<td>44 (54%)</td>
<td>0.551</td>
</tr>
<tr>
<td>Effusion</td>
<td>102 (10%)</td>
<td>16 (20%)</td>
<td>0.012</td>
</tr>
</tbody>
</table>

BACTERIOLOGY

<table>
<thead>
<tr>
<th>Type</th>
<th>Population (%)</th>
<th>TSA Population (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>S+C+</td>
<td>850 (84%)</td>
<td>63 (78%)</td>
<td>0.812</td>
</tr>
<tr>
<td>S-C+</td>
<td>111 (11%)</td>
<td>16 (20%)</td>
<td>0.114</td>
</tr>
<tr>
<td>Hist</td>
<td>50 (5%)</td>
<td>2 (2%)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

TIME TO NEGATIVE DIFECT

<table>
<thead>
<tr>
<th>Time</th>
<th>Population (%)</th>
<th>TSA Population (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month</td>
<td>47%</td>
<td>33%</td>
<td>0.05</td>
</tr>
<tr>
<td>2 months</td>
<td>80%</td>
<td>51%</td>
<td>0.0001</td>
</tr>
<tr>
<td>3 months</td>
<td>96%</td>
<td>74%</td>
<td>0.0001</td>
</tr>
</tbody>
</table>
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CHEMOPROPHYLAXIS OF TUBERCULOSIS

Paul Kelly, MA,DCH,MD,MRCPI
Luke Clancy, FRCPE,FRCPI,FCCP
The intention with chemoprophylaxis is to prevent the occurrence of active tuberculosis in patients with evidence of recent infection and thus to curb the spread of tuberculosis in the community.

Isoniazid is usually given for up to 12 months. Six months therapy may be acceptable as it would appear to combine reasonable effectiveness, low cost and low toxicity. It may only reduce the occurrence of tuberculosis by 50-60%. Rifampicin combined with Ethambutol is probably the best option in Isoniazid resistant tuberculosis.

In the U.S.A. where Isoniazid prophylaxis is widely used the American Thoracic Society and the Centres for Disease Control (American Review of Respiratory Disease, 1986; 134: 355), have issued detailed recommendations for prophylactic treatment of tuberculosis in the U.S.A. and recommend treatment for 6-12 months for the following categories of patients who exhibit a positive tuberculin skin test:

1. Household members and close contacts of infectious tuberculosis patients. In the case of small children with negative skin tests treatment for up to three months with repeat skin test at that stage and continuation of therapy if the skin test has become positive.

2. Patients whose skin tests have become positive within the last two years.
3. Patients with past tuberculosis who have not received documented adequate chemotherapy.

4. Patients with abnormal X-rays. They recommend prophylaxis for 12 months.

Note: We feel (PK: LJC) that patients who have abnormal X-rays due to TB and who have not been given adequate treatment should receive a full course of definitive combination chemotherapy rather than Isoniazid prophylaxis.

5. Prophylaxis is also recommended for patients in special clinical situations such as those with silicosis, diabetes mellitus, myeloproliferative disorders, lymphoma, renal failure, receiving immunosuppressive therapy or patients with the Acquired Immuno Deficiency Syndrome or a positive test for HIV virus.

6. The neonate of a mother with current tuberculosis should be treated with Isoniazid for 2-3 months or at least until the mother is smear and culture negative. Isoniazid may be discontinued after 3 months if the mother is sputum negative and the infant tuberculin skin negative. In high risk situations BCG vaccination is considered after treatment with Isoniazid has been completed. BCG vaccination however is recommended for routine use only when Isoniazid cannot be used.
It is clear that the most effective proven form of chemoprophylaxis lasts for 12 months whereas currently recommended treatment for active disease may be as short as six months.

Note: It must be borne in mind however that routine BCG vaccination is not commonplace in the U.S.A. and thus positive skin tests are easier to interpret. The epidemiology of tuberculosis is significantly different in Ireland.

These recommendations have been challenged by Taylor et al (Annals Internal Medicine, 1981; 94: 808) who had already concluded from a decision analysis study that the benefits of prophylaxis with Isoniazid did not clearly outweigh the risks of tuberculin positive patients between the ages of 20 and 34 years. Rose et al (Journal American Medical Association, 1986; 256: 2709) consider that Taylor has underestimated the effectiveness of Isoniazid and using similar methods found that Isoniazid prophylaxis would be of benefit for all ages analysed between 10 and 80 years old, but that the margin of benefit is small for those over 65 years.

Stead et al (New England Journal of Medicine, 1985; 312: 1483) in a study of nursing homes in Arkansas showed that elderly patients in institutions were at greater risk of developing tuberculosis and perhaps
should be considered for prophylaxis. Many clinicians however only recommend Isoniazid prophylaxis for patients aged 35 years or younger unless other factors such as recent tuberculin conversion are involved.

The International Union Against Tuberculosis and Lung Disease (IUATLD) and the WHO have stated that chemoprophylaxis has virtually no role in developing countries.

**HOW LONG SHOULD PATIENTS RECEIVE PROPHYLAXIS?**

Results of a five year follow-up study involving 7 Eastern European countries under the aegis of the IUATLD (Bulletin World Health Organisation, 1982; 60: 555) involving 28,000 tuberculin positive patients with fibrotic pulmonary lesions, showed that the risk of developing tuberculosis was reduced by 21% if Inah was given for 12 weeks; 65% if Inah was given for 24 weeks and 75% if Inah given for 52 weeks. This was a placebo controlled study. Hepatitis developed in 0.5%, typically occurring in the first 12 weeks of treatment. Hepatitis developed in 0.1% of those receiving the placebo.

Krebs et al (Bulletin IUATLD, 1982; 57: 81 and 1983; 58: 167) showed that a 12 week regimen was only temporarily effective and that 24 weeks of treatment was as effective as 52 weeks Isoniazid prophylaxis. This report dealt with 8 to 10 years follow-up. Snider et al (Journal of American Medical Association, 1986; 255: 1579) calculated that 24 weeks
of treatment was more cost effective than 12 or 52 weeks and Comstock (Annals Internal Medicine, 1983; 98: 663) has recommended that patients with fibrotic lesions of the lungs consistent with pulmonary TB and who have not completed a full course of anti-tuberculous therapy, should receive Isoniazid prophylaxis.

The actual number of cases prevented in these studies, particularly the large study under the IUATLD was quite small and Goldman (Lancet, 1983; 1: 592) considered that the efficacy of 24 weeks of treatment was too low and apart from patients with an increased risk of breakdown of lesions such as Asians, immigrants, patients with immunosuppression, that Isoniazid prophylaxis was undesirable and perhaps unnecessary.

Some authors disagree with the policy of prophylaxis if the X-ray is abnormal and we recommend that if the chest X-ray is abnormal that the patients should receive definitive treatment if being offered any chemotherapy.
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   the IUAT Trial.
SHOULD ROUTINE B.C.G. VACCINATION BE ABANDONED IN IRELAND?

Dr. P. Kelly
Dr. J. Stinson
Dr. L. Clancy
B.C.G. vaccination protects against tuberculosis but there is debate about the level of protection. There is no uniform policy towards B.C.G. vaccination in Ireland (I.M.J. 1988; 81 (1): 7). The question arises as to whether B.C.G. vaccination is of value in Ireland or whether routine vaccination should be abandoned.

Using data from the National Tuberculosis Survey (1986) and the National Census (1986) we compared the incidence of tuberculosis throughout the 32 community care areas in Ireland to determine if there were any differences associated with B.C.G. vaccination policy. We divided the country into - (a) areas which have a policy of neonatal BCG; (b) areas which vaccinate at 12-14 years; (c) areas which never routinely use BCG vaccination.

RESULTS

Showed significantly higher rates of TB in people aged 15 years or younger in areas which do not have a policy of neonatal BCG.

<table>
<thead>
<tr>
<th>INCIDENCE OF TB IN PEOPLE AGED ≤ 15 YRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal BCG                           = 5.33/100,000 *</td>
</tr>
<tr>
<td>BCG 12-14 yrs                          = 15.01/100,000</td>
</tr>
<tr>
<td>No BCG                                = 18.69/100,000</td>
</tr>
<tr>
<td>No. of cases ≤ 15 yrs nationally       = 77 cases</td>
</tr>
<tr>
<td>= 7.51/100,000</td>
</tr>
</tbody>
</table>

\[ \text{p < 0.001 - X analysis} \]
We estimate that 86 cases of TB were prevented by neonatal B.C.G. and that 600-800 infants need to be vaccinated to prevent one case of TB in the under 15 year age group in Ireland. Before making a rational decision to discontinue BCG vaccination it is recommended that the rate of natural infection, the rate of progress from infection to active disease and the rate at which these two factors are changing should be determined. This information cannot be made available for Ireland. A benefit ratio of 2000 children to be vaccinated to prevent one case has been used internationally.

CONCLUSION

1. Neonatal BCG vaccination protects against TB in the paediatric (<15 yrs) age group.

2. Before abandoning neonatal BCG vaccination the impact of this change in policy on the epidemiology of tuberculosis in each area needs to be assessed.
APPRAOCH TO TUBERCULOSIS IN LONGTERM PSYCHIATRIC HOSPITALS/
MENTAL HANDICAP UNITS

Paul Kelly, MA, DCH, MD, MRCPI
Luke Clancy, FRCPE, FRCP, FCCP
PREVIOUS OUTBREAKS OF TUBERCULOSIS

Determine the number of outbreaks/individual cases of tuberculosis among longterm residents in the unit for the last five years.

Attempt to quantify workload in terms of financial cost, clinical work, radiological work and problems of contact tracing.

SUGGESTED STRATEGY FOR DEALING WITH TUBERCULOSIS

1. Suggest all patients have chest X-ray and Mantoux test. Make record of previous personal and family history of tuberculosis and previous Mantoux status and history of BCG vaccination.

2. Patients who had been previously adequately treated for tuberculosis should be eliminated from specific surveillance once they have completed treatment and are two years post treatment.

3. All patients who have abnormal x-rays consistent with tuberculosis should be evaluated for active disease. This may include bronchoscopy if deemed appropriate on clinical grounds.

Specific attention will have to be paid to patients with fibrotic and cavitating lesions.
4. Patients with a radiological/clinical or microbiological diagnosis of tuberculosis should have a standard treatment course of antituberculous drugs. If patients are being treated on the basis of clinical diagnosis with radiological support but negative sputum, no special isolation procedures are required.

5. Patients with negative chest x-rays but significantly positive tuberculin skin tests should be offered single drug prophylaxis with isoniazid for 6 months duration as a minimum.

6. All staff should have a chest x-ray and Mantoux status established. Notwithstanding recommendations to the contrary, experience at Peamount Hospital suggested that there is little value in doing repeated skin tests or repeated chest x-rays on hospital staff. Some authorities would recommend repeat chest x-rays at 18 month intervals for staff exposed to patients.

TREATMENT OF TUBERCULOSIS:

Patients being treated for tuberculosis should receive a standard course of Rifampicin, Isoniazid, Pyrazinamide for 2 months followed by Rifampicin and Isoniazid to a total of 4 months. If any of the isolates are bovine tuberculosis or resistant tuberculosis, treatment schedules will need to be modified. It can be anticipated that the order of 10% of patients will experience some difficulty with treatment. Typically this will be drug induced hepatitis.
Strategy for dealing with drug induced hepatitis would be withdrawal of anti-tuberculous drugs; allow liver function to settle to normal; check hepatitis A and hepatitis B titres. Once liver function has returned to normal anti-tuberculous drugs should be re-introduced starting with combined Isoniazid and Ethambutol. Once patients are established on Isoniazid and Ethambutol, Rifampicin and/or other drugs can be introduced slowly. Patients should receive a nine month treatment course from the time they are restarted on adequate treatment with Rifampicin in combination with Isoniazid.

The majority of nursing/para medical/medical staff will have significantly positive tuberculin skin tests. The reasons for this are felt to be previous BCG vaccination, a boosting effect on skin responsiveness due to patient exposure. We would not recommend Isoniazid prophylaxis for health care workers as per British Thoracic Society or American Thoracic Society recommendations as, if these were followed, in excess of 60% of health care workers in Ireland would need to be given prophylaxis. This is obviously inappropriate. Staff who have abnormal x-rays should be offered treatment or prophylaxis as appropriate.

PATIENTS WITH ABNORMAL X-RAYS NOT DUE TO TB:

These patients should be referred to specialist services as appropriate for evaluation.
If a significant number of patients in the unit need treatment for tuberculosis, this will produce a variation in the expected epidemiology of TB in the area, it will have significant drug costs and radiological costs and this will have to be anticipated. The longterm benefits however, of having a longterm care unit tuberculosis free are obvious. All future patients entering longterm care should have their tuberculin status and chest x-ray status established at admission. The cost benefit ratio/analysis will have to be done on the overall work.
GUIDELINES FOR PREVENTION OF TUBERCULOSIS

IN HOSPITAL EMPLOYEES

REPORT OF A SUB-COMMITTEE OF THE

IRISH THORACIC SOCIETY

Report prepared by Dr. Luke Clancy, Peamount Hospital, Newcastle, Co. Dublin, Professor John Prichard, St. James' Hospital, Dublin, Dr. Harry Hitchcock, Merlin Park Regional Hospital, Galway and Dr. Charles Bredin, (Sub-Committee Co-ordinator), Regional Hospital, Cork.

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GUIDELINES FOR PREVENTION OF TUBERCULOSIS IN HOSPITAL EMPLOYEES

INTRODUCTION

The risk of infection by Mycobacterium Tuberculosis is a recurring source of anxiety among hospital employees. The problem of prevention of this disease in health-care personnel in Ireland is hampered by lack of consistency in attitudes and preventive procedures from hospital to hospital and even from ward to ward within the same hospital. Some of these practices are illogical or outdated.

The following general guidelines are offered with the objective of standardizing and updating these preventive measures.

GENERAL

1. The number and location of TB patients admitted to the hospital should be ascertained to determine risk of employee exposure in the hospital as a whole and certain units or wards in particular (1).

2. The level of infection in the community, by M. Tuberculosis, should be ascertained. This information is available from the Community Care Service in the hospital area.

3. A history of BCG does not preclude an initial screening test. A Mantoux of 10mm, or greater of induration, using 10 Tuberculin units, or a Heaf Test grade 3 or 4 should be considered as potentially due to M. Tuberculosis infection rather than due to BCG. A Heaf Test Grade 2 may be due to M. Tuberculosis infection or BCG.
4. In practice the only source of tuberculosis infection is a person with pulmonary TB in whose sputum bacilli are present in sufficient numbers to be seen on direct examination of sputum smears. Extra-pulmonary TB is in practice non-infectious even though tubercle bacilli may be cultured from specimens from the lesions (1). Therefore, no special precautions are required with extra-pulmonary tuberculosis beyond the usual procedures for sanitary care of dressings and urine (2).

5. The guidelines in this statement refer in general to asymptomatic employees. Symptomatic hospital employees or applicants for employment require full investigation.

6. A TB prevention programme should be the responsibility of the hospital occupational health department. If no such department exists then the programme should be directed by one physician rather than being left to individual units or departments to implement as they see fit.

RISK GROUPS OF HOSPITAL STAFF

A systematic approach to TB prevention in hospital staff is facilitated by dividing the employees into risk groups or categories (2) as outlined below:

**Group 1** - No higher risk compared to the community.

**Group 2** - Some higher risk compared to the community.

**Group 3** - Staff at much higher risk.

**Group 4** - Staff in neonatal and children's departments.

Further description of the above four groups of employees is as follows:

**Group 1** - No contact with patients.
Group 1 - Regular or casual contact with patients.
Group 3 - Staff in predictable contact with patients who have Pulmonary Tuberculosis e.g. patients on Tuberculosis Units, or Respiratory Disease Wards.
Group 4 - Staff in neonatal and children's wards are assigned special status because of the vulnerability of neonates and children to Tuberculosis.

PREVENTION PROCEDURES

Group 1: This group requires no special precautions compared to non-hospital employees.

Groups 2-4: A tuberculin skin test should be done on all staff in these groups, applied to the anterior surface of the forearm. If the Mantoux Test is used, an area of induration of 10 mm or more is regarded as positive. The reaction is read 48-72 hours after injection. Alternatively, if the Heaf Test is used, the reaction is read 7 days after injection. Grades 2-4 reactions of the Heaf Test are regarded as positive. Chest x-ray examination should be performed, or satisfactory evidence of a normal chest x-ray within the year prior to commencement of hospital employment should be available.

According to the results of the Tuberculin test and the chest x-ray the following further procedures are advised:

Negative Tuberculin Test, Normal Chest X-Ray: BCG vaccination should be offered. After vaccination is carried out the site should be checked for evidence of a BCG lesion. If there is no lesion, the Tuberculin test should be repeated in 8 weeks. If the second Tuberculin test is negative, the employee should be referred to a Consultant Physician. If a Tuberculin test negative employee refuses BCG vaccination even after the risk of acquiring tuberculosis and subsequently infecting others is explained to him or her, then it is preferable that this employee should not be assigned to wards or units with
vulnerable patients. These vulnerable patients include the immunosuppressed, dialysis patients, children and neonates.

**Positive Tuberculin Test, Normal Chest X-Ray:** Chest x-ray should be repeated at 6 months and 1 year.

**Positive Tuberculin Test, Abnormal Chest X-Ray:** Evidence of active tuberculosis should be sought, and treated with appropriate chemotherapy if found. If no evidence of active tuberculosis is found in an employee not previously treated for TB, then chemoprophylaxis is advised. If unable or unwilling to take chemoprophylaxis then the risk of re-activation of tuberculosis in the future should be explained to the employee: preferably also he or she should be assigned to areas outside of those containing vulnerable patients, as in the examples given above.

**FOLLOW-UP**

1. Once successful treatment or chemoprophylaxis of pulmonary tuberculosis has been achieved, indefinite follow-up of these employees is now considered unnecessary. A total of two years from the commencement of treatment or one year from commencement of chemoprophylaxis should be sufficient provided they remain asymptomatic.

2. After successful administration of BCG to an employee, special follow-up is not required.

3. Because of the higher risk, staff in Group 3 should be offered annual chest x-rays.

**OPERATING THEATRE - PREVENTIVE MEASURES**

1. For elective surgery it is preferable to wait until the patient with pulmonary TB is sputum smear negative.
2. Special precautions are necessary only if the patient has sputum smear positive pulmonary TB. Precautions should include sterilization of inner parts of anaesthesia equipment which have been in contact with the patient's breath or use of disposable closed circuit anaesthetic equipment (1).

INHALATION THERAPY EQUIPMENT

Care of equipment is the same as for anaesthetic equipment.

REFERENCES


PREVENTION OF TUBERCULOSIS IN HOSPITAL EMPLOYEES/HEALTH CARE WORKERS
There are published guidelines for the prevention of tuberculosis in health care workers in the United States of America and in the United Kingdom. Draft guidelines from the Irish Thoracic Society are included in the course manual.

B.C.G. is widely administered in Ireland and hence a majority of young employees will have had B.C.G. vaccination. In this retrospective analysis we regard a positive test as 10 mm induration in response to a Mantoux test. The study covers the period 1970-1987 and in early years the Tyne test was sometimes used. We regard the Tyne test as equivalent to 5 TU Mantoux.

Student nurses are essentially school leavers (no previous patient contact) and the medical students are in their preclinical years (no patient contact yet) in medical school. In Peamount skin test and chest X-rays were performed prior to taking up employment. Repeat Mantoux tests were performed 6-8 weeks after B.C.G. vaccination. The general hospital figures are a cross-sectional study taken on employees who were already in employment.

RESULTS

Overall results indicate that 70% of health care workers have at least a 10 mm response to 10 TU Mantoux; this rises to 90% for medical staff and general nurses. As we can see from the data on medical students and student nurses only some 60% have a 10 TU positive Mantoux. Mantoux
testing after B.C.G. vaccination in student nurses and general staff showed that approximately 80-90% were positive to 10 TU Mantoux 6-8 weeks after vaccination. In the general hospital of staff with minimal or no patient contact only approximately 30% were positive to 10 TU Mantoux.

Further analysis of our results shows that those over 30 years of age were significantly more likely to be 1 TU positive than those less than 20 years of age. There was no other significant age difference between the groups.

Of 1527 X-rays available, 58 (4%) showed an abnormality, typically a small area of calcification. Four of these patients had a personal history of pulmonary tuberculosis; 4 had a family history of tuberculosis and 7 had no response to 10 TU Mantoux.

DISCUSSION

The data show that staff with close patient contact are significantly more likely to be skin test positive. In Ireland medical, nursing and physiotherapy students are skin tested prior to commencement of training and if negative referred for B.C.G. vaccination. Thus health care workers in Ireland (medical, nursing, paramedical) may be Mantoux positive because they have had B.C.G. vaccination in childhood, a primary infection prior to commencing training or are referred for B.C.G. vaccination during training. The degree of positivity may reflect a boosting phenomenon of exposure to patients on an underlying positive response.
## Hospital Staff Tuberculin Response 1970-1987

<table>
<thead>
<tr>
<th>Occupation</th>
<th>N</th>
<th>NEG/100TU</th>
<th>10 TU</th>
<th>Time</th>
<th>1TU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical</td>
<td>99</td>
<td>10%</td>
<td>12%</td>
<td>25%</td>
<td>53%</td>
</tr>
<tr>
<td>SRN/Sen</td>
<td>253</td>
<td>8%</td>
<td>11%</td>
<td>68%</td>
<td>13%</td>
</tr>
<tr>
<td>RMNH/Psych</td>
<td>79</td>
<td>20%</td>
<td>28%</td>
<td>19%</td>
<td>33%</td>
</tr>
<tr>
<td>Paramedical</td>
<td>18</td>
<td>17%</td>
<td>39%</td>
<td>27%</td>
<td>17%</td>
</tr>
<tr>
<td>General Staff</td>
<td>624</td>
<td>32%</td>
<td>12%</td>
<td>47%</td>
<td>9%</td>
</tr>
<tr>
<td>Std. Nurses</td>
<td>531</td>
<td>39%</td>
<td>17%</td>
<td>37%</td>
<td>7%</td>
</tr>
<tr>
<td>Med Students</td>
<td>525</td>
<td>36%</td>
<td>46%</td>
<td>0%</td>
<td>18%</td>
</tr>
<tr>
<td>Total</td>
<td>2186</td>
<td>31%</td>
<td>22%</td>
<td>33%</td>
<td>14%</td>
</tr>
</tbody>
</table>

Covers all staff coming to work at Peamount. Tuberculin tests were performed before starting employment.

## General Hospital

<table>
<thead>
<tr>
<th>Occupation</th>
<th>N</th>
<th>1TU/10TU Pos</th>
<th>10TU Neg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical</td>
<td>23</td>
<td>95.6%</td>
<td>4.4%</td>
</tr>
<tr>
<td>Nurses</td>
<td>123</td>
<td>91.9%</td>
<td>8.1%</td>
</tr>
<tr>
<td>Physios</td>
<td>8</td>
<td>87.5%</td>
<td>12.5%</td>
</tr>
<tr>
<td>Radiographers</td>
<td>6</td>
<td>83.5%</td>
<td>16.7%</td>
</tr>
<tr>
<td>Lab Staff</td>
<td>5</td>
<td>60.0%</td>
<td>40%</td>
</tr>
<tr>
<td>Min Pt Contact</td>
<td>82</td>
<td>70.7%</td>
<td>29.3%</td>
</tr>
<tr>
<td>No Pt Contact</td>
<td>19</td>
<td>78.9%</td>
<td>21.1%</td>
</tr>
</tbody>
</table>

All staff were already in employment at the hospital.
### STUDENT NURSES 1981-1987

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>NEG/100TU</th>
<th>10TU</th>
<th>1TU</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.C.G.</td>
<td>95</td>
<td>36.1%</td>
<td>35.85</td>
<td>25.0%</td>
</tr>
<tr>
<td>No B.C.G.</td>
<td>20</td>
<td>50.0%</td>
<td>45.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>?BCG BUT NO SCARS</td>
<td>101</td>
<td>56.6%</td>
<td>32.5%</td>
<td>8.4%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>216</td>
<td>45.9%</td>
<td>35.4%</td>
<td>15.6%</td>
</tr>
</tbody>
</table>

TUBERCULIN TEST RESULTS ON STUDENTS NURSES STARTING FIRST TRAINING.

### MEDICAL STUDENTS

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>NEG/100TU</th>
<th>10TU</th>
<th>1TU</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.C.G.</td>
<td>393</td>
<td>22%</td>
<td>56%</td>
<td>22%</td>
</tr>
<tr>
<td>No B.C.G.</td>
<td>132</td>
<td>83%</td>
<td>11%</td>
<td>6%</td>
</tr>
</tbody>
</table>

TESTS PERFORMED ON PRECLINICAL STUDENTS BEFORE ENTERING HOSPITAL TRAINING

### POST B.C.G. TUBERCULIN TEST

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>100TU/NEG</th>
<th>10TU</th>
<th>1TU</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Student Nurses</strong></td>
<td>68</td>
<td>0</td>
<td>16%</td>
<td>84%</td>
</tr>
<tr>
<td><strong>All Staff</strong></td>
<td>298</td>
<td>6%</td>
<td>17%</td>
<td>62%</td>
</tr>
</tbody>
</table>

(15% Pos Tine Test)

72
DRAFT GUIDELINES FOR MANAGEMENT OF TUBERCULOSIS IN THE COMMUNITY

By: Eastern Health Board Tuberculosis Advisory Committee
PROTOCOL FOR MANAGING TUBERCULOSIS: THE COMMUNITY

INTRODUCTION

The Republic of Ireland has the fourth highest incidence of tuberculosis in the European Community yet there is no national plan to deal with the problem. The responsibility of managing tuberculosis in the community rests with the Director of Community Care/Medical Officer of Health. Recent studies have shown that there is a need for a co-ordinated approach to managing tuberculosis in the community and this protocol aims to provide guidelines for the detection and treatment of tuberculosis in the Eastern Health Board.

INVESTIGATIVE METHODS

This section deals briefly with the methods at one's disposal in the fight against tuberculosis.

(a) Clinical: Most patients with tuberculosis have pulmonary disease and hence have respiratory symptoms. The commonest respiratory complaint is that of a prolonged productive cough. Haemoptysis, anorexia, night sweats occur in only a minority of cases. Physical examination often reveals little and if there is any doubt about the diagnosis a chest x-ray is mandatory. For patients with non-pulmonary disease, symptoms and signs are usually localised to the affected site but particular attention should be paid to the patient with an acute onset of a psychiatric illness in order to rule out T.B. meningitis.

(b) Mantoux testing: The Mantoux method of assessing tuberculosis status is the method recommended by the World Health Organisation. Unfortunately the tuberculin units used are not standardised internationally. In the U.S.A. five international tuberculin units are used (5 I.T.U.) whereas in Europe different quantities are used. What must be remembered though is that 5 I.T.U. used in U.S.A. is practically the same as two tuberculin units in Europe (2 T.U.). Given the situation the Serum Statden Institute (who make the tuberculin) recommend that 2 T.U. be used if the Mantoux test will only be carried out as a one-stage procedure, however if one is contemplating BCG on the basis of a negative Mantoux test, then a further test with 10 T.U. should be given first. This will solve many of the operational difficulties experienced with trying to get people to return for 1 T.U., 10 T.U., and 100 T.U. tests.

The test is performed by giving an intradermal injection of 0.1 ml of tuberculin dilution, preferably at the middle third of the palmar aspect of the lower left arm using a 26G microlance needle. The area is viewed 48 - 72 hours later and a positive reaction displays a flat, slightly rough infiltration with a well defined area of redness of at least 6mm in diameter.
(c) Heaf Testing: An acceptable alternative to the Mantoux test when large numbers (e.g., schoolchildren) need to be done quickly is the Heaf method. This is performed using undiluted tuberculin which is applied (same site as for Mantoux) over a circular area of about 1 cm. The Heaf gun (preferably the fixed head type as doubts about the validity of using the magnetic head gun have been expressed) is held firmly against the area and fired. Children under two years should have the apparatus set at 1 mm, all others at 2 mm. The test should be read at 3 - 10 days later. A positive result is recorded only if there is a palpable induration around at least four of the puncture sites. If no induration is felt a negative result of Heaf 0 is recorded. Four grades of positive response are recognised:

- Heaf I: at least four small indurated papules.
- Heaf II: indurated ring formed by confluent papules.
- Heaf III: solid induration 5 - 10 mm wide.
- Heaf IV: induration greater than 10 mm.

In practice Heaf 0 and Heaf I are regarded as being tuberculin negative.

Whether one uses the Mantoux method or the Heaf method, there is no age cut-off point for either tests. They apply equally to a one year old and a seventy year old. However, a problem that does arise as a person gets older is that of skin anergy and boosting phenomena. A particular problem arises in contact tracing those over 65 years, in establishing their true tuberculin status. All patients over 65 who are found to be tuberculin negative on initial testing should be re-tested five days later if Mantoux method, seven days later if Heaf, with the same strength of tuberculin in order to avoid future confusion and to ascertain their correct tuberculin status.

(d) Chest X-Rays: A Postero-Anterior film is all that is usually required, however in children it is recommended that they also have a lateral film which gives a clearer picture of lymphadenopathy. The clinical situation will dictate how often a CXR is required, in general though, CXR's are taken for all contacts prior to chemotherapy, two months later, at the completion of chemotherapy and thereafter six monthly for 1-2 years.

(e) Laboratory Specimens: Ideally early morning samples (though not exclusively) are sent for direct smear examination and for culture and sensitivity testing. The smear status is very important from an epidemiological as well as a clinical viewpoint. Whilst all patients with tuberculosis are infectious prior to chemotherapy those whose sputum is positive direct (S+) are much more infectious than those who are smear negative (S-) and as such require more urgent attention.
Ideally samples for laboratory analysis should be examined monthly until the patient is smear negative and thereafter at the end of therapy and six monthly for 1-2 years. Should a patient remain smear positive after three months of chemotherapy, one should look for sensitivity tests, but more importantly check to make sure that the patient is compliant with chemotherapy.

(f) BCG status: Many patients are unaware of their BCG status - a quick check at the deltoid area of the left arm for evidence of scarring will often be helpful.

TREATMENT

It is generally recommended that prior to commencing chemotherapy the following indices are checked:

FBC, Platlets, Hepatic enzymes, Biliru in, serum creatinine/urea and uric acid if using pyrazinamide. Patients should be monitored clinically on a monthly basis and LFT's only rechecked if clinically indicated. All patients receiving Ethambutol should have their visual acuity and red/green colour discrimination checked. Children should not receive ethambutol. All patients receiving Isoniazid should get Pyridoxine 20 mg per day.

The following is an outline of chemotherapy used. (The paediatric dose for Rifampacin and Isoniazid is 10 - 20 mg/kg and for pyrazinamide 15 - 30 mg/kg).

(a) Pulmonary Tuberculosis: The recommended treatment for pulmonary tuberculosis is as follows:

Rifampacin - 600 mg daily (450 mg if < 50 kg) X 6 months
Isoniazid - 300 mg daily ........................ X 6 months
Pyrazinamide - 2.5 gr if - 75 kg)
   (daily) 2.0 gr if 50 - 75 kg) X 2 months
   1.5 gr if - 50 kg
Ethambutol - 15 mg/kg daily  X 2 months

(b) Non-Pulmonary Disease: This will often depend on the clinician dealing with the case, however, in general, the regimen below is considered adequate.

Rifampacin 600 mg daily (450 mg if < 50 kg) X 9 months
Isoniazid 300 mg daily  X 9 months
Ethambutol 25 mg/kg daily  X 2 months

(c) Pregnancy and Lactation: Untreated tuberculosis is a far greater hazard to a pregnant woman and her foetus than treatment of the disease. Effective chemotherapy should be given to all pregnant and lactating mothers. The above regimen in (b) is recommended.

Pyrazinamide is avoided in pregnancy because of inadequate teratogenic data.
The neonate born of a mother with current tuberculosis should be treated with isoniazid for 2 - 3 months or at least until the mother is smear and culture negative and known to be complying with treatment. If after 3 months treatment, the mother has a negative sputum and the infant is tuberculin negative with a clear chest x-ray then isoniazid may be stopped. If the infant is tuberculin positive then it should receive isoniazid and rifampacin for nine months.

(d) Chemoprophylaxis: This consists of giving isoniazid in a daily dose of 300 mg (children 10 - 14 mg/kg max. daily dose for all - 300 mg). Every effort should be made to see that patients are compliant for at least six months.

CONTACT TRACING

The extent to which one examines contacts is dependant on the status of the index case. If the index case is smear positive then all household contacts, close associates (friends and workmates) and general associates (occasional friends and workmates) need to be screened. If the index case is smear negative, then only household contacts and close associates need be considered for screening. If the index case has non-pulmonary disease contact tracing is not indicated. In all situations where the index case is of Asian origin, contact tracing should be as for smear positive patients.

Particular care should be paid to contact tracing if tuberculosis affects a school population. Contact tracing is necessary only if the index case has pulmonary tuberculosis. If the index case is smear negative then only classmates need screening, if the index case is smear positive then all children in the same year and all teachers/staff should be screened.

Screening is by Mantoux testing or Heaf testing plus a chest x-ray. Figure I outlines the procedure to adapt when investigating contacts. The algorithm applies to contacts of smear positive patients. For contacts of smear negative patients, there is no need to begin chemoprophylaxis for those still in contact with the index case.

SCHOOL VACCINATION PROGRAMME

The Heaf method of screening is frequently used in the school vaccination programme, however the Mantoux method is preferable where possible. Figure II outlines the sequence of events to follow.

NOTIFICATION

The Eastern Health Board has devised a new notification form for all doctors. Notifying doctors have frequently pointed out, in the past, that they had difficulty in ascertaining to what community care area they should notify a particular case of tuberculosis to. To overcome this problem, it will be sufficient to notify the Director of Community Care/Medical Officer of Health in the area where the doctor is practicing and the respective Director of Community Care/Medical Officer of Health will forward the
notification to his/her relevant colleague. A draft notification form is included for reference.

Each community care area will have a designated person in charge of tuberculosis who will register all cases and submit them for processing centrally so that it will be possible to produce regular reports re the epidemiology of tuberculosis in the Eastern Health Board.
FIGURE I - CONTACT TRACING PROTOCOL

HEAF/MANTOUX (2 T.U.)

- **Tuberculin Negative**
  - CXR
  - Normal
  - If continuing contact with index or if > 15 years, repeat Mantoux/Heaf at 3/12

- **Tuberculin Positive**
  - CXR
  - Abnormal (IB)
  - If contact maintained or if ≤ 15 years, repeat Mantoux/Heaf at 3/12
  - Abnormal (IB) Normal
  - ≤ 15 yrs > 15 years
  - Repeat CXR for 6/12

- **Tuberculin Negative**
  - BCG

- **Tuberculin Positive**
  - D/C Chemo. + BCG

- **Tuberculin Negative**
  - Repeat CXR

- **Tuberculin Positive**
  - Repeat CXR

- Abnormal

- Normal

- TX and contact trace

- Non

- TX and monitor carefully for resistance

- Continue Chemo prophylaxis for six months
FIGURE 11 - SCHOOL VACCINATION PROGRAMME
HEAF/MANTOUX (2 T.U.)

Previous BCG (Scar +)

Grade 0,1
Revaccinate

Grade 2,3
Nil

Grade 4
CXR

Normal
Abnormal

Repeat CXR 6/12
Tx and contact trace

No previous BCG (Scar -)

Grade 0,1
Vaccinate

Grade 2,3,4
CXR

Normal
Abnormal

Chemoprophylaxis

Abnormal

Tx and contact trace
Is Bovine, Atypical or Resistant Tuberculosis a problem?

CONOR COLLINS  PAUL KELLY  COLM BYRNE  FIONA DENHAM  LUKE CLANCY

Ireland has one of the highest reported incidences of tuberculosis in Europe and Peamount Hospital treats approximately one third of all reported new cases.

In a review of tuberculosis over a 20-year period in this hospital (1962-1981), it was noted that bovine tuberculosis in man had become uncommon, that resistant organisms had dwindled to a mere handful, and that 13 (0.95%) out of 1314 isolates between 1977 and 1981 were due to atypical mycobacteria. Tuberculosis also remains a problem among cattle in Ireland and some authors have suggested that man may be a reservoir for M. bovis rather than the traditional belief that cattle were the source of M. bovis infection in man. We explore this possibility as well as reviewing the incidence of atypical mycobacterial infection and resistant tuberculosis in our hospital.

Patients and Results
The study is based on 1002 consecutive culture positive cases of tuberculosis from January 1962 to December 1982; histological diagnoses without positive culture and presumptive cases are not included. The laboratory data and case records of all patients who had bovine, atypical or drug resistant strains of tuberculosis isolated were analysed with particular attention to previous antituberculosis treatment, gastrointestinal or chest surgery, significant other illness as well as age, sex etc. and site of disease.

Nine (0.9%) bovine, 11 (1.1%) atypical and 16 (1.6%) resistant human bacillus strains were isolated. The 11 atypical strains isolated were classified as M. avium/intracellulare (3), M. malmoense (2), M. xenopi (2), M. fortuitum (1), M. smegmatis-pheri (1) and M. gordonae (1). Multiple drug resistance in vitro was common in the atypical strains. Of the 16 resistant human strains isolated, 12 showed resistance to a single agent: Isoniazid (5), Streptomycin (5), P.A.S. (2). Four strains showed multiple drug resistances: P.A.S, streptomycin and isoniazid (1) streptomycin and P.A.S. (1); rifampicin, ethambutol and isoniazid (1) rifampicin, ethambutol, streptomycin and pyrazinamide and P.A.S. (1).

Only 4 patients with bovine tuberculosis had definite contact with livestock; one of these with cervical node involvement, was negative on direct examination and culture of sputum. Only 3 had a positive family history of tuberculosis; one patient was a U.K. national. Of the 11 patients with atypical mycobacteria isolated, 7 had a history of significant gastrointestinal disease, including 4 who had surgery. Another 3 patients had a history of chest surgery and one had carcinoma of the lung. Three of the atypical patients had not been offered antituberculosis treatment and remain well on review, and a fourth returned home to the U.K. for management. Coincidently, seven of both the atypical and the resistant strains had been treated previously for tuberculosis. All but one of the patients with bovine tuberculosis had pulmonary disease and M. bovis was isolated from sputum. Six of the bovine, 8 of the atypical and 8 of the resistant patients had other major diseases as well as tuberculosis.

Discussion
This study suggests that most cases of tuberculosis in Ireland are due to fully sensitive Mycobacterium Tuberculosis Hominis and that drug resistance is not a major problem. Only a handful of isolates are of bovine or atypical mycobacterial strains and three of the latter have not required any treatment to date.

Tuberculosis remains a problem among cattle in Ireland and despite considerable expenditure and effort has not yet been eradicated. The reasons for this are said include the exceptionally high amount of cattle movement in Ireland, residual background infection in other species and illicit practices in the movement of potentially infected animals. The fragmentation of Irish farm holdings may also be a factor. It has been suggested that man may be a reservoir for Bovine tuberculosis but we believe that this is unlikely. Only four of nine patients with bovine tuberculosis had definite contact with farming and in these the history and clinical features suggested reactivation of disease contracted decades earlier.

The low incidence of atypical tuberculosis is noteworthy as much higher incidences of these infections have been reported particularly from North America and among patients who are immunocompromised. Management of atypical tuberculosis is difficult as multiple in vitro drug resistances are usual and available second line drugs are in general more toxic and less effective. Clinical cure can be achieved despite these resistances but because of the small number of these patients the long term prognosis is unclear.

Resistance in Mycobacterium Tuberculosis Hominis may reflect management in previous

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decades as the most common resistance seen was to isoniazid and streptomycin.

Our study leads us to conclude that humans are not a significant reservoir for bovine tuberculosis. Almost all tuberculosis seen in man in Ireland are fully sensitive human strains and drug resistance is not a major problem and atypical strains are few in number.

References
Mortality from tuberculosis: a cause for concern

FENTON HOWELL  RISTEARD O LAOIDE  PAUL KELLY  PAT SALMON  LUKE CLANCY

Tuberculosis kills more people in Ireland than any other notifiable infectious disease. The published mortality for tuberculosis is higher in Ireland than in other E.E.C. states (Figure 1). Despite a reduction in the mortality from tuberculosis since the National Tuberculosis Survey there were, on average, 159 tuberculosis deaths from 1,096 newly notified patients per year in the years 1973-1984.

Methods and Results

We examined the case notes of 336 patients who died between 1973-84 of tuberculosis related causes. Of these, 92 died as a direct result of tuberculosis and our analysis deals with this group. There were more males (76%), widowed (29%), elderly (83% > 65 years) and members of Social Group 5 (30%) and 6 (38%) [Central Statistics Office Classifications, 1981] than in the national population. Ninety-one patients were referred with a diagnosis of tuberculosis: teaching hospitals (36%), county hospitals (35%), psychiatric hospitals (6%), family practitioners and Community Health Services (4%), and other institutions (14%). Only 29 patients were on anti-tuberculous therapy at referral and only 3 were on acceptable regimes. The mean delay from onset of symptoms to referral or initiation of correct therapy was 11 weeks attributed respectively to: the patient (9.7 weeks), primary care (2.4 weeks) and to secondary/hospital care (2.2 weeks). All patients had a bacteriological and/or histological diagnosis of tuberculosis. Other than hyponatraemia (33 out of 55 patients) laboratory data was non-contributory. Radiologically 83 patients had bilateral extensive disease, 71 had cavities and 40 had a pleural effusion. Figure 2 shows the cumulative mortality from the time of admission. Within 48 hours of admission 21 patients died. Seventy patients died from pulmonary T.B., 11 from pulmonary and extra-pulmonary T.B., 10 from miliary T.B., and one from tuberculous meningitis. The table shows the national statistics for tuberculosis; 32% of all new cases notified were treated at Peamount Hospital. When compiling mortality data it is recommended that the underlying cause of death is recorded as the official cause of death.3 Applying these guidelines to our patients 225 (5.5%) would have had tuberculosis recorded as the underlying cause of death compared to the national figure of 15%. The 92 patients which we regard as "true" tuberculosis deaths represent a mortality rate of 2.2%.

Discussion

This study is the first since 1968 in these islands to examine the true tuberculous mortality rather than mortality based on death certification data.4 Typically the patients who died were elderly, male, widowed, from lower social groups and had obvious extensive disease. Delay in the initiation of treatment played a major role in these patients' deaths. The largest component of delay was patient dependent and shows the need for continued education and vigilance. The hospital delay (> 2 weeks) seems unduly long and is the most immediately correctable element.

Death certification data are an unreliable way of assessing the true mortality from tuberculosis. The national data while useful for comparison between states, overestimate the true tuberculosis mortality. Peamount Hospital as a referral centre treats 32% of all cases of tuberculosis in...
Ireland with a mortality only 12% of the national figure. Therefore, 88% of reported deaths from tuberculosis occur in 68% of the reported cases. No information about these deaths is available.

Our study, like other surveys,\textsuperscript{5,6} indicates that tuberculosis does not have adequate prominence in medical education and coupled with complacency on the part of the medical profession and society contributes to the failure to prevent tuberculosis. The winding down of the T.B. services because of economic factors is shortsighted at a time when we top the list for this disease among our European neighbours. We cannot hope to eradicate or control tuberculosis if we reduce resources which are already inadequate.

\begin{table}
\centering
\begin{tabular}{|c|c|c|c|c|c|}
\hline
\textbf{YEAR} & \textbf{NEW CASES} & \textbf{TOTAL DEATHS} & \textbf{\% DEATHS} & \textbf{NEW CASES} & \textbf{PERCENTAGE OF TOTAL} \\
\hline
1973 & 1182 & 117 (16) & 9 & 228 & 10 (4.4) \\
1974 & 1201 & 174 (15) & 17 (4.0) & 620 & 35 (5.7) \\
1975 & 1154 & 156 (13) & 10 (6.5) & 480 & 36 (7.5) \\
1976 & 1081 & 136 (16) & 10 (4.5) & 411 & 39 (9.5) \\
1977 & 1218 & 182 (16) & 14 (7.7) & 379 & 33 (8.8) \\
1978 & 1151 & 206 (19) & 14 (6.8) & 372 & 32 (8.6) \\
1979 & 1090 & 182 (17) & 18 (4.4) & 367 & 35 (9.4) \\
1980 & 1132 & 158 (14) & 18 (6.9) & 365 & 30 (8.3) \\
1981 & 1019 & 155 (12) & 10 (4.8) & 307 & 30 (10.0) \\
1982 & 975 & 120 (12) & 18 (6.0) & 272 & 29 (10.8) \\
1983 & 924 & 110 (12) & 18 (6.0) & 267 & 29 (11.3) \\
1984 & n/a & n/a & n/a & 283 & 18 (6.4) \\
1985 & 1109 & 149 (13) & 18 (6.5) & 398 & 32 (8.2) \\
1986 & 1212 & 156 (13) & 225 (5.5) & 82 (2.2) \\
\hline
\end{tabular}
\caption{Irish new case and mortality data.}
\end{table}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{cumulative_mortality}
\caption{Cumulative mortality from time of admission.}
\end{figure}

\textbf{References}
\begin{enumerate}
\end{enumerate}
National tuberculosis survey (1986)

J STINSON, P KELLY, F HOWELL, L CLANCY
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Abstract
To determine a precise epidemiological and clinical picture of tuberculosis in Ireland in a single year we surveyed all Directors of Community Care, hospital Clinical Consultants and Heads of Diagnostic laboratories in Ireland.

A total of 756 cases were notified by DCCs and this gives an incidence of 21.37 cases per 100,000 population for the country during 1986. The age distribution of patients was under 15 yrs (9.4%), 15-35 yrs (24%), 35-65 yrs (20%), over 65 yrs (47%). The site of disease was: pulmonary TB (71%), pulmonary and extrapulmonary TB (2.7%), extrapulmonary TB (15%), primary TB (6.3%) and tuberculosis with site unidentified (4.7%).

There was no uniform policy towards BCG vaccination, method or extent of contact tracing nor method of tuberculin skin testing. Surprisingly only 12 of the 32 DCCs (37.5%) and 31 (37%) of the 80 clinical consultants who indicated their current treatment for pulmonary tuberculosis, were using recommended standard treatment regimes. While the tendency was to continue treatment beyond standard duration, three community care areas and 21 hospital consultants were using regimes which are potentially inadequate.

All 40 microbiological laboratories replied and 22 reported that they examined specimens for TB. A total of 58,427 specimens were examined for TB but 89% of these were examined in six major laboratories. Sixteen laboratories were examining less than two specimens per day for tuberculosis. This probably represents inadequate numbers of specimens to maintain a satisfactory level of technical expertise.

We feel that there is an urgent need for a national consensus on TB management, contact tracing and treatment. There is also a need for more emphasis on TB in medical education.

Introduction
The Republic of Ireland has one of the highest reported incidences of tuberculosis and death from tuberculosis in western Europe. Unlike many of our neighbours we do not have a large third world immigrant population which would tend to exaggerate the incidence of tuberculosis. The incidence of tuberculosis in the Republic of Ireland is 2-4 times that of the United Kingdom or Northern Ireland.

In 1953 Deeny produced a detailed epidemiological survey of tuberculosis in the Republic of Ireland. Subsequently the Department of Health produced an annual epidemiological report on tuberculosis but since 1972 there had only been minimal statistics published. De Buitleir and Fitzgerald described the caseload during a five year period in a general hospital where on average 20 cases per year were seen. Briscoe and Gill covering a ten year period in a major paediatric hospital, described only 26 cases.

We have reported the mortality patterns and epidemiology of tuberculosis as seen from a national referral centre. In view of the above we felt it appropriate at this time to produce a profile of tuberculosis in the Republic of Ireland in the 1980s.

Aims
The aims of this study were to produce a national profile of tuberculosis from management, contact tracing and epidemiological viewpoints, and to document practices with respect to chemoprophylaxis and BCG vaccination.

Methods
We used a postal questionnaire which was sent to each individual Director of Community Care (DCC) (n = 32); Hospital Clinical Consultants (n = 509) (Consultants with clinical responsibility and excluding laboratory Consultants, Radiologists, Anaesthetists); the Directors or Heads of Function in specialists hospitals e.g. psychiatric hospitals, mental handicap hospitals (n = 61) and the Director or Heads of Function of all pathology (n = 37) and microbiology laboratories (n = 40) in the country.

The questionnaires were sent with a self addressed, stamped envelope. Two months after the initial postal due date repeat questionnaires were sent to non respondents. A third questionnaire was sent two months later to those from whom a reply had not been received. Thereafter non respondents were contacted either in person or by telephone to try and maximise our response rate.

To determine incidence rates for tuberculosis in the various regions of the country we used the results of the national population census of 1986. We regarded the number of cases reported by each Director of Community Care as mutually exclusive and used these figures to form the basis of the national incidence of tuberculosis. As each patient would only have been notified from one community care area this avoided the possibility of double counting of patients if the figures were based purely on clinical consultants. It is not all clinical consultants responded to the questionnaire and some had no data available this final cumulative figure from the Directors of Community Care forms our "gold standard" for the incidence of notified tuberculosis in 1986.

Results
A total of 617 questionnaires were posted and 451 (73.9%) were eventually returned. The cumulative reply rate for each group was: Directors of Community Care (100%); Microbiology laboratories (100%); Hospital Clinical Consultants including Directors of special hospitals/units (71%); Histopathology laboratories (65%).
A total of 756 cases of tuberculosis were notified by the Directors of Community Care. A further 188 patients were on chemoprophylaxis of whom 88 came from a single community care area. Table 1 shows the breakdown of cases for each Health Board area. The incidence for the country was 21.37 cases per 100,000 population (26.72 if the 188 patients on chemoprophylaxis are included) and varied from 16.27 in the North Eastern Health Board area to 34 in the North Western Health Board area. The relatively high rate of tuberculosis in the North Western Health Board area may be explained by a localised outbreak of tuberculosis which occurred in the same year. Because community care areas do not always follow boundaries it is not possible to give the incidence of TB per county.

**TABLE 1—The incidence of TB in each Health Board area**

<table>
<thead>
<tr>
<th>Health Board</th>
<th>DCC</th>
<th>TB</th>
<th>Population</th>
<th>TB per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>EHB</td>
<td>10</td>
<td>232</td>
<td>1,231,293</td>
<td>18.66</td>
</tr>
<tr>
<td>SHB</td>
<td>5</td>
<td>134</td>
<td>336,545</td>
<td>25.05</td>
</tr>
<tr>
<td>WHB</td>
<td>3</td>
<td>75</td>
<td>347,747</td>
<td>21.60</td>
</tr>
<tr>
<td>NWB</td>
<td>2</td>
<td>72</td>
<td>212,407</td>
<td>34.00</td>
</tr>
<tr>
<td>MWHB</td>
<td>3</td>
<td>78</td>
<td>315,000</td>
<td>24.76</td>
</tr>
<tr>
<td>MHB</td>
<td>3</td>
<td>41</td>
<td>207,871</td>
<td>19.70</td>
</tr>
<tr>
<td>SEHB</td>
<td>3</td>
<td>75</td>
<td>384,657</td>
<td>19.50</td>
</tr>
<tr>
<td>NEHB</td>
<td>3</td>
<td>49</td>
<td>301,673</td>
<td>16.27</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>32</td>
<td>756</td>
<td>3,537,195</td>
<td>21.37</td>
</tr>
</tbody>
</table>

A = Number of community care areas  
B = Actual number of cases of TB notified  
C = Population of each health board area  
D = Incidence of TB per 100,000 population.

**Directors of Community Care:** All 32 Directors of Community Care replied. Of the 756 cases notified, 71% were pulmonary disease alone; 15% were extrapulmonary tuberculosis without pulmonary involvement; 2.7% had coexisting pulmonary and extrapulmonary TB; 6.3% were primary tuberculosis and 4.7% were tuberculosis with site unknown to the respondent. The age distribution of patients was: less than 15 yrs (9.4%), 15-38 yrs (24%), 35-55 yrs (20%), 55 yrs. or more (47%). Fifteen per cent (15%) of patients were treated solely by the community care services and the remainder were treated in conjunction with hospital based services.

With respect to BCG vaccination policy there was no uniformity among DCCs, of the 32 community care areas, four never use BCG vaccination, ten administer BCG at birth; three administer BCG at 12-14 years; 13 administer BCG at birth and recheck and administer the vaccine at 12-14 years if tuberculin skin test is negative; and there was no stated policy in two care areas. In 16 community care areas BCG vaccine uptake was checked either by the presence of scars or tuberculin skin testing. There was no uniformity in the method used nor at the time this was done (range of 6-12 weeks). Table 2 shows the method of tuberculin skin testing in use in the 32 community care areas.

**TABLE 2—The method of tuberculin skin testing in use in community care areas**

<table>
<thead>
<tr>
<th>Method of Tuberculin Skin Testing</th>
<th>Number of Areas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mantoux</td>
<td>4</td>
</tr>
<tr>
<td>Heaf</td>
<td>12</td>
</tr>
<tr>
<td>Both Mantoux and Heaf</td>
<td>9</td>
</tr>
<tr>
<td>Moro</td>
<td>1</td>
</tr>
<tr>
<td>Mantoux and Moro</td>
<td>4</td>
</tr>
</tbody>
</table>

There were 11 different chemotherapeutic regimens in use for treating *pulmonary tuberculosis.* Twelve community care areas were using the standard regimen for *pulmonary tuberculosis* (Rifampicin, Isoniazid, Ethambutol regimen for nine months). Fourteen community care areas used longer treatment regimens. The tendency was to prolong treatment with Ethambutol beyond the initial two month period or to continue total duration of treatment for longer than nine months. The stated treatment regimen in use in three community care areas would be considered inadequate by current standards and in three community care areas there was no stated routine treatment regimen. A total of 188 patients were on chemoprophylaxis for tuberculosis. Eighty eight of these came from a single community care area. Again there was no uniformity with respect to chemoprophylactic regimens. Fourteen (14) community care areas used Isoniazid alone for 6-12 months; nine use Rifampicin and Isoniazid in combination for six months duration; and six community care areas were using different combinations and durations. Three community care areas had no stated policy.

Our results showed a lack of uniformity in the methods and extent of contact tracing. When the index case was bacteriologically proven all DCCs screened household contacts, close family and close friends and the majority (87%) screened work mates and school mates in addition. When the index case was bacteriologically negative all DCCs screened household contacts and this screening was extended to family and close friends by over two-thirds of DCCs (68%) and to work mates and school mates by almost one third (28%).

**Hospital Clinical Consultants:** A total of 509 questionnaires were posted and 356 (71%) were returned. Only 127 clinical consultants responded that they had diagnosed and/or treated tuberculosis during 1986. On average chest specialists treated 3.75 cases (range 1-7) and non chest specialists treated 2.28 cases (range 1-14). Only 80 clinical consultants indicated their current treatment regimens for pulmonary tuberculosis and a total of 44 different combination chemotherapeutic regimens were recorded. The standard three drug, nine month regimen was used by thirty (36%) respondents; the shorter four drug, six month regimen was used by one respondent (1.25%). Twenty nine (36%) respondents used treatment regimens which would be considered adequate. As with DCCs the tendency was to prolong treatment with Ethambutol beyond the initial two month period or to prolong the total duration of treatment. Twenty one respondents (26%) were using non recommended and potentially inadequate treatment regimens. Allowing for referral patterns 16% of patients treated by hospital based services were receiving potentially inadequate treatment for their pulmonary tuberculosis.

**Microbiology Laboratories:** All 40 microbiology laboratories surveyed replied and 22 examine specimens for tubercle bacilli. Of these laboratories fifteen do direct smear and culture for tuberculosis and seven do direct smear only.
four laboratories do direct smear, culture, sensitivity and identification. A total of 58,427 specimens were examined for tuberculosis (Table 3), however, 89% (51,461 specimens) were examined in six major laboratories. Sixteen laboratories were examining less than two specimens per day for tuberculosis.

### Table 3—The number of specimens examined for tuberculosis in 1986

<table>
<thead>
<tr>
<th>Microbiological Data</th>
<th>Laboratories Surveyed</th>
<th>Laboratories Examining Specimens</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>40</td>
<td>22</td>
</tr>
<tr>
<td>Total number of specimens examined</td>
<td>58,427</td>
<td></td>
</tr>
<tr>
<td>Pramount Hospital</td>
<td>17,307 (30%)</td>
<td></td>
</tr>
<tr>
<td>Cork Regional</td>
<td>13,479 (23%)</td>
<td></td>
</tr>
<tr>
<td>UCG</td>
<td>7,366 (13%)</td>
<td></td>
</tr>
<tr>
<td>St James's</td>
<td>6,469 (11%)</td>
<td></td>
</tr>
<tr>
<td>LCCD (Earlsfort Tcc.)</td>
<td>4,144 (7%)</td>
<td></td>
</tr>
<tr>
<td>Crumlin</td>
<td>2,696 (5%)</td>
<td></td>
</tr>
</tbody>
</table>

*Sixteen Laboratories examine less than two specimens per day.*

A total of 521 patients had positive cultures for TB but because of between-laboratory referral pattern it was possible for the same patient to be counted more than once so that this figure (521) may be an over-estimate of the total number of culture positive tuberculosis patients.

**Histopathology Laboratories:** Of 37 laboratories surveyed 24 (65%) replied. Fourteen of these respondents had no information available. The remaining ten reported a total of 33 specimens histologically positive for TB; ten specimens positive on direct stain and eight positive on culture. Of 1,741 post mortem examinations seven showed active TB undiagnosed during life and three confirmed an ante mortem diagnosis of TB.

**Discussion**

Based on the data from this survey and on comparisons with our European neighbours, Ireland has an unacceptably high level of tuberculosis, particularly in young adults and children. Unlike many of our neighbours we do not have large immigrant populations and the incidence of tuberculosis in Ireland is probably the highest in a western European population. The reasons for this are unclear. We have had a state funded, free tuberculosis treatment service for over three decades, yet, while the incidence of tuberculosis had declined quite significantly, it has reached a plateau. This plateau phenomenon has been observed in most developed countries but why it should be higher in Ireland that elsewhere is unclear. While some affluent northern European countries may be close to eradicating the disease, much work remains to be done in this country.

Standard treatment regimens which have the force of international recommendations are well publicised and detailed in most standard texts. Yet many patients seem to receive, in our view, unnecessarily prolonged chemotherapy with the associated toxicity and cost. It is alarming to note that 16% of patients treated from hospital based services were reported to be prescribed less than optimum therapy. That there is no uniform policy towards chemoprophylaxis is worthy of note but should be viewed in the context that decisions concerning chemoprophylaxis are not as simple in Ireland where BCG vaccination is widely used compared to North America where typically BCG vaccination is only offered to high risk groups. While it is commonly believed that a strongly positive (1 TU) Mantoux is indicative of tuberculous infection, we have shown in a study of hospital employees that a strongly positive tuberculin reaction may in fact be attributable to prior BCG vaccination rather than infection with tuberculosis. This may complicate decisions about chemoprophylaxis. It has been suggested that part of the difference in incidence of tuberculosis between the Republic of Ireland and Northern Ireland is that in the Republic we may be counting patients who are being given chemoprophylaxis. Based on our data this hypothesis is speculative and accounts for only a fraction of the difference.

BCG vaccination has been in use in Ireland for over three decades. It is disappointing therefore that no uniform policy is available even within a given health board. We suggest that an agreed national policy on BCG vaccination is overdue. Contact tracing, which in the main appeared to be adequate or even excessive again had no uniform practice.

One aspect of the problems of a country with tuberculosis in decline is that older physicians with experience in treating and managing tuberculosis are retiring and that younger physicians have little experience of the disease. In our study chest specialists were seeing an average of three cases per year. Tuberculosis does not receive adequate emphasis in either undergraduate or postgraduate education and younger physicians are unlikely to be experienced in the management of this disease unless they undergo plans training in a unit caring for a substantial number of patients with tuberculosis. Our analysis of mortality showed that the majority of patients spent a median of more that two weeks inpatients in general hospitals prior to the diagnosis of tuberculosis being made and that treatment in many cases was inadequate. This highlights one of the consequences of inadequate emphasis on tuberculosis in medical education.

This survey demonstrates the lack of uniformity in the approach to management of tuberculosis both at hospital and community level. The differences between community care area and between hospital clinicians are in matters of detail. Nevertheless detail is important when dealing with a communicable disease and the advantages of a consistent uniform policy is accepted worldwide. In this small country it should be possible to have a single agreed policy with regard to BCG, contact tracing, notification and treatment regimens. Eradication of tuberculosis is largely a function of socio-economic conditions. The contribution of the health services is of the order of 25%. It is imperative that in a country where the resource has been made available to supply free of charge to the patient the best drugs available and a free vaccination, contact tracing and evaluation service that health care workers cooperate to make the most efficient use of these resources.

**Conclusions**

To overcome the problems which are identified in this survey we believe that the following would be helpful:-

1. That the medical schools agree a uniform approach to undergraduate training in tuberculosis.
2. That there be a formalised approach to post-graduate training coupled with a comprehensive research programme.
3. That there be an agreed reference laboratory service for identification and typing of mycobacterial isolates, sensitivity testing and maintenance of quality control.
4. That a national tuberculosis committee be established whose functions would include the formulation of agreed policy with regard to BCG, extent of contact tracing, evaluation of notifications and mortality patterns as well as clear guidelines on treatment regimens.
Acknowledgements
We would like to thank all those who responded to the questionnaires and in particular to DCCT. We would also like to thank Grainne Feeney and Karen Kearns for secretarial and typing assistance.

References

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Short course chemotherapy for pulmonary tuberculosis

A randomised controlled trial of a six month versus
A nine month oral regimen

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Peamount Hospital, Newcastle, Co. Dublin.

Abstract
We report on the first trial in the Republic of Ireland to look at chemotherapy for TB. This management trial, carried out in single unit, which treats a third of all TB cases in the Republic of Ireland compared the effectiveness of a three drug/nine month regimen (Rifampicin (R), Isoniazid (H), supplemented with Ethambutol (E)) for the first two months = RHE9) with a four drug six months regimen (R, H supplemented with E and Pyrazinamide (Z) for the first two months = RHEZ6). Two hundred and eighty eight patients (288) were entered into the study. A total of 143, (76 were in the RHE9 group and 67 in the RHEZ6 group) completed the trial as planned. At the end of the third month, significantly more patients in the RHEZ6 regimen (98%) were culture negative compared to the RHE9 regimen (88%). All were culture negative at the end of chemotherapy. Drug intolerance was seen in 35 (12%) patients with no significant difference in hepatitis between the two regimens. Toxicity from Pyrazinamide was minimal. One hundred and forty five (145) patients were invalid for analysis for the following reasons: bacteriologically negative TB (41), drug intolerance (35), death (23), non-compliance (19), diagnosis not TB (10), drug resistance (7), extrapulmonary disease (4), consent withdrawn (3), Mycobacteria other than tuberculosis (3). All patients are being followed to monitor relapse rates.

Introduction
Effective chemotherapy of tuberculosis not only decreases morbidity and mortality, it also plays a major role in controlling further spread of infection. Following the British Thoracic and Tuberculosis Association’s Trial on short course chemotherapy (1972/73), it was recommended that chemotherapy for pulmonary tuberculosis be reduced to daily Rifampicin (R) and Isoniazid (H) for nine months plus Ethambutol (E) for the first two months. Subsequent to this trial and with a better understanding of the action of antituberculosis drugs, particularly Pyrazinamide (Z), it has been shown that an oral six month course of Rifampicin, and Isoniazid supplemented by Ethambutol and Pyrazinamide in the first two months to be highly effective in treating pulmonary tuberculosis. The British Thoracic Society (BTS) now recommend this regimen as standard chemotherapy for pulmonary tuberculosis.

Epidemiological evidence shows that patients with tuberculosis in the Republic of Ireland differ significantly from their United Kingdom counterparts, particularly in the extent of disease at presentation. Therefore, we felt it would be useful to investigate the effectiveness of an oral six month regimen amongst our own population before recommending the BTS regimen. We also took the opportunity to evaluate a lower dose of Ethambutol (15mg/kg) than the BTS study (25mg/kg). We felt this was necessary because lower doses of Ethambutol have been introduced in some areas and because the role of a companion drug to RHZ is becoming unclear. Furthermore, we felt that introducing a lower dose of Ethambutol would be worthwhile because of the anxiety at present concerning the ocular toxicity of Ethambutol. This trial was facilitated by being carried out in a single unit which treats a third of all new cases of pulmonary tuberculosis notified in the Republic of Ireland.

Patients and methods
A total of 288 patients were randomised to one or other of the treatment regimens but only those patients who were culture positive and who had pulmonary tuberculosis alone were evaluated at analysis. Pregnancy, clinical evidence of renal or hepatic disease, gout or impaired visual function and patients who had received more than one week antituberculosis therapy before assessment were excluded. Written consent was obtained from all patients, or from their legal guardians, and patients were then randomly allocated to one of the following regimens:

(i) Rifampicin and isoniazid for six months plus Ethambutol and Pyrazinamide for the first two months (RHEZ6),
(ii) Rifampicin and isoniazid for nine months plus Ethambutol for the first two months (RHE9).

Patients received the following daily dosages: Rifampicin 600mg or 450mg if the patient weighed less than 50 kg; Isoniazid 300mg; Ethambutol 15mg/kg; Pyrazinamide 15mg/kg if the patient weighed less than 50kg; 2 grams if the patient weighed between 50 and 74kgs and 2.5 grams if the patient weighed 75kgs or more. All patients were treated initially as in-patients and drugs were administered under supervision, usually on an empty stomach. Subsequent management was supervised by the community care service. The current available brands of Isoniazid and Pyrazinamide were used. The study was approved by the National Drugs Advisory Board and the Ethics Committee at the hospital.

Prior to the commencement of chemotherapy a minimum of two specimens of sputum were sent for analysis throughout the trial two sputum samples were examined at least monthly. Posterior-anterior chest radiographs were assessed both pre- and post-treatment. These were assessed using a standard classification by a single observer (PK) without knowledge of the regimen allocated to the patients.
Biochemical analysis of liver function tests were carried out prior to the therapy and at monthly intervals. Samples of urine were randomly checked for metabolites of Rifampicin. All laboratory investigations were carried out at our laboratory.

All patients had their treatment initiated at the study centre and were assessed at this unit at the end of the initial two-month phase and on completion of chemotherapy. Thereafter patients are to be assessed at regular intervals for a period of two years to monitor relapse. Statistical analysis was by Chi² testing.

Results

Of the 288 patients entered into the trial, 68 did not fulfil the entry requirements for the reasons outlined in Table 1. Thus 220 patients (M = 137, F = 83) were valid for further analysis. Of these 220 patients, 112 were allocated to the nine month regimen (RHE9) and 108 to the six month regimen (RHEZ6). At the end of the treatment, 77 patients had not completed the allocated regimen as planned (cf Table 2). For twenty-eight patients this was because of adverse drug effects. Of the 23 who died, five died from pulmonary tuberculosis. In four of the 19 cases of non-compliance, a non-trial regimen was administered. Of the four patients with extrapulmonary tuberculosis, three had renal and the remaining patient had bone involvement.

There was no significant difference in such characteristics as: age; sex; social, occupational and employment status; alcohol and cigarette consumption rates, between those withdrawn (Table 2) and those not, neither were there any significant differences in the above characteristics between the remaining 76 patients in the RHE9 regimen and the 67 patients in the RHEZ6 regimen. Table 3 shows the pretreatment characteristics of the 143 patients who completed chemotherapy in accordance with the protocol. The monthly rates of sputum conversion for these patients are shown in Table 4. At the end of the initial two month phase of chemotherapy, 86% of patients in the RHEZ6 regimen had negative cultures compared with 76% in the RHE9 regimen. This did not reach statistical significance. At the end of the third month, the figures were 98% and 88% respectively and this difference was statistically significant, p<0.02. After six months chemotherapy all patients in both groups were consistently negative on culture.

At completion of chemotherapy there was a marked improvement in chest x-ray appearances. Of the 16 patients with pleural effusions, all resolved, but they all showed some residual pleural thickening. At entry to the study 69% had bilateral disease, 52% advanced disease and 57% had cavities. Following treatment the figures were 36%, 1% and 57% respectively. Only three patients had complete radiological resolution. There was no significant differences between the two regimens in the degree of resolution obtained.

On entry to the trial all patients were treated on an in-patient basis for a varying period depending on their clinical status (90% - four weeks, 52% - eight weeks). The dispensing of treatment was fully supervised by the nursing staff and all random urine samples taken on in-patients (more than 200 samples) were positive for metabolites of Rifampicin. Following discharge from the hospital patients were then monitored by our out-patients department and by their local community care services where regular pill counting checks were introduced and though far from ideal, they did help in monitoring compliance.

Drug intolerance was the commonest cause of withdrawals, there was no significant difference between the two treatment

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**Table 1 - Patients studied**

<table>
<thead>
<tr>
<th>Number allocated to chemotherapy</th>
<th>288</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excluded for failure to satisfy protocol</td>
<td>68</td>
</tr>
<tr>
<td>Pretreatment negative cultures</td>
<td>48</td>
</tr>
<tr>
<td>Mycobacterium bovis isolated</td>
<td>2</td>
</tr>
<tr>
<td>Mycobacterium kansasii isolated</td>
<td>1</td>
</tr>
<tr>
<td>Isoniazid resistance</td>
<td>7</td>
</tr>
<tr>
<td>Diagnosis not TB</td>
<td>10</td>
</tr>
</tbody>
</table>

| Number valid for analysis | 220 |

**Table 2 - Patients not completing all regimens**

<table>
<thead>
<tr>
<th>RHE9</th>
<th>RHEZ6</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number starting chemotherapy</td>
<td>112</td>
<td>108</td>
</tr>
<tr>
<td>Reasons for withdrawal:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug intolerance</td>
<td>11</td>
<td>17</td>
</tr>
<tr>
<td>Died during treatment</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Non-compliant</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Extrapulmonary disease</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Consent withdrawn</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Total withdrawals</td>
<td>36</td>
<td>41</td>
</tr>
<tr>
<td>Number completing chemotherapy</td>
<td>76</td>
<td>67</td>
</tr>
</tbody>
</table>

**Table 3 - Pretreatment characteristics of 143 valid patients**

<table>
<thead>
<tr>
<th>Drug Regimens: RHE9 RHEZ6 TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Mean age</td>
</tr>
<tr>
<td>Radiographic extent of disease</td>
</tr>
<tr>
<td>Unilateral</td>
</tr>
<tr>
<td>Bilateral</td>
</tr>
<tr>
<td>Minimal disease</td>
</tr>
<tr>
<td>Moderate disease</td>
</tr>
<tr>
<td>Advanced disease</td>
</tr>
<tr>
<td>Cavities</td>
</tr>
<tr>
<td>Pleural effusions</td>
</tr>
<tr>
<td>Bacteriological status</td>
</tr>
<tr>
<td>Smear positive/ Culture positive</td>
</tr>
<tr>
<td>Smear negative/ Culture positive</td>
</tr>
</tbody>
</table>

**Table 4 - Cumulative percentage of patients culture negative at each month**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>RHE9</td>
<td>76</td>
<td>58</td>
<td>76</td>
<td>88*</td>
<td>96</td>
<td>99</td>
<td>100</td>
</tr>
<tr>
<td>RHEZ6</td>
<td>67</td>
<td>52</td>
<td>86</td>
<td>98</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

* <p>0.02

regimens (X² = 1.734, NS) however, females were significantly more affected than males (F - 20%, M - 8%, p<0.01).

Hepatitis, defined as the presence of persistently abnormal liver function tests with or without symptoms was the most important adverse drug reaction occurring in 6% (seven of 112) of the RHE9 regimen and 12% (13 of 108) of the RHEZ6 regimen. This difference is not statistically significant (X² = 2.228, NS). Of these 20 patients who had significant hepatitis, two were clinically jaundiced and only three were asymptomatic. Six patients developed a drug induced rash (RHE9-4, RHEZ6-2), three of whom also had hepatitis. Three patients in the RHEZ6 regimen developed arthralgia, two with raised uric acid levels and the arthralgia subsided on withdrawal of Pyrazinamide. Isoniazid was implicated in causing systemic lupus erythematosus in one
patient (RHE9 regimen) and acute psychosis in another (RHE9 regimen). There was no significant difference in the incidence of side-effects experienced in either regimen.

In all cases of hepatitis, attempts were made to establish the drug (or drugs) responsible. Following the cessation of therapy, liver function tests were allowed to return to normal before the reintroduction of each drug in turn, starting with Rifampicin, until the allocated regimen was resumed or until liver function tests became significantly abnormal. Rifampicin alone was implicated on six occasions (RHE9-4, RHEZ-2), Isoniazid on four occasions (RHEZ-6-4), Ethambutol once (RHEZ6) and no specific drug on nine occasions (RHE9-3, RHEZ6-6).

The possible occurrence of relapse is of course very important. Traditionally a two-year follow-up period was thought to be necessary and entirely adequate. The British Thoracic Association trial however* showed that there was one radiographic relapse after more than four years follow-up. It is of particular note that all their six cases of bacteriological relapse occurred within the first 15 months of follow-up. While our patients will be followed for at least two years after chemotherapy, relapse seems very unlikely in that period based on previous evidence. To date all patients have completed eighteen months post chemotherapy follow-up without a single relapse either culture positive or radiological.

Discussion
The purpose of this trial was to establish if we could reproduce the success of previous trials, in different populations, on six months therapeutic regimens for pulmonary tuberculosis when applied to our population. The two most important variables studied were efficacy and toxicity. Our expectations were, based on the results of previous trials, that the six month regimen should be as effective as the nine month regimen in eliminating tubercle bacilli from sputum and that there should be no increase in toxicity to the patients. This trial has shown that the six month regimen achieved culture negative sputum faster than the nine month regimen (p<0.02 at three months) with no significant increase in toxicity. The rate of drug induced hepatitis seen in our trial is higher than in the BTS's trial but it is in line with our previous experience.

Other benefits that might also be expected from the shorter six month regimens are — enhanced patient compliance because of its shorter duration; savings of the order of 25% in terms of the cost of the drugs and savings in health care, in hospitalisation and in shorter supervision, all of which are important in the current economic climate.

In so far as the future is concerned, it is not expected, with the current drugs available to reduce the period of chemotherapy further. However, many trials are presently being carried out to refine the six month regimen even further e.g. by decreasing or eliminating Ethambutol (in our study we used Ethambutol at a dosage of 15mg/kg as compared to the British Thoracic Association's regimen of 25mg/kg), by using fixed combinations of oral drugs or by introducing intermittent instead of daily chemotherapy. We look forward to the results of these developments. Based on the results of this trial, we have adopted and recommend the six month regimen of Rifampicin and Isoniazid for six months supplemented by Pyrazinamide and Ethambutol (at the stated dosage) in the treatment of pulmonary tuberculosis.

Acknowledgements
We wish to acknowledge the help received from the staff of Peamount Hospital and of each participating Community Care Area without whose assistance this study would not have been possible.

References

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Pulmonary tuberculosis in the Republic of Ireland: an epidemiological profile from a single unit

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We present a retrospective epidemiological analysis of 1011 adults with a first time diagnosis of pulmonary TB seen between 1980-1985. Most (98.7%) were from the Republic of Ireland and 68.4% were male. Both males and females showed a bimodal age distribution with 37.6% of females and 18.8% of males aged younger than 30 years. More than half (58.6%) of patients smoked cigarettes and 63.7% consumed alcohol. Two patients indulged in the use of hard drugs. Only 5% of patients were asymptomatic and 0.9% of patients had symptoms for longer than 1 year. Radiologically, 54.7% of patients had bilateral disease; 58.5% had cavities and 10% had pleural effusions. Mantoux testing was positive to 1 tuberculin unit in 76.0%; to 10 tuberculin units Mantoux in 3.7%; and negative to 100 tuberculin units in 5.0%. Primary drug resistance occurred in 0.9% of patients. Ninety (9.0%) of patients died before completing antituberculous treatment and in 40 patients tuberculosis was the principle or main cause of death.

Introduction

In Europe in 1983, some 142,000 cases of tuberculosis were notified. The average rate per 100,000 population was 32.7 (range: Norway, 5.8; Yugoslavia, 72.8). The Republic of Ireland has the fourth highest incidence of tuberculosis within the European Community at 28/100,000 population (1). These crude rates are initially misleading as many of these countries have a significant first generation immigrant population from areas with a high incidence of tuberculosis. In England and Wales the crude rate for 1983 was 12.7/100,000 but the rate for the indigenous caucasian population (6.9/100,000) is nearly half that, and only a fraction of the rates for the Bangladeshi (169/100,000) and Pakistani (178/100,000) communities (2). A similar pattern is seen in Denmark where in 1982 the rate for the indigenous population (11/100,000) was also only a fraction of that for the immigrant community (146/100,000) (3). Data from the 1981 census of population showed that 93.2% of the population from the Republic of Ireland to be indigenous with less than 0.2% of the population being from countries with naturally high rates of tuberculosis (4).

The problem of tuberculosis in the Republic of Ireland is therefore one for the indigenous caucasian population and it is against this background that international comparisons should be made and the tuberculous problem be put into proper perspective.

Despite our relatively high incidence of tuberculosis, the published epidemiological data for tuberculosis is quite scant (5-10). Only conglomerate data are available from the Public Health Division in our Department of Health to whom the disease is statutorily notified. Unfortunately, only gross figures are available outlining the total number of new cases notified annually and as to whether they are pulmonary or nonpulmonary cases. No information regarding the age, sex, extent of disease or other epidemiological parameters are available. Furthermore, there is no national policy or co-ordinating body to oversee the provision of the tuberculosis service which has become fragmented and practices with respect to prevention, contact tracing and treatment are far from being standardized (9).

The chest unit, established by Lady Aberdeen in 1912 as a sanatorium, has evolved over the years into a general respiratory unit with a particular interest in the treatment of pulmonary tuberculosis. No other unit comparable to ours exists in the Republic of Ireland and hence, because of our long association with the treatment of tuberculosis and the expertise gained, patients are referred to our unit from every sector of the health services and from every Health Board authority. Between 1980-1985 inclusive some 4625 new cases of pulmonary tuberculosis were notified nationally of which 1480 (32.0%) were treated at our unit. Patients with nonpulmonary tuberculosis may be referred to our centre when inpatient care is required. These referrals may be directly to us or come from other specialist departments. Similarly, admission of
Patients and Methods

We analysed the available epidemiological data for all new patients treated at our unit between 1980-1985 inclusive. A total of 1641 patients were identified. Of these 1011 were adults, had a first time diagnosis of pulmonary tuberculosis alone and had their diagnosis confirmed by culture or histology. It is this group of patients that form the basis of subsequent discussion.

Data pertaining to the national population was obtained from the 1981 census (4). Social class was determined according to the guidelines of the Irish Social Class scale (11). A standard drink (st. dr.) is equivalent to a half glass of spirits, a bottle of beer or a half pint of draught beer. Hard drugs include heroin, morphine, cocaine and the major tranquillisers. Chest radiographs were reported on using a predetermined classification system (12).

Results

Of the 1011 patients with proven pulmonary tuberculosis, 998 (98.7%) were from the Republic of Ireland; ten (1%) from the Asian/Indian/African continents; and 3 (0.3%) from the European Community. Just over two thirds, 692 (68.4%) were male. The age distribution for all patients and for males and females separately is shown in Fig. 1. Both males and females show a bimodal age distribution. More than a third (37.6%) of females were aged less than 30 years compared to 18.8% of males.

Table 1 outlines the distribution of patients according to marital status, social class and employment status. The majority of patients, 58.6%, smoked cigarettes (males, 65.9%; females, 42.6%) as against the national average of 35.0% for the study period. A further 31 (3.1%) patients smoked a pipe, one patient smoked cigars and 102 (10.1%) were exsmokers. The median cigarette consumption was 20/day (range 1-90). Forty-four (6.4%) males and six (0.9%) females smoked more than 40/day. Most of the patients, 63.7%, consumed alcohol (males, 74.1%, females, 41.1%). Overall, the median consumption of alcohol was 10 st. dr./week, however, 57.3% of males as compared to only 12.2% of females drank more than this amount. Only two patients (0.2%) admitted to or were known to have indulged in the use of hard drugs.

Patients were referred to our unit from the following sources: Teaching Hospitals (27.4%); General Hospitals (27.2%); Community Health Services (24.4%); General Practitioners/Family Doctors (12.4%); Psychiatric Hospitals (5.1%) and Nursing Homes/Others (3.5%). Antituberculous therapy had been commenced in 204 (20.2%) patients prior to arrival at our unit with a standard regimen in 80.1%. A further 339 (33.5%) were on antibiotics other than antituberculosis therapy at the time of referral and the remaining 468 (46.3%) were therapy free.

Table 2 outlines the number of patients with particular symptoms at presentation as well as the number of patients suffering from other disease. Cough, sputum production and malaise were the commonest symptoms experienced. Only 51 (5%) patients were asymptomatic and of the remainder 189 (18.7%) had symptoms for less than 1 month; 455 (45.0%) had symptoms lasting between 1 and 3 months; 198 (19.6%) had symptoms for 4-6 months; 109 (10.8%)
Table 1  Marital status, social class and employment status of all 1011 patients as percentages

<table>
<thead>
<tr>
<th>Marital status</th>
<th>Male (%)</th>
<th>Female (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single</td>
<td>47.4</td>
<td>39.5</td>
<td>44.9</td>
</tr>
<tr>
<td>Married</td>
<td>40.0</td>
<td>40.8</td>
<td>40.3</td>
</tr>
<tr>
<td>Widowed</td>
<td>8.8</td>
<td>18.5</td>
<td>11.9</td>
</tr>
<tr>
<td>Separated</td>
<td>3.8</td>
<td>1.4</td>
<td>2.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.7</td>
<td>1.9</td>
<td>1.8</td>
</tr>
<tr>
<td>2</td>
<td>6.7</td>
<td>9.4</td>
<td>7.5</td>
</tr>
<tr>
<td>3</td>
<td>12.9</td>
<td>17.9</td>
<td>14.4</td>
</tr>
<tr>
<td>4</td>
<td>23.0</td>
<td>15.4</td>
<td>20.6</td>
</tr>
<tr>
<td>5</td>
<td>21.1</td>
<td>20.4</td>
<td>20.9</td>
</tr>
<tr>
<td>6</td>
<td>34.1</td>
<td>21.3</td>
<td>30.1</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.6</td>
<td>13.8</td>
<td>4.7</td>
</tr>
<tr>
<td>Employment status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>41.9</td>
<td>27.9</td>
<td>37.5</td>
</tr>
<tr>
<td>House duties</td>
<td>0.6</td>
<td>50.2</td>
<td>19.9</td>
</tr>
<tr>
<td>Retired</td>
<td>28.3</td>
<td>6.9</td>
<td>21.6</td>
</tr>
<tr>
<td>Unemployed</td>
<td>19.4</td>
<td>5.0</td>
<td>14.8</td>
</tr>
<tr>
<td>Institutional care and/or long term disabilities</td>
<td>6.6</td>
<td>3.4</td>
<td>5.6</td>
</tr>
<tr>
<td>Students</td>
<td>3.2</td>
<td>6.3</td>
<td>4.2</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
</tr>
</tbody>
</table>

experienced symptoms for 7–12 months; and 9 (0.9%) patients had symptoms for over a year before they were diagnosed as tuberculosis. Most of the patients, with another major illness, had had the illness for at least 5 years prior to the diagnosis of tuberculosis. The exception to this were those patients with cancer and sarcoidosis, who developed tuberculosis within a year of their other illness being diagnosed. Approximately a quarter (25.1%) of the patients were on some form of long term medication.

Only 151 (14.9%) patients were aware that they had been previously vaccinated with BCG and 209 (20.6%) were certain that they had never received BCG. The remaining 651 (64.4%) were unaware of their BCG status and since the presence or absence of vaccination scars was not documented their vaccination status remains unclear. Two hundred and ninety-two (28.2%) patients gave a positive family history for tuberculosis and of these 167 were aware of a close contact with a known tuberculosis patient in the previous 2 years and, for 117 of these, the contact was in the home. No information concerning the bacteriological or treatment status of the index cases was available to us.

Table 3 shows the radiological extent of disease at presentation for all patients and the haematological data for the 468 patients who received no antibiotic/chemotherapy prior to investigation. Of the 926 patients who had their Mantoux status recorded 704 (76.0%) were positive to 1 tuberculin unit (T.U.), 142 (15.3%) were positive to 10 T.U., 34 (3.7%) were positive to 100 T.U. and 46 (5.0%) were negative to 100 T.U. Bacteriologically 850 (84.1%) patients were sputum positive on both direct smear and on culture (S+, C+); 111 (11.0%) were positive on culture alone (S−, C+); and the remaining 50 (4.9%) patients had their diagnosis confirmed histologically, e.g. pleural biopsies. Of the 961 culture positive patients only nine (0.9%) displayed resistance to one or other chemotherapeutic agents. Five were resistant to isoniazid; two to streptomycin; one to para-aminosalicylic acid (P.A.S.); and one to rifampicin, ethambutol and isoniazid.

Patients referred to our unit for further investigation or treatment were initially admitted. Duration of inpatient stay was variable and related not only to their tuberculosis but to other factors as well, viz, other illnesses, socio-economic circumstances, compliance with therapy, drug toxicity or resistance, as well as the availability of an adequate service in their own community. The mean duration of inpatient stay was 16.4 ± 15.3 weeks (range, 1 day–172 weeks), however
Table 2 Presenting symptoms and past medical history for 1011 patients with pulmonary tuberculosis

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>No.</th>
<th>%</th>
<th>Past medical history</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>904</td>
<td>89</td>
<td>C.O.P.D.†</td>
<td>190</td>
<td>18</td>
</tr>
<tr>
<td>Sputum</td>
<td>847</td>
<td>83</td>
<td>Alcoholism</td>
<td>120</td>
<td>11</td>
</tr>
<tr>
<td>Malaise</td>
<td>745</td>
<td>73</td>
<td>Peptic ulcer</td>
<td>101</td>
<td>10</td>
</tr>
<tr>
<td>Weight loss</td>
<td>568</td>
<td>56</td>
<td>C.V.A./I.H.D.‡</td>
<td>90</td>
<td>9</td>
</tr>
<tr>
<td>Anorexia</td>
<td>517</td>
<td>51</td>
<td>Psychiatric illness§</td>
<td>65</td>
<td>6</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>409</td>
<td>40</td>
<td>Gastric surgery</td>
<td>56</td>
<td>5</td>
</tr>
<tr>
<td>Pleuritic pain</td>
<td>365</td>
<td>36</td>
<td>Cancer</td>
<td>55</td>
<td>5</td>
</tr>
<tr>
<td>Night sweats</td>
<td>322</td>
<td>31</td>
<td>Diabetes mellitus</td>
<td>38</td>
<td>3</td>
</tr>
<tr>
<td>Fever</td>
<td>233</td>
<td>23</td>
<td>Hypertension</td>
<td>35</td>
<td>3</td>
</tr>
<tr>
<td>Menstrual dist*</td>
<td>26</td>
<td>19</td>
<td>Asthma</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>184</td>
<td>18</td>
<td>Fibrotic lung</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>103</td>
<td>10</td>
<td>Pneumocociosis</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Wheeze</td>
<td>83</td>
<td>8</td>
<td>Sarcoidosis</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>92</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Menstrual disturbance in females 15–50 years only.
†C.O.P.D., chronic obstructive pulmonary disease.
‡C.V.A., cerebrovascular accidents; I.H.D., ischaemic heart disease.
§Psychiatric illness requiring at least one year inpatient therapy.

most of the patients, 55.7%, were inpatients for less than 12 weeks. Patients at our unit receive either a 6 month or 9 month regimen of short course chemotherapy (13). Our patients received the following medications: rifampicin (R), 98.4%; isoniazid (H), 99.5%; ethambutol (E), 97.0%; pyrazinamide (Z), 15.9%; and streptomycin (S), 9.1%. The percentage of patients experiencing toxicity from a particular drug was as follows: R, 8.7%; H, 3.2%; E, 1.6%; Z, 4.3%; and S, 3.2%. All patients received their medication in a supervised manner from the duty nurse, thus enhancing compliance.

For the period that the patients remained in our unit, sputum samples were collected and analysed on a weekly basis to ascertain their bacteriological state until they become negative. Following discharge, patients were monitored either by our out-patient unit, the community care services or a combination of both and sputum samples were obtained on a monthly basis until it became bacteriologically negative (S−, C−) and again on completion of their chemotherapy. Further follow-up is usually for a 2 year period either at our unit or the local community care clinic, whichever is most suitable for the patient. It was possible to ascertain, within 4 week time-bands, the length of time to go bacteriologically negative for 775 (80.6%) of the 961 culture positive patients and 672 (79.1%) of the 850 direct smear positive patients. Table 4 outlines the results for each time span and the cumulative totals. Ninety (9.0%) patients died, of whom tuberculosis was the principle or main contributing cause of death in 40.

Discussion

Although the incidence of tuberculosis has declined dramatically in the Republic of Ireland (14), it still remains a significant health problem. This epidemiological study deals with a third of all new cases of pulmonary tuberculosis treated nationally over a 6 year period. As there are no comparable data available on the national tuberculosis population to compare our figures with, it is not possible to state with certainty whether our study represents the adult pulmonary tuberculosis population. We believe, however, that it is representative given the numbers referred, the wide range in extent of disease, distribution of referrals and the similarity in age and sex as found by a national tuberculosis survey which we conducted in 1986 (9) and by a committee of the Eastern Health Board authority (10).

The occurrence of this preventable disease in so many of our young population has serious implications. Firstly, the morbidity to those afflicted and secondly, that despite our public health and preventive measures there is still significant transmission of tuberculosis to our young population. This is contrary to the picture of tuberculosis seen in most other European Community countries.
Table 3  Pretreatment radiological/hematological data

(a) Radiological data (n = 1011 patients)

<table>
<thead>
<tr>
<th>Disease status</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral disease</td>
<td>458 (45.3)</td>
</tr>
<tr>
<td>Bilateral disease</td>
<td>553 (54.7)</td>
</tr>
<tr>
<td>Cavities</td>
<td>591 (58.5)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>102 (10.1)</td>
</tr>
<tr>
<td>Minimal disease</td>
<td>130 (12.9)</td>
</tr>
<tr>
<td>Moderate disease</td>
<td>432 (42.7)</td>
</tr>
<tr>
<td>Advanced disease</td>
<td>449 (44.4)</td>
</tr>
</tbody>
</table>

(b) Haematological data (n = 468 patients, chemotherapy/antibiotic free at referral to our unit)

<table>
<thead>
<tr>
<th>Hb* Concentration (g dl⁻¹)</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;11.5</td>
<td>97 (20.7)</td>
</tr>
<tr>
<td>11.5-16.5</td>
<td>355 (79.9)</td>
</tr>
<tr>
<td>&gt;16.5</td>
<td>16 (3.4)</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>13.1 ± 2.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>White cell count† (cells x 10¹⁰ l⁻¹)</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.4</td>
<td>19 (4.1)</td>
</tr>
<tr>
<td>4-11</td>
<td>396 (84.6)</td>
</tr>
<tr>
<td>11</td>
<td>53 (11.3)</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>8.3 ± 2.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Erythrocyte sedimentation rate‡ (mm h⁻¹)</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.15</td>
<td>125 (26.7)</td>
</tr>
<tr>
<td>0.15-15</td>
<td>175 (37.4)</td>
</tr>
<tr>
<td>&gt;15</td>
<td>168 (35.9)</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>28.6 ± 16.5</td>
</tr>
</tbody>
</table>

Table 4 Duration of chemotherapy required to achieve negative sputum culture and negative direct smear

<table>
<thead>
<tr>
<th>Time span (weeks)</th>
<th>Negative Culture</th>
<th>Direct Smear Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>Cumulative total (%)</td>
</tr>
<tr>
<td>0-4</td>
<td>370 (47.7)</td>
<td>370 (47.7)</td>
</tr>
<tr>
<td>5-8</td>
<td>250 (32.3)</td>
<td>620 (80.0)</td>
</tr>
<tr>
<td>9-13</td>
<td>125 (16.1)</td>
<td>745 (96.1)</td>
</tr>
<tr>
<td>14-26</td>
<td>23 (3.0)</td>
<td>768 (99.2)</td>
</tr>
<tr>
<td>27-52</td>
<td>4 (0.5)</td>
<td>772 (99.6)</td>
</tr>
<tr>
<td>&gt;52</td>
<td>3 (0.4)</td>
<td>775 (100.0)</td>
</tr>
</tbody>
</table>

The misconception that tuberculosis is a disease that affects only the elderly, alcoholics and drug abusers is shown not to be true in the Republic of Ireland. While it is impossible, because of the lack of national data, to ascertain the risk of tuberculosis to any particular group, our study shows that the majority of our patients were aged less than 65 years, were gainfully employed or in full-time education, were not alcoholics and were not drug abusers.

Preliminary experience with HIV positive intravenous drug abusers in Dublin suggests that this group may become more significant in the near future (15).

Symptomatically, the majority of the patients gave a history of a persistent respiratory tract infection with
little evidence of the classical symptoms such as night
sweats or haemoptysis. Information regarding
status was disappointing, however, given the age
distribution of the population analysed, many of
whom would not have had the opportunity to receive
BCG and given that BCG is not offered as routine
throughout the country (9), the findings are not
surprising. What is evident is that steps must be taken
to ensure standardization of BCG policy nationally.
Furthermore, the fact that 167 patients were aware of a
recent tuberculosis contact, most of them in the home,
underscores the need for making contact tracing a
priority in our preventive measures.

Laboratory data, other than microbiological,
proved to be unhelpful. The radiological extent of dis-
ease was surprising in that it was so extensive at the
time of presentation. This is in marked contrast to that
seen in England and Wales where only 17.0% of the
caucasian population with pulmonary tuberculosis
had disease that extended beyond the volume of one
lung and only 35.0% had cavitation (16). This picture
of extensive disease along with the duration of symp-
toms reflect delay in diagnosis and may lead to serious
consequences (8).

We believe that where possible, ambulatory treat-
ment should be carried out. A recent survey has shown
that 85.0% of all patients have their treatment initiated
by the hospital services (9). Many factors influence
the length of in-patient stay, not least among them is
compliance. It is difficult to ensure compliance unless
one has a standardized management policy through-
out the country. Another important factor is the stan-
dardization of treatment. A recent survey carried out
by our unit found that 44 different combination
chemotherapeutic regimens were being used and
16.0% of patients treated by hospital based services
were receiving potentially inadequate treatment for
their pulmonary tuberculosis (9).

A sense of complacency has developed concerning
tuberculosis in that it is no longer regarded as a prob-
lem. This may be because of the major improvements
in drug therapy, the decline in incidence and the possi-
bility of ambulatory treatment. In our study 40
patients died from their disease. Most of these patients
are included in a previous study carried out in our
unit and reported elsewhere in which it was found that
delay in diagnosis and in initiation of treatment played
a major role in these deaths (8). There is also ample
evidence to suggest that outbreaks of tuberculosis with
much subsequent morbidity to those involved can
and do occur even with minimal exposure to infection
(17-20). Emphasis must be placed on early detection
and treatment of infectious cases, the collection of
adequate epidemiological data as the profile of the
disease will change with decreasing incidence as well as
giving priority to contact tracing and prophylactic
treatment in the continuing efforts to eradicate this
preventable disease.

Acknowledgements

We wish to acknowledge the help of Grainne Feeney
and Karen Kearns for preparing the manuscript. We
are particularly grateful to John Dunne for his invaluable
advice on the analysis of the data.

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Detection of IgG and IgA Antibodies to PPD in Tuberculosis

S. Browne¹, A. Murray¹, A. Whelan¹, P. Kelly², L. Clancy² and C. Feighery¹

SUMMARY
This study describes a biotin-streptavidin enzyme-linked immunosorbent assay (ELISA) technique for the measurement of antibodies to purified protein derivative of tuberculin (PPD). Raised IgG antibodies were found in 15 of 20 patients with active tuberculosis. In addition, IgA antibodies were elevated in 16 patients: antibodies of this isotype were not significantly raised using a standard ELISA technique in an earlier study. Combining the results of the IgG and IgA assays, 19 of the 20 patients had raised antibody levels; in contrast, these antibodies were elevated in only 13 of 67 control individuals. The findings of this pilot study are sufficiently encouraging to test this assay in a prospective fashion with appropriate disease control groups.

METHODS
Subjects
Serum was collected from 20 patients with microbiologically proven active tuberculosis. All patients had been receiving treatment for less than one month, in order to avoid the effect of therapy on antibody levels. Serum was also obtained from 32 healthy controls and 54 disease controls: the latter included 16 patients with Crohn's disease, 9 with dermatitis herpetiformis and 19 with rheumatoid arthritis. In addition, 10 rheumatoid factor positive sera were investigated.

Enzyme linked immunosorbent assay (ELISA)
Purified protein derivative of tuberculin (Evans Medical Ltd. England) was used as antigen. This was diluted 1/20 in coating buffer (carbonate/bicarbonate, pH 9.6) and 100ul per well was used to coat a 96 well Dynatech microELISA plate. The plates were incubated at 4°C overnight and washed three times with phosphate buffered saline (PBS)/Tween. 100 ul of serum diluted in PBS/Tween (1/100 for IgG and IgA assays; 1/200 for the IgM assay) was added to the wells in triplicate. Six blank wells with 100ul of PBS/Tween only and three wells with serum pooled from seven normal subjects were included in each plate. The plates were incubated at 37°C for one hour and washed three times with PBS/Tween. Biotinylated goat

INTRODUCTION
Although tuberculosis (TB) is conventionally diagnosed by standard microbiological assays, interest remains in the adjunctive information which can be obtained by measuring antibodies to TB antigens. Using a standard enzyme linked immunosorbent assay (ELISA), we recently reported that raised IgG antibodies to purified protein derivative of tuberculin (PPD) were present in 65% of 47 patients with active tuberculosis. However, raised IgA and IgM antibodies were infrequently present. In this current study, an enhanced ELISA system was used employing a biotin-streptavidin system: using this technique, both IgG and IgA PPD antibodies were detected in the majority of a small group of patients (20) with active tuberculosis.

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², Peamount Hospital, Newcastle, Co. Dublin.
antihuman whole antibody (Amersham) was used as conjugate. This was diluted in PBS/Tween (1/1000 for IgG assays, 1/200 for IgA and IgM assays) and 100ul was added to each well. The plates were again incubated at 37°C for one hour and washed thrice with buffer. Then 100ul of streptavidin-avidinylated peroxidase complex (Amersham) diluted 1/200 in PBS/Tween was added to each well. After a further incubation and washing step, 100ul of orthophenylene diamine substrate was added to each well. After approximately 20 mins (when a slight colour change was observed in the pooled serum wells) the reaction was stopped with 100ul of 2M H$_2$SO$_4$. The optical density (OD) of each well was measured using a Titer-Tek MultiScan Plus.

The mean and standard deviation (SD) were calculated for the normal controls included in each plate. Any OD value lying 2 SD above the mean was considered elevated: the positive range was arbitrarily divided into four categories:

1+ = < 10% above the mean + 2 SD
2+ = > 10% above but < 2 times the mean + 2 SD
3+ = > 2 times but < 5 times the mean + 2 SD
4+ = > 5 times the mean + 2 SD

RESULTS
Raised IgG anti PPD antibodies were found in 15 of 20 patients with microbiologically proven TB (Fig. 1). In 10 of these patients antibody levels were in the 3+ range or greater. In contrast, raised antibodies were found in 5 of 67 control sera, with only one of these above the 2+ range.

IgA anti PPD antibodies were elevated in 16 of the patients with active TB and in 12 of the 67 control sera. Again 10 patients had markedly raised levels (3+ or greater). The majority of the 12 positive sera from the control subjects had lower levels of PPD antibodies; however, three rheumatoid factor positive sera had high levels (3+ or greater). To investigate this further, sera from 19 patients with clinical rheumatoid arthritis were tested: 9 had elevated anti PPD antibodies with all except two of these in the low range ie. 2+ or lower (results not illustrated).

Different populations were detected by the IgG and IgA assays. If the results of both assays were combined 19 of the 20 TB patients were positive, as were 15 of the 67 control sera.

In the patients with active TB IgG and IgA anti PPD antibodies were significantly elevated in comparison to the combined control groups (p<0.004 and p<0.05 respectively).

The IgM assay did not distinguish between active TB and control populations. Raised IgM anti PPD antibody was detected in only 4 of the 20 active TB patients and in 3 of 38 control sera.

DISCUSSION
In an earlier study, using a conventional enzyme linked immunosorbent assay (ELISA) raised IgG antibodies to PPD were detected in 65% of patients with active tuberculosis1. Raised IgA antibodies were present in only a minority of these patients even though anti PPD antibodies of this isotype were found to be elevated in another study1. In the current study, the ELISA assay was enhanced by incorporating a biotin-streptavidin step and sera from a further 20 patients with active tuberculosis were investigated: using this system IgG and IgA anti PPD antibodies respectively. Combining the results from the two assays, raised antibodies were found in 19 of the patients and in 50% of these, marked antibody elevation was observed.

Since this was a pilot study, no attempt was made to assess the value of the assay with appropriate disease controls. Of the control individuals tested, 15 of 67 had
Figure 1. IgG and PPD antibodies measured by biotin-strepavidin ELISA. Based on the optical density result, values greater than two standard deviations above the mean in the control group were arbitrarily divided into four categories of positivity.

Figure 2. IgA anti PPD antibodies measured by biotin-strepavidin ELISA. Based on the optical density result, values greater than two standard deviations above the mean in the control group were arbitrarily divided into four categories of positivity.

84
raised antibody levels. IgA anti PPD antibodies were more frequently elevated (in 12 subjects) than in IgG antibodies (5 subjects).

In general, anti PPD levels were only slightly raised in these controls but occasional patients with dermatitis herpetiformis, Crohn's disease and rheumatoid arthritis had marked antibody elevation. The raised IgA anti PPD antibodies found in patients with rheumatoid arthritis (RA) was particularly striking with two of nine patients having markedly elevated (3+) values. This finding is of particular interest, since T cell sensitisation to mycobacterial antigens has been reported in this disease. Furthermore, raised IgA antibody levels to crude mycobacterial antigens was also recently noted in RA patients. Indeed, it is postulated that an immune response to mycobacterial antigens (or cross reactive antigens) may play a role in the pathogenesis of RA.

With the results obtained in this study, it seems reasonable to test this assay in a prospective fashion in patients with suspected TB and in particular to include appropriate disease controls with a spectrum of pulmonary disease. Because of the low incidence of TB in Ireland, it is unlikely that the predictive values generated by this serodiagnostic test would make such assays useful in screening the population as a whole. In view of the predominant T cell response to mycobacteria, it is unlikely that a serological assay can achieve a sensitivity of 100%. Enhanced specificity might be achieved by examining reactivity against specific TB antigens, for example by using a monoclonal antibody blocking technique as advocated by Ivanyi and colleagues. Finally, the continuing interest in mycobacterial serological assays presumably reflects the aspiration that some diagnostic role can be played by antibody measurement. The speed and simplicity of an ELISA technique, such as that described here are important features of such a diagnostic aid.

REFERENCES
Isoaiazid resistant tuberculosis in a school outbreak: the protective effect of BCG


ABSTRACT: An outbreak of isoniazid resistant tuberculosis occurred in a large second level school. A total of 1,160 teenage pupils were at risk. Nineteen cases of tuberculosis were diagnosed, 15 were students, 9 of whom were among 251 non-vaccinated students and 6 among 909 vaccinated students. Two cases of miliary tuberculosis, one of whom also had tuberculous (TB) meningitis, occurred in the non-vaccinated group. The number of children with Heaf grade +3 or +4 was significantly greater among children who had been given Bacille Calmette-Guérin (BCG) vaccination (8 vs 4.4%). This suggests a boosting effect on the response in vaccinated children. The protective effect of neonatal BCG vaccination in this school outbreak suggests that it provides significant protection against tuberculosis lasting into adolescence.

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Keywords: Bacille Calmette-Guérin (BCG); isoniazid resistance; mini-epidemic; school outbreak; tuberculosis.

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Localized outbreaks or mini-epidemics of tuberculosis are well described [1-7]. In this study we describe a mini-epidemic of tuberculosis occurring in a large second level school. It is of note that the organism was found to be isoniazid resistant. A large number of teenage children were involved and it allowed a unique opportunity to compare the outcome in Bacille Calmette-Guérin (BCG) vaccinated and non-vaccinated children.

The school

The school involved is a large second level school (day pupils only) of 1,138 pupils aged 12-18 yrs. It services a large area of north east Donegal in the north west part of the Republic of Ireland. The community is largely agricultural/fishing and mainly rural. The children travel by bus into school in the town from outlying districts. While the policy in the Community Care Area is to give neonatal BCG vaccination, many children at the school were born outside the area or were the children of returned emigrants and had not received BCG vaccination.

Index cases

Between late February and early April, 1986, three teenage girls at the school were diagnosed as having tuberculosis.

Case 1: Aged 17 yrs. History of neonatal BCG vaccination; pleural effusion from which tubercle bacilli were cultured.
Case 2: Aged 19 yrs. History of neonatal BCG vaccination. Large right-sided pleural effusion. Pleural biopsy was positive for tuberculosis.
Case 3: Aged 14 yrs. No BCG vaccination. Miliary tuberculosis and tuberculous meningitis. Cerebrospinal fluid was positive for culture for tuberculosis.

The three index cases all had a positive response (greater than 10 mm) to 1 tuberculin unit (TU) Mantoux. All three girls presented to their family doctors.

Population and methods

All pupils, teachers and ancillary staff at the school were screened. A record was made of each persons BCG vaccination history and whether scars were present, and personal or family history of tuberculosis. Basic personal data was available from the school computer files. BCG vaccination records were available from the Public Health Department.

In addition to the above, the families and home contacts of children and staff diagnosed as having tuberculosis were screened, as were staff in recreational areas, e.g. local cafes, shops, transport, facilities frequented by the students.

All persons screened had a Heaf test and chest X-ray. The Heaf test was used in preference to the Mantoux test.
PROTECTIVE EFFECT OF BCG VACCINATION

Table 1. - The Heaf test results for 1,160 children attending the school, (including 25 children who had recently left school) for the first screening test

<table>
<thead>
<tr>
<th></th>
<th>Neg.</th>
<th>+1</th>
<th>+2</th>
<th>+3</th>
<th>+4</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG</td>
<td>909</td>
<td>312</td>
<td>217</td>
<td>308</td>
<td>62</td>
</tr>
<tr>
<td>(34%)</td>
<td>(24%)</td>
<td>(34%)</td>
<td>(7%)</td>
<td>(1%)</td>
<td></td>
</tr>
<tr>
<td>No BCG</td>
<td>251</td>
<td>205</td>
<td>10</td>
<td>25</td>
<td>6</td>
</tr>
<tr>
<td>(82%)</td>
<td>(4%)</td>
<td>(10%)</td>
<td>(2.3%)</td>
<td>(2%)</td>
<td></td>
</tr>
</tbody>
</table>

Those regarded as having had BCG vaccination had a record of vaccination or BCG scars present or both. BCG: Bacille Calmette-Guérin.

Table 2. - Details of patients

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age yrs</th>
<th>Sex</th>
<th>Date of BCG vaccination</th>
<th>Date of diagnosis</th>
<th>Mantoux</th>
<th>Tuberculin test</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>17</td>
<td>F</td>
<td>Yes</td>
<td>22/2/86</td>
<td>+3</td>
<td>Pleural effusion</td>
<td>C+ (fluid)</td>
</tr>
<tr>
<td>2*</td>
<td>19</td>
<td>F</td>
<td>Yes</td>
<td>13/3/86</td>
<td>+3</td>
<td>Pleural effusion</td>
<td>Bx positive</td>
</tr>
<tr>
<td>3*</td>
<td>14</td>
<td>F</td>
<td>No</td>
<td>03/4/86</td>
<td>+3</td>
<td>Miliary &amp; meningitis</td>
<td>S+, C+, CSF+</td>
</tr>
<tr>
<td>4*</td>
<td>17</td>
<td>F</td>
<td>No</td>
<td>23/4/86</td>
<td>+3</td>
<td>Pulmonary LMZ lesion</td>
<td>Negative</td>
</tr>
<tr>
<td>5</td>
<td>16</td>
<td>F</td>
<td>No</td>
<td>25/4/86</td>
<td>+3</td>
<td>Pulmonary - military</td>
<td>C+</td>
</tr>
<tr>
<td>6</td>
<td>15</td>
<td>M</td>
<td>No</td>
<td>25/4/86</td>
<td>+3</td>
<td>Consolidation RLL</td>
<td>Negative</td>
</tr>
<tr>
<td>7</td>
<td>18</td>
<td>F</td>
<td>Yes</td>
<td>02/5/86</td>
<td>+2</td>
<td>Lesion right apex</td>
<td>C+</td>
</tr>
<tr>
<td>8*</td>
<td>14</td>
<td>F</td>
<td>Yes</td>
<td>02/5/86</td>
<td>+2</td>
<td>Opacity &amp; cavity RLL</td>
<td>Negative</td>
</tr>
<tr>
<td>9</td>
<td>17</td>
<td>M</td>
<td>No</td>
<td>02/5/86</td>
<td>+2</td>
<td>RLL consolidation</td>
<td>C+</td>
</tr>
<tr>
<td>10</td>
<td>15</td>
<td>F</td>
<td>No</td>
<td>02/5/86</td>
<td>+2</td>
<td>Opacity &amp; cavity LMZ</td>
<td>S+, C+</td>
</tr>
<tr>
<td>11*</td>
<td>18</td>
<td>F</td>
<td>No</td>
<td>16/5/86</td>
<td>+3</td>
<td>R. pleural effusion</td>
<td>Negative</td>
</tr>
<tr>
<td>12</td>
<td>13</td>
<td>M</td>
<td>No</td>
<td>23/5/86</td>
<td>+2</td>
<td>Opacity right apex</td>
<td>C+</td>
</tr>
<tr>
<td>13*</td>
<td>19</td>
<td>F</td>
<td>Yes</td>
<td>30/5/86</td>
<td>Neg.</td>
<td>Small opacity R. apex</td>
<td>Negative</td>
</tr>
<tr>
<td>14</td>
<td>16</td>
<td>M</td>
<td>Yes</td>
<td>11/7/86</td>
<td>+3</td>
<td>Pleural effusion</td>
<td>Negative</td>
</tr>
<tr>
<td>15*</td>
<td>17</td>
<td>M</td>
<td>Yes</td>
<td>06/8/76</td>
<td>+2</td>
<td>Pleural effusion</td>
<td>C+ (fluid)</td>
</tr>
</tbody>
</table>

Non-students

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age yrs</th>
<th>Sex</th>
<th>Date of diagnosis</th>
<th>Date of diagnosis</th>
<th>Mantoux</th>
<th>Tuberculin test</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>16*</td>
<td>29</td>
<td>M</td>
<td>23/4/86</td>
<td>No</td>
<td>+2</td>
<td>Opacity left apex</td>
<td>S+, C+</td>
</tr>
<tr>
<td>17*</td>
<td>28</td>
<td>M</td>
<td>06/6/86</td>
<td>No</td>
<td>+2</td>
<td>Opacity right apex</td>
<td>Negative</td>
</tr>
<tr>
<td>18</td>
<td>2</td>
<td>M</td>
<td>31/7/66</td>
<td>No</td>
<td>+3</td>
<td>RML collapse</td>
<td>Negative</td>
</tr>
<tr>
<td>19*</td>
<td>2</td>
<td>M</td>
<td>15/11/66</td>
<td>No</td>
<td>+3</td>
<td>Consolidation RMZ</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Bact./Hist.: Bacteriological/Histological status; *: initial three cases; †: diagnosis made on clinical/radiological grounds; ‡: teacher; S+: smear positive; C+: culture positive; Bx: biopsy positive; CSF+: cerebrospinal fluid positive; RLL: right lower lobe; RML: right middle lobe; RMZ: right middle zone; LMZ: left middle zone.

Test as it was considered easier to administer to a large group. The test was read in a standard manner as recommended [8]. Those with abnormal chest X-rays or symptoms were assessed for active disease.

As the screening programme evolved, and because the pupils came from a wide geographical area and many had siblings attending primary school, all children in the local primary schools were Heaf tested. Social contacts and contacts in other second level schools of children with tuberculosis were also screened. Open access, walk-in clinics were also operated.

Two months after the initial screening all pupils who had been negative on the initial test were Heaf tested again and chest X-rays repeated on high risk individuals. Those with negative response to the second Heaf test were offered BCG vaccination. Screening was on a voluntary basis. The Chi² test was used in all comparisons.

Results

All 1,135 students (excluding the three index cases) attending the school were screened as were 25 of 30 children who had recently left school (1,160 students). Results of their Heaf tests and BCG status are given in table 1. The degree of positivity by Heaf testing (Heaf grade +3 and Heaf grade +4) was statistically significantly more positive in those children who had been vaccinated (p=0.001).
Table 2 shows details of all 19 persons who had a diagnosis of TB and the date of diagnosis is indicated on the table. The 3 index cases and cases number 15 and 18 presented with symptoms. The remaining cases, including what may have been the source case, were detected by screening. In all, 15 students - 6 in the BCG vaccinated group (including two of the index cases) and 9 who had not received vaccination, had tuberculosis. and another with miliary tuberculosis and tuberculous meningitis. The difference in incidence of tuberculosis between children who had been vaccinated and the non-vaccinated children was statistically significant (p=0.001; Chi²=10.997; DF=1). The relative risk of non-vaccinated children getting tuberculosis as compared to vaccinated children was 5.43 (95% confidence interval (CI); 1.95–15.1). Two hundred and ten children had received vaccination in primary school. None of these children had active tuberculosis. Analysis comparing those who had only had neonatal BCG with those who never had BCG also shows a protective effect of the BCG vaccine which was statistically significant (p=0.004).

The possibility that stratified behaviour within the school, social outlets in the school, or in general social outlets or transport might have been responsible for a different level of exposure for students who had BCG and those who had not was investigated but no bias in terms of exposure could be demonstrated.

Seventy eight teachers were screened. Two teachers (Cases 16 and 17) had active pulmonary tuberculosis, one being spurnum positive at the initial screening and the other diagnosed at the two month follow-up examination. Three other teachers had evidence of old inactive tuberculosis. Forty two ancillary school staff were screened and four had evidence of previous primary infection. None had active disease.

Of 331 family contacts screened, 2 were given chemoprophylaxis and 6 others had evidence of old inactive lesions. A 2 yr old boy who was not screened in the initial contact tracing was subsequently diagnosed as tuberculous (Case 18). Another 16 yr old boy (Case 14), who had neonatal vaccination but who had left school prior to screening, presented to his family doctor with a tuberculous pleural effusion. One 19 yr old pupil (Case 13) had tuberculosis but a negative skin test. She had recently recovered from an episode of chickenpox and it was felt that this may have been responsible for the initial negative skin reaction. A further 30 children who had recently left secondary school were also identified and 25 of these attended for screening. None had evidence of tuberculosis.

Publicly advertised open clinics were held in the two main towns. A 2 yr old boy (no previous BCG) had a +3 Heaf result and a right middle lobe consolidation radiologically (Case 19). No definite contact could be established with the school and he was not bacteriologically proven as tuberculous. He responded to therapy. No tuberculosis was found in any of his contacts. For completeness he is included in this study but he may not have been part of the outbreak.

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The second screening of the students at the school and the screening of the primary school contacts yielded no further cases of tuberculosis.

All isolates were identified as Mycobacterium tuberculosis and all were strongly resistant to isoniazid. All cases of tuberculosis were treated with a three drug regimen of rifampicin, isoniazid and ethambutol for a minimum duration of twelve months. Treatment for miliary tuberculosis and TB meningitis was more prolonged. Children who had a +3 or +4 Heaf without previous BCG vaccination and children with a +4 Heaf with previous BCG vaccination were given chemoprophylaxis. Initially chemoprophylaxis had been started with isoniazid alone but when the isolates were identified as isoniazid resistant chemoprophylaxis was changed to rifampicin and ethambutol for a six month period.

Dealing with non-medical aspects of the epidemic

Tuberculosis causes anxiety and is often associated in the minds of the public with chronic ill health and death. Because of the number of children involved in the screening process and the number of cases diagnosed, public anxiety needed to be allayed. The school principal and school authorities were instrumental in keeping parents informed of developments. All patients were circulated with a letter informing them that an outbreak of tuberculosis had occurred and requesting consent for Heaf testing and screening of each child. They were also given an information sheet giving an outline of tuberculosis, its cause and methods of transmission and reassuring them that it was treatable and curable. Meetings were held with the teaching staff to explain the situation, the diagnosis and the measures which had to be taken.

Where there was a chest X-ray abnormality or a suspicion of active disease the patients and family were met by one of us and the findings and diagnosis discussed. Each general practitioner in the area was informed by letter of the problem and the steps being taken in contact tracing and their co-operation was enlisted in allaying anxiety.

The Medical Officer of Health met with the general practitioners in the area, the teachers staff association and the parents of the school children to detail the epidemic, the screening measures necessary and to allay their fears. This co-operation together with the assistance of the Departments of Radiology, the physicians and paediatricians in Letterkenny General Hospital was an important factor in dealing with the epidemic.

The media

As could be anticipated with a significant outbreak the national and local media picked up the story and it was carried in national newspapers and television. Initial response was somewhat sensational which contributed to


RÉSUMÉ: L’on a observé une épidémie de tuberculose résistante à l’isoniazide dans une grande école de niveau secondaire. La population soumise à risque était de 1,160 élèves “teenagers”. L’on a diagnostiqué 19 cas de tuberculose, dont 15 étaient des étudiants, parmi lesquels 9 se trouvaient parmi les 251 étudiants non vaccinés et 6 parmi les 909 étudiants vaccinés. Deux cas de tuberculose miliare, dont un associé à une méningite tuberculeuse, sont survenus dans le groupe non vacciné. Le nombre d’ênes ayant des tests de Heaf de niveau +3 ou +4, est significativement plus élevé chez les enfants vaccinés par le BCG (8 vs 4.4%). Ceci suggère un boosting effet sur la réponse chez les enfants vaccinés. L’effet protecteur d’une vaccination néo-natale au BCG dans cette épidémie scolaire suggère qu’elle assure une protection significative contre la tuberculose jusqu’à l’adolescence.

A school microepidemic of tuberculosis

C P Bredin, M Godfrey, J McKiernan

Abstract

Background  Microepidemics of tuberculosis continue to occur in countries with a low incidence of tuberculosis.

Methods and results  A microepidemic of tuberculosis in a secondary school with 604 girls in Cork city, Ireland, in 1986 with follow up to 1990 is described. Neonatal BCG vaccination was discontinued in the city in December 1972 so most of the 342 pupils who had received BCG were aged 14 years or more. Six active cases and 75 tuberculin positive cases were found. Four of the six girls with active disease had had neonatal BCG. The 75 pupils with a positive (grade 3 or 4) Heaf test response were given chemoprophylaxis with rifampicin and isoniazid for six months; none had developed active tuberculosis four years later. The brother of the girl who was the probable index case, however, developed active tuberculosis in 1988 despite similar chemoprophylaxis.

Conclusion  The episode highlights the fact that children who have had neonatal BCG can develop active tuberculosis as teenagers.

Although the incidence of tuberculosis continues to fall in the Republic of Ireland, group infections or microepidemics continue to occur, as in the United Kingdom and other European countries. Such an episode occurred in 1986 in a girl's secondary school in Cork city, where the policy of neonatal BCG vaccination had been discontinued in December 1972. The area has a low tuberculin positivity rate (1.4 per cent Heaf grade 2 or greater in non-BCG 12 year olds), although higher than the national average (0.9 per cent). All the girls were white.

Cases and contact tracing

A 13 year old girl (case A) developed tuberculous meningitis in February 1986 (table 1). Contact tracing of close contacts, including her family, yielded no further cases of tuberculous infection. Two months later a 14 year old pupil at the same school (case B) presented with excessive vaginal bleeding and a diagnosis of endometrial tuberculosis was made (positive histological specimen and culture). Contact tracing of close contacts again identified no further cases. Four months later smear positive pulmonary tuberculosis was diagnosed in another pupil (case C). Her chest radiograph showed extensive consolidation. Tuberculin tests gave positive responses in her three brothers. Contact tracing was then extended to all pupils and staff at the school.

The student body consisted of five years (1st to 5th) of approximately equal size, age range 12-18 years. A tuberculin test (Heaf) was carried out on all pupils and siblings of individuals with active disease. To allow for the effect of neonatal BCG vaccination and non-tuberculous mycobacterial infection, only Heaf test grades 3 and 4 were interpreted as positive responses, if the Heaf test response was positive a chest radiograph was obtained; if it was negative the test was repeated after six weeks. Adult family contacts and school staff, in accordance with local policy, had chest radiography only. Those with active disease were treated with rifampicin 450 or 600 mg and isoniazid 300 mg daily for nine months, with ethambutol 15 mg/kg for the first two months. Pupils with a positive response to the Heaf test and a normal chest radiograph were given rifampicin and isoniazid as chemoprophylaxis for six months. Neonatal BCG vaccination was confirmed by the presence of a scar or signed community care records, or both. Where there was no scar and no record the pupil was included in the non-BCG group.

Results

The results of contact tracing of the 604 pupils are outlined in table 2. Seventy eight pupils had a positive Heaf test response, three of whom had an abnormal chest radiograph. These three pupils were treated for active tuberculosis (table 1, cases D, E, and F); the other 75 pupils received prophylaxis. Patient D had smear positive pulmonary tuberculosis and a single 2 cm cavity in the right upper lobe on the chest radiograph. Contact tracing of her family and of several families in the neighbourhood for whom she acted as a babysitter had negative results. As the contact

Table 1  Tuberculosis in the school: details of active cases

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (y)</th>
<th>Month of presentation (1986)</th>
<th>Type of tuberculosis</th>
<th>Neontal BCG</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>13</td>
<td>Feb</td>
<td>Tuberculous meningitis</td>
<td>No</td>
</tr>
<tr>
<td>B</td>
<td>14</td>
<td>May</td>
<td>Tuberculosis meningitis</td>
<td>Yes</td>
</tr>
<tr>
<td>C</td>
<td>14</td>
<td>Aug</td>
<td>Endometrial</td>
<td>Yes</td>
</tr>
<tr>
<td>D</td>
<td>14</td>
<td>Sep</td>
<td>Smear positive</td>
<td>Yes</td>
</tr>
<tr>
<td>E</td>
<td>14</td>
<td>Oct</td>
<td>Pulmonary tuberculosis</td>
<td>Yes</td>
</tr>
<tr>
<td>F</td>
<td>13</td>
<td>Oct</td>
<td>Primary pulmonary tuberculosis</td>
<td>No</td>
</tr>
</tbody>
</table>

*Cases B-E were in the third year. C was the probable source case. There was no regular social contact between the two smear positive cases (C and D) and the two second year cases (A and F). All cases were tuberculin positive.
A school microepidemic of tuberculosis

| Table 2 | Contact tracing in school pupils: tuberculin \n| Head test and radiographic results |
|-----------------------------|---------|
| **INITIAL TESTS (n = 604)** |        |
| **Head response** | 530 |
| Negative | 74 |
| Positive |        |
| Chest radiograph* | 71 |
| Normal |        |
| Abnormal | 3 |
| **REPEAT TUBERCULIN TEST IN 6-8 WEEKS (n = 530)** | 526 |
| **Head response** | 4 |
| Negative |        |
| Positive |        |
| Chest radiograph* | 4 |
| Normal |        |

*Chest radiographs obtained from children with Head grades 3-4.
*Cases D, E, and F (table 1).

tracing results of the family of the other girl with smear positive pulmonary tuberculosis (case C) were positive we concluded that she was the probable index case.

In the bacteriologically confirmed cases (A-D) *Mycobacterium tuberculosis* was sensitive to isoniazid, rifampicin, ethambutol, and streptomycin. None of the six girls with active disease relapsed after treatment, and none of the 75 pupils given chemoprophylaxis had developed active tuberculosis by 1990. The 9 year old brother of the girl who was the probable index case (case C) developed pulmonary, pleural, and cervical gland tuberculosis in October 1988. At contact tracing in 1986 he had a grade 3 positive Head test response and a normal chest radiograph and had received six months' chemoprophylaxis.

In the third year classes 36% were tuberculin positive. This was the year of the probable index case and the two smear positive cases. In this year 68 had had neonatal BCG and 49 had not. Four of the six active cases had had neonatal BCG but not case A, the girl who developed tuberculosis. Of the 342 children who had received neonatal BCG, 63% had a grade 1 or 2 Head result, compared with 85% of the 262 children who had not had neonatal BCG. No active cases of tuberculosis were found among the school staff.

**Discussion**

This report shows that microepidemics of tuberculosis may occur in areas of low prevalence of the disease and in teenagers who had received neonatal BCG. The protective effect of neonatal BCG in teenagers cannot be determined because the number of active tuberculosis cases in the BCG (n = 4) and non-BCG pupils (n = 2) is too small for statistical comparison and because the proportion of children who had had neonatal BCG varied in the different years and hence confounds the effect of contact with the index case. There are no good grounds to revert to the pre-1972 policy of routine neonatal BCG, though the occurrence of tuberculous meningitis (case A) in a non-BCG pupil is a cause for concern.

Since this paper was submitted a similar secondary school episode in 1986, in north west Ireland (Donegal), has been reported. This suggests a protective role for neonatal BCG in teenagers. This apparent lesson from Donegal may not be applicable to at least some other areas in Ireland, including Cork city, because of two possibly interrelated factors. Firstly, the Donegal episode was due to isoniazid resistant *Mycobacterium tuberculosis* and, secondly, many of the Donegal teenagers were children of returned emigrants or were born outside the school community care area. In Cork, however, isoniazid resistance is very rare, and the teenagers we have described were born mainly in the school locality.

The development of active tuberculosis in 1988 in a brother of the probable index case, despite six months' chemoprophylaxis with isoniazid 300 mg and rifampicin 450 mg daily, raises the question of the value of chemoprophylaxis. There was no evidence of non-compliance with his regimen and no evidence of drug resistance. No active disease had developed in the 75 school contacts given chemoprophylaxis by 1990, supporting the value of chemoprophylaxis in preventing active tuberculosis despite its failure in one patient.

Infectiousness of tuberculosis

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The only important method of transmission of the tubercle bacillus in low prevalence countries is by inhalation of aerosolised sputum from a patient with pulmonary tuberculosis. The principle approaches to the reduction of infectivity therefore depend on the early detection of sputum-positive cases of pulmonary tuberculosis and the introduction of effective chemotherapy. The result of the introduction of chemotherapy is usually a decline in cough frequency and a reduction in the excretion of bacilli (1). Other putative mechanisms such as a concentration of drugs in droplet nuclei or the reduction in the virulence of organisms do not seem to be important.

The radiological extent of disease and the presence or absence of cavities on chest X-ray are regarded as pointers when assessing the potential of a patient to transmit infection before treatment has begun. More important however is the bacteriological status and the cough frequency which do not always correlate with the X-ray changes. Other additional factors which may also influence spread include living conditions, in particular the existence of overcrowding, the nutritional status and of course the immune status of the exposed individual. In low prevalence countries factors such as the method of ventilation and recirculation of air and the closeness of contacts in the case of tuberculin negative individuals will also be important. While large volumes of thick, purulent sputum may contain very high bacterial counts, often a less viscous, watery sputum may be a more ideal vehicle for aerosolisation and therefore prove more pathogenic. Psychological stress in the form of life events while not playing a role in the transmission of infection may influence the likelihood of developing disease (2). Host resistance will of course be influenced by whether there was previous exposure or whether there was a previous successful BCG vaccination.

The efficacy of appropriate anti-tuberculous chemotherapy in reducing infectiousness is widely accepted. The South India study (3) was the most important early evidence in support of this. Extrapolating from the conditions in that study in the 50s to low prevalence countries in the 90s may not be valid. There are other studies which tend to support the Madras study. Most of them however are flawed. There is nevertheless much reassurance in the study from Jindani et al. (4) suggesting a very rapid fall-off in the bacterial counts of patients who are on effective anti-tuberculous drugs. This study was largely done to try and identify the most effective drug combinations. It made a significant contribution to our knowledge in that field.

The number of patients in each treatment group was small, typically 4 patients. These showed wide variation but the answers were expressed as means. While this may be adequate for the purpose for which the study was designed, to extrapolate from that to the occurrence in millions of patients with tuberculosis is invalid. In our experience with the best available antituberculous regimens it takes some 4 months for 96% of patients to become culture-negative (5).

To try and add to the basic knowledge in this field we took samples of sputum from patients before chemotherapy and thereafter for as long as sputum was available (6). We divided the samples and injected half of a suitably prepared specimen sub-cutaneously into guinea pigs. They were sacrificed at 8 weeks and the presence and extent of disease noted and classified. We then compared the results of smear, culture and guinea pig inoculation and found a very good correlation between both the smear positivity (r = 0.77), culture positivity (r = 0.78) and the likelihood of producing lesions in guinea pigs whereas the relationship to the duration of chemotherapy was weak (r = 0.21). It is therefore clear from our studies that the presence of bacilli in the sputum especially if they are culturable is closely correlated with pathogenicity in the guinea pig. This is not surprising but suggests to us that we must be careful in our approach to patients with tuberculosis who are still sputum smear- and culture-positive no matter how long they have been on chemotherapy.

We therefore advise caution particularly if such patients are in hospital because of the danger they represent to the staff and more particularly to other patients especially the immunocompromised. We think this is important especially in the AIDS era. We feel that the notion that patients were no longer infectious after a few days' or even 2 weeks' chemotherapy has become elevated to the status of a dogma. We think this is wrong and feel that in an area where the prevalence of tuberculosis is high this generalisation is possibly safe but that in low prevalence countries especially when we are considering immunosuppressed hospital patients, it represents a dangerous and unsustainable stance which must be revised.

REFERENCES

The pathogenicity of *Mycobacterium tuberculosis* during chemotherapy


ABSTRACT: We used the guinea pig as an experimental model to investigate the pathogenicity of *Mycobacterium tuberculosis*. Sputum samples were injected subcutaneously into guinea pigs and the animals were killed and an autopsy performed after eight weeks. The likelihood of the sputum samples producing tuberculosis in the guinea pig was related to culture positivity rather than to duration of chemotherapy. This study does not support the belief that a change in pathogenicity occurs during treatment of pulmonary tuberculosis.

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Inhalation of aerosolised sputum from a patient with pulmonary tuberculosis is by far the most common method of transmission of tuberculosis today [1]. Anti-tuberculosis chemotherapy is highly effective in preventing the transmission of the disease from a patient to a susceptible or non-immune host, and infectiosity for intimate household contacts seems to diminish quickly following the introduction of chemotherapy [2]. Nevertheless the time at which a patient becomes non-infectious has never been established. It has, however, become accepted that after two weeks chemotherapy a patient does not represent a serious infectious risk [3]. The most important result of anti-tuberculosis drugs is probably the reduction in the number of bacilli in the sputum and the reduction in cough [3-5]. Patients are regarded as non-infectious, even if their sputum remains positive on smear and culture, which suggests that anti-tuberculous chemotherapy brings about a change in pathogenicity. We have used the guinea pig as an animal model to test this hypothesis.

Methods

Twenty-nine sputum samples from 21 patients with direct smear positive pulmonary tuberculosis were taken and prepared in a standard manner. All patients were receiving supervised triple therapy with Rifampicin, Isoniazid and Ethambutol and had infection with fully sensitive *Mycobacterium tuberculosis*. 2 ml of each sputum sample was treated with 4% NaOH for 15 min; then 16 ml of distilled water was added and the preparation was centrifuged at 3000 rpm for 15 min. The deposit was resuspended in 1 ml of water, divided into two aliquots one of which was cultured on Lowenstein-Jensen slopes and the other injected subcutaneously into the thigh of a guinea pig.

The guinea pigs were killed after 8 weeks and an autopsy was performed. The presence and extent of disease in the guinea pigs was classified as follows: no evidence of tuberculosis (Grade 0); evidence of local disease with or without regional lymph node involvement (Grade 1); disseminated tuberculosis with minimal involvement of the spleen and no lesions in the peritoneal cavity (Grade 2); generalised disease including involvement of spleen and peritoneal cavity (Grade 3).

Direct staining of sputum was performed using an immunofluorescence technique and was graded as follows:

- Microscopy: > 10 AFB per oil emersion field +++
- 1 - 10 AFB per oil emersion field ++
- 10 - 99 AFB per 100 oil emersion fields +
- 1 - 9 AFB per 100 oil emersion fields ±
- No AFB per 100 oil emersion fields None seen

Culture results on Lowenstein-Jensen medium were graded as follows:

- No growth 0
- < 20 colonies ±
- 50-100 colonies +
- >100 colonies ++

We used multiple regression analysis (MRA) as described by ARMITAGE and BERRY [6] to analyse the relationship between the extent of guinea pig lesions and the three parameters - duration of chemotherapy, direct smear positivity and culture positivity.
Results

Figures 1, 2 and 3 show the relationship between direct smear, Lowenstein-Jensen culture and duration of treatment, respectively, and the extent of disease produced in the guinea pigs by aliquots from the same specimens. There were 25 specimens of sputum which were positive for acid fast bacilli on direct staining and of these 17 produced tuberculous lesions in the guinea pigs. There were 21 positive sputum cultures and 16 of these produced guinea pig tuberculous lesions. There were four positive cultures of sputum, the aliquots of which did not produce lesions in the guinea pigs. There were, however, no more than 4 colonies on any of these cultures. Whilst there was a relationship between the duration of treatment and the absence of tuberculous lesions in inoculated guinea pigs, the ability to produce lesions in the guinea pig was associated with the degree of positivity of the sputum and not the duration of therapy alone. MRA showed that the correlation between severity of the guinea pig lesions was strongest with culture positivity \((r=0.78)\), weaker with sputum positivity on direct smear \((r=0.77)\) and weakest with duration of chemotherapy \((r=-0.21)\).

**Fig. 1.** - The extent of tuberculous lesions in relation to direct smear positivity. C: Specimens of sputum with positive direct smear; 0: Specimens of sputum with negative direct smear.

Culture of guinea pig tissue was carried out on four animals. In two cases the sputum had been positive both on direct staining and on culture, there were extensive lesions present in the guinea pig and in both cases guinea pig tissue culture grew *Mycobacterium tuberculosis*. In a third case the sputum was weakly positive on direct staining and on culture, produced minimal lesions in the guinea pig but no mycobacteria were grown on tissue culture. In the fourth case the sputum was positive on direct smear but negative on culture, there were no lesions present in the guinea pig and the tissue culture was negative for *Mycobacterium tuberculosis*.

**Fig. 2.** - The extent of tuberculous lesions in relation to culture positivity. C: Specimens of sputum with positive culture; 0: Specimens of sputum with negative culture.

**Fig. 3.** - The extent of tuberculous lesions in relation to duration of therapy. C: Specimens of sputum with positive culture; 0: Specimens of sputum with negative culture.

Discussion

Our primary aim was to determine whether tubercle bacilli from patients who were receiving chemotherapy remained pathogenic despite treatment, provided that the bacilli were still present in the sputum and that this was independent of the duration of chemotherapy. If pathogenicity was dependent on the duration of therapy alone it would become obvious in the protocol used and would be independent of the route of infection. The limitations
of an animal model raises the question as to whether such an approach is any more significant than culture in an artificial medium. It has long been accepted that sputum may remain culture positive for several weeks following the initiation even of modern anti-tuberculosis therapy. In our experience it takes four months therapy on standard doses of Rifampicin, Isoniazid and Ethambutol for 96% of patients to become culture negative [7]. Based largely on the Madras experience and a number of other indirect studies there has been a tendency to assume that these organisms are non-pathogenic [2, 8-11]. Chemotherapeutic agents in sputum will tend to inhibit bacillary growth whereas artificial culture media tend to encourage growth. It is difficult therefore to predict the effect of aerosolized sputum, from tuberculous patients on chemotherapy, in susceptible humans. In these circumstances it is argued that an organism which has been exposed to chemotherapy might become of such low virulence that it was unable to cause disease even though it may grow in an artificial medium.

The best model, therefore, would have been normal man, but of course this would be unacceptable. It was with that background that the use of an animal model was considered of greater significance than a positive culture in an artificial medium.

We are aware of the problem of extrapolating from guinea pig models to man. Furthermore the route of infection (subcutaneous injection), is artificial and does not mimic natural infection in man. Nevertheless since an animal model is essential for this study the guinea pig is suitable. It is difficult to be sure of the relative susceptibility to infection of guinea pigs compared to man. It is known that the susceptibility of guinea pigs is equivalent to that of anthropoids and monkeys for the human bacillus and slightly greater for bovine strains [12]. The subcutaneous route of experimental infection is used because it is reliable and known to be effective. The alternative route of aerosolization of sputum might seem nearer to the human situation but although the guinea pig is susceptible to tuberculosis they rarely contract the disease naturally and while they may excrete the tubercle bacillus in urine and faeces, natural infection among cage mates is uncommon and the lungs are seldom prominently involved [13].

Our study does not offer conclusive proof that bacilli from patients on anti-tuberculous drugs cause disease in man. However, consideration of the evidence supporting claims that non-infectivity could be assumed at two or three weeks or even two months shows that it is based on inadequate data and is not supported by our study. In fact there is no direct evidence and some of the indirect evidence is poor [14].

Modern chemotherapy rapidly and dramatically reduces the number of bacilli in the sputum and is effective in reducing cough, and by these mechanisms greatly and quickly reduces the risk of spreading infection. We know from epidemiological studies that the risk of infection in close family contacts, once chemotherapy has been established, is negligible but to extrapolate that this is due to chemotherapy is unwarranted. The index case is most infectious before initiation of therapy. If transmission of infection to close family contacts has not occurred in the pre-treatment phase it will not occur after therapy has begun. What this study shows is that if the patient continues to cough and remains sputum positive, particularly culture positive, he produces bacilli which are pathogenic. It therefore re-opens the question as to the possibility of transmitting infection from patients on chemotherapy to non-immune new contacts. It also raises the possibility of infecting patients already immunocompromised, either by co-existing disease or iatrogenically or by AIDS. The position with regard to the discharge of patients with tuberculosis on chemotherapy to their own homes is clear [2, 5]. We suggest, however, that patients who have sputum positive tuberculosis and are in hospital despite being on effective chemotherapy cannot be regarded as non-infectious. The organisms from such patients retain the ability to cause disease in guinea pigs and there is no direct evidence that their pathogenicity for susceptible or hypersusceptible humans is different.

References
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Tuberculosis elimination in the countries of Europe and other industrialized countries
Based on a workshop held at Wolfheze, Netherlands, 4–9 March 1990,
under the joint auspices of the IUATLD (Europe region) and WHO


ABSTRACT: The working group summarized the conclusions of the workshop with the intention of providing a guide for the preparation of national plans for tuberculosis elimination. The basic strategies that appear consistently effective are:

1. Direct government responsibility for diagnosis, treatment and prevention of tuberculosis (the government is responsible by law for assuring that tuberculosis is identified early, and that cure of the patients is achieved).
2. Maintenance (or development) of properly designed disease surveillance and a programme monitoring system.
3. Availability of specialized tuberculosis personnel at regional and provincial level, responsible for close monitoring of the diagnostic skills and patient prioritization in general health institutions.

Regarding research it was felt that no immediate practical applications of new techniques in the diagnosis of mycobacterial diseases, in treatment, or in vaccination can be recommended, but that further basic research in the field of mycobacteria should be pursued and supported.

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Operational definitions
To base the discussion on a common language, a few operational definitions were proposed:

1. “Infection with M. tuberculosis” was defined as the subclinical, latent infection with tubercle bacilli (by common understanding also including infection with M. bovis and M. africanum).
2. “Tuberculosis” refers to clinically, bacteriologically and/or radiologically active disease.
3. “Low incidence countries”, a term used when the incidence of all forms of active tuberculosis is below 10 per 100,000 population.
4. “Elimination phase” is said to have been achieved when the incidence of all forms of active tuberculosis has fallen below the level of 1 per 100,000 population.
5. “Elimination” is said to have been reached when the incidence of sputum smear-positive tuberculosis is 0.1 per 100,000 population (1 per million). Alternatively, “elimination” may be said to have been achieved when the prevalence of infection with M. tuberculosis in the general population has fallen below 1% and continues to decrease.
6. “High risk groups” are groups with an incidence 100 per 100,000 population or more. This level is
selected because it represents a level at which active case finding may be cost-effective and because the majority of cases in low incidence countries arise from these groups.

7. "Preventive therapy" is a term used to denote treatment of subclinical infection with *M. tuberculosis* to prevent progression to tuberculosis. The term "chemoprophylaxis" (which, in its strict sense, applies to prophylactic treatment of persons exposed to infectious cases, but not yet infected with *M. tuberculosis*) is used here interchangeably.

**Epidemiology**

There is still a wide range in the incidence of notified tuberculosis cases among European and other industrialized countries. The incidence varies, however, not only between, but also within, countries by area or population segments.

The incidence of tuberculosis has been decreasing in all industrialized countries. The rate of decline in the United States has been halted and this has raised concern in other industrialized countries. This failure of tuberculosis to decline in the United States appears, in part at least, to be attributable to HIV infection, to tuberculosis among immigrants, and to microepidemics. Because of the decrease of tuberculosis among the majority of the indigenous population, the incidence of tuberculosis cases among minorities, including immigrants and refugees, will become a relatively more important problem in the future. An adaptation of available intervention strategies to an ever changing situation is thus required if elimination is to be achieved.

**Surveillance**

To achieve elimination of tuberculosis, low incidence countries should establish, maintain and evaluate, focused surveillance systems that identify socioeconomic groups or geographic areas with high rates of disease or infection. Specific programmes can then be designed to reduce the emergence of disease and the spread of infection through early case detection and treatment, identification of infected individuals and intervention with preventive chemotherapy. Such surveillance and intervention programmes can only be effected through the maintenance of efficient tuberculosis control services in each country.

New parameters for monitoring tuberculosis need to be established, e.g. monitoring of recent infection in young people might be developed as a means of monitoring hidden transmission of tuberculosis especially where bacille Calmette-Guérin (BCG) is not widely applied. The criteria and methods used for recording new cases should be standardized. Death from tuberculosis has become a relatively rare event in most low incidence countries but continues to occur. Diagnosis of tuberculosis at autopsy is unfortunately not rare and may be a useful monitoring tool but only where the frequency of autopsies is high. A major factor contributing to fatality appears to be the failure of diagnosis or misdiagnosis.

The annual risk of infection with *M. tuberculosis* is regarded as a very useful index, but its derivation from infection prevalence data is fraught with problems where BCG has been widely used. In low incidence countries an increasingly larger number of individuals need to be tested to obtain a reliable estimate. Furthermore, the predictive value of the test declines with decreasing prevalence of infection.

The evaluation of the efficiency of tuberculosis control measures is often poorly performed and needs to be strengthened. The role of BCG vaccination programmes in low incidence countries is decreasing with decreasing incidence of tuberculosis. The emphasis in tuberculosis control should shift to the increased use of other tools of intervention in order to interrupt the transition from exposure to disease. The efficacy of modern treatment regimens under controlled trial conditions is well established, but there are very few data available on treatment effectiveness and efficiency under routine programme conditions in low incidence countries. The high frequency of abandonment of treatment even in some industrialized nations must urgently be addressed. A more frequent utilization of directly administered regimens is needed to deal with this problem. Local conditions and the needs of the individual patient will usually dictate the form of treatment supervision that is necessary. It may vary from daily supervised treatment, to intermittent supervised treatment, to in-patient care for any individual patient. The use of treatment regimens other than those recognized as the shortest possible and most effective continues to be common, especially where patients are cared for in the private sector. Resistance of *M. tuberculosis* to the most potent anti-tuberculosis drugs is at present uncommon and unlikely to have a large impact on the control of tuberculosis in industrialized countries. However, emergence of drug-resistant strains, and even outbreaks of drug-resistant tuberculosis, continue to be reported and pose challenges to containment and control.

**Reference centres**

Inevitably, the number of health care workers fully trained in tuberculosis is declining in low incidence countries. It is therefore essential that centres of expertise be maintained or established where they do not (or no longer) exist. These centres should play a leading role in developing programmes to improve surveillance and in the evaluation of established programmes. They should also act as a resource offering service guidance, training and support for all health care workers dealing with tuberculosis.
Intervention strategies

The community of public health workers and clinicians has three major tasks to accomplish with respect to tuberculosis:
1. those who have tuberculosis must be cured;
2. those who are infected with *M. tuberculosis* must be prevented from developing the disease;
3. those who are not infected with *M. tuberculosis* must be protected from acquiring the infection;

To accomplish these tasks three intervention tools are available:

1. short-course chemotherapy of disease;
2. preventive chemotherapy (chemoprophylaxis) of those already infected but not considered to have disease;
3. vaccination with BCG of new born among those segments of the population that have a high potential of exposure to sources of infection, and in which the feasibility of delivering other control measures, such as contact tracing, chemoprophylaxis and ensuring follow-up is uncertain.

Undoubtedly, the most efficient method of prevention of new infections is case-finding and cure of infectious cases.

Chemotherapy

Short-course chemotherapy is the treatment of choice in all low incidence countries for all forms of tuberculosis. In most instances, a two month initial phase of treatment with rifampicin, isoniazid and pyrazinamide, followed by a four month continuation phase with rifampicin and isoniazid is the standard regimen, but a fourth drug, such as ethambutol or streptomycin, should be added to the initial phase of the regimen in individuals suspected of harbouring drug-resistant organisms (such as in persons born in countries with a high prevalence of drug resistance). If resistance is confirmed, the continuation phase will also have to be modified. The necessary duration of treatment and the need of an additional drug for tuberculosis in HIV infected individuals is still uncertain. In some countries, the same regimen, but for a minimum of nine months and for at least six months beyond documented culture conversion, has been recommended. The role of supervised chemotherapy in achieving compliance was strongly endorsed.

A review of new drugs for the treatment of tuberculosis and *M. avium* complex disease was disappointing. None of the new drugs has definitively been shown to be superior to available drugs. However, some developments among fluoroquinolones, macrolides, the new rifamycin derivatives, and phenazines are promising.

Hospitalization for isolation purposes is usually unnecessary. The main indications for hospitalization are treatment of patients who are seriously ill because of extensive disease, miliary disease or tuberculous meningitis. Toxic reactions to drugs or multiple drug resistance may sometimes warrant in-patient management and investigation. Admission for diagnosis of suspected tuberculosis may be needed and is commonly used. Admission because of social and/or other medical conditions may be necessary. Patients with pulmonary tuberculosis who are in hospital and who are bacteriologically positive, or are suspected of being so, should be separated from patients without tuberculosis.

Most patients with pulmonary tuberculosis quickly become non-infectious once they are diagnosed and placed on an effective treatment regimen. This greatly facilitates the use of domiciliary treatment. Some patients continue to excrete viable bacilli for a prolonged period of time and may also continue to be infectious for susceptible humans especially for those who are particularly vulnerable. This is an important consideration before deciding to discontinue isolation of hospitalized patients with bacteriologically positive pulmonary tuberculosis. It should also be considered when deciding to allow patients with tuberculosis to return to regular work, especially should such work involve potential exposure of susceptible individuals (as may arise when the patient's occupation involves working with immunosuppressed individuals or young children).

Preventive chemotherapy (chemoprophylaxis)

Preventive chemotherapy in tuberculosis, that is the treatment of persons with latent, subclinical infection with *M. tuberculosis*, has proved to be very efficacious in preventing progression to tuberculosis. It is however, an inefficient tool, if used indiscriminately, i.e. a large number of infected individuals has to be treated to prevent the occurrence of a single case. It is thus necessary to clearly define groups at particularly high risk of developing tuberculosis in whom preventive chemotherapy provides individual and public health benefit. Such individuals include in particular persons with *M. tuberculosis* infection who are also infected with HIV, persons with fibrotic lesions on chest radiography in the absence of active disease), and persons with recently acquired infection. In order to achieve the goal of elimination of tuberculosis in low incidence countries, preventive therapy must play a major role in tuberculosis control.

**BCG vaccination**

The role of BCG vaccination in prevention of tuberculosis deserves continued consideration. The efficacy of BCG vaccines is well accepted in European countries, the degree of confirmed protection being up to 80%. Nevertheless, the impact of BCG vaccination should continue to be carefully assessed in order to measure its cost-effectiveness in the light of the continuing decrease in the incidence of tuberculosis.
The overall epidemiological impact of BCG is negligible, as its main role is in the prevention of non-infectious tuberculosis in children. Data from Sweden and Czechoslovakia suggest that discontinuation is acceptable even if it results in (albeit comparatively small) increases in the incidence of tuberculosis in non-vaccinated cohorts. Although used in many countries, there is little evidence to support a programme of revaccination of tuberculin-negative BCG vaccinated persons in low incidence countries. It is felt, however, that because of the much higher incidence of tuberculosis infection and disease in some groups, BCG vaccination should be maintained or considered afresh in those identified risk groups. In countries considering discontinuing BCG vaccination it is imperative that a reliable surveillance system be in place so that comprehensive tuberculin testing in contact tracing can be undertaken.

BCG should not be given to known HIV-positive persons in low incidence countries. However, there is no indication for HIV testing before vaccination of new-borns.

Case finding

Methods

Passive case-finding remains the principle source of new notifications of tuberculosis in low incidence countries. The identification of risk groups makes active case-finding a possibility by intensive screening, especially of contacts of tuberculosis cases. The identification of risk groups is dependent on reliable methods of surveillance which must include an appropriate notification system under the direct supervision of tuberculosis experts. Special aspects of tuberculosis control in low incidence countries, which must be anticipated, include the frequent occurrence of micro-epidemics, tuberculosis in displaced people, individuals or groups with special likelihood of infection and other high risk groups.

These problems can best be handled when the epidemiological baseline data are accurate and when suitably trained personnel are available to implement the programme.

Micro-epidemics

As the incidence of tuberculosis decreases it is likely that small epidemics will become more commonly recognized. An appropriate plan to evaluate such outbreaks must take into account whether BCG has been used in the population or not. Those persons with most exposure in terms of duration and closeness of contact with a potentially infectious case should be tested with tuberculin. If no reactions are found among these, then it is unlikely that transmission will have occurred outside this close circle. Where reactors are identified, a decision has to be made about how widely further skin testing should be performed. If the background prevalence of infection in the general population is known, skin testing can be discontinued when the proportion of reactors approximates that which is to be expected. Where the proportion of identified reactors exceeds the expected, less close contacts in the "next circle" need to be tested. Radiographic examination of positive reactors should be carried out during such contact tracing to rule out active tuberculosis. Preventive chemotherapy should then be offered to those tuberculin positive contacts who are likely to have become infected by the index case. Finding of even small tuberculin reactions should be considered as suspicious for new infection, particularly if the contacts had not been vaccinated with BCG and the prevalence of sensitization to environmental mycobacteria is low. Where BCG has been used, the cut-off of what is considered to be a significant tuberculin reaction will need to be raised, based on local epidemiological expectations. The advantages of a gain in specificity however, have to be weighed against the errors that might be made in falsely classifying a person as uninfected who has a small reaction because of loss of sensitivity. Thus, in the evaluation of skin test results, errors are inevitable.

Identification of high risk groups

Population segments with high incidence of tuberculosis

An appropriate surveillance system should provide epidemiological information that allows the identification, within each country, of population groups that have an incidence of tuberculosis that is greatly in excess of that in the general population. From numerous studies it is known that there are factors among individuals with pre-existing infection with M. tuberculosis that put them at particular risk of developing the disease. The identification of such groups and persons is important, because they may gain particular benefit from preventive interventions. Several such populations segments and persons have been identified in various countries and are discussed here to the extent that such findings appear to be generally applicable.

Minorities, immigrants and displaced persons. Tuberculosis in immigrants largely mirrors the prevalence of infection with M. tuberculosis in the country of origin. The incidence is usually slightly lower than in the country of origin but may be modified to some extent by host country factors including population density and socio-economic status. The trend of tuberculosis incidence among immigrants continues to parallel that in the country of origin, which suggests that the most important determinant of the development of disease in low incidence countries is remote infection. Tuberculosis in immigrants from high incidence countries seems to account for a
The elderly. In many low incidence countries, tuberculosis in the indigenous, non-minority population has become a disease of the elderly. It is common that the incidence rates are highest in the oldest segments of the population. In several low incidence countries also a significant proportion of the cases are found in the population segment aged 65 yrs and older. This can be explained by a high prevalence of infection in this population segment that has lived through periods when the risk of infection was much higher than today. Most cases in this age group are attributable to reactivation of subclinical infection with M. tuberculosis acquired in the remote past. Given infection, the elderly may also be more susceptible to reactivation because of a downgrading of the functioning of cellular immunity in old age. Because symptoms and signs of tuberculosis in the elderly may mimic those of other commonly encountered ailments and conditions in this age groups, particularly malignancies, the necessity of including tuberculosis in the differential diagnosis of conditions encountered in the elderly patient cannot be overemphasized. This should help to reduce unnecessary and premature death from tuberculosis and hidden transmission to those who are in contact with this group.

Individuals infected with M. tuberculosis at increased risk of tuberculosis

Numerous factors that increase the risk of progression to tuberculosis from latent, subclinical infection with M. tuberculosis have been identified. Some of these factors bear a very high risk and are also fairly prevalent, others bear a high relative risk, but are rarely encountered, while others are associated with a low (but still increased) relative risk, but are fairly common. Such considerations need to be addressed when designing preventive intervention strategies.

Persons with HIV infection. Infection with HIV has emerged as the strongest yet identified factor to increase the risk of progression to tuberculosis among those infected with tubercle bacilli. Subjects infected with M. tuberculosis among persons with HIV infection should be identified, in order to provide them with preventive therapy (after exclusion of current tuberculosis). Tuberculosis is the major disease in HIV infected persons that is transmissible to non-HIV infected persons and which is both preventable and curable. Because the spread of HIV infection is likely to continue for some time to come, tuberculosis control programmes must urgently address the problem and formulate guidelines that help clinicians and public health workers to deal with the problem.

In low incidence countries the contribution of HIV infection to the spread of tuberculosis in the general population is likely to be small. This contribution will critically depend on the underlying prevalence of infection with M. tuberculosis in the community, especially in the 15–50 yr old age group. In population segments with a high prevalence of infection with M. tuberculosis, the impact of HIV will become increasingly relevant. In low incidence countries this is likely to be significant in special groups, such as intravenous drug users, in whom the risk of tuberculosis and of HIV infection is relatively high.

Recent infection. Recent infection with M. tuberculosis has been identified as a strong risk factor for tuberculosis. The risk of tuberculosis following infection is highest in the years immediately following infection. Contact investigation among newly discovered cases must thus have priority next to treatment of new cases, because the yield in discovering new transmission is likely to be high. Thus, preventive therapy in such cases will be particularly efficient.

Persons with fibrotic lesions. Persons who have had an episode of tuberculosis in the past that has spontaneously regressed without specific treatment and healed with residual fibrotic lesions in the lungs are at high risk of recurrence of tuberculosis. Whenever a chest radiograph is taken for whatever reason and fibrotic lesions are seen and active tuberculosis has been excluded, preventive therapy should be considered for those in whom it is not contraindicated for other reasons.

Persons with other risk factors. Numerous other factors have been identified that increase the risk of progression to tuberculosis among persons infected with M. tuberculosis. Notably these include silicosis, haemodialysis, diabetes mellitus, carcinomas (particularly of the head and neck), immunosuppressive treatment, gastrectomy, underweight, and jejunoileal bypass. Some of these are important, because they might be common (such as diabetes or underweight), others have only anecdotal relevance (such as jejunoileal bypass for obesity).

Laboratory services

Microscopy and culture for mycobacteria, identification and differentiation of species and drug sensitivity testing remain the most important laboratory techniques in mycobacteriology at present. Mycobacterial laboratory services are faced with problems in quality assurance in low incidence countries. The maintenance of proficiency and high quality services requires that laboratories regularly receive positive specimens. A service based on the recommendations in table 1 is likely to be satisfactory in terms of availability and required standard of performance and reliability.
Table 1. — Prospective organization of laboratory services for tuberculosis (TB) in low incidence countries

<table>
<thead>
<tr>
<th>Class</th>
<th>Expertise</th>
<th>Amount of work</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level I: local</td>
<td>Smear only (Ziehl-Neelsen)</td>
<td>Occasional</td>
</tr>
<tr>
<td>Level II:</td>
<td>Smear (Ziehl-Neelsen or fluorescence)</td>
<td>45–50 pathological specimens daily</td>
</tr>
<tr>
<td>1–4 million inh.</td>
<td>Culture</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Standard identification tests for TB only</td>
<td></td>
</tr>
<tr>
<td>Level III:</td>
<td>Elaborate identification tests</td>
<td>2–20 mycobacterial strains daily</td>
</tr>
<tr>
<td>5–10 million inh. or national</td>
<td>Drug sensitivity tests</td>
<td></td>
</tr>
</tbody>
</table>

It is particularly recommended that services such as differentiation of mycobacterial species, drug sensitivity testing, studies on drug resistance and the development and testing of new technology should be reserved for reference laboratories that serve a national population or some 5–10 million inhabitants of larger countries.

Research

**Treatment and prevention**

The continued investigation of drug combinations and the development of new anti-mycobacterial drugs remain absolutely essential. Non-compliant behaviour combined with the rising frequency of drug resistant organisms in less-developed countries and the growing role of opportunistic environmental mycobacteria in human disease all contribute to the urgent necessity to identify new therapeutic agents.

There is an urgent need for the evaluation of new preventive therapy regimens. It seems unlikely that isoniazid as a single agent, which has been used for some 40 yrs, will remain a practical preventive chemotherapeutic modality. Fully effective short-course regimen of 6 months for active disease make preventive therapy of one year duration unacceptable in today’s circumstances. Animal studies suggest that complete elimination of dormant organisms by isoniazid alone is less effective than combinations of drugs for a shorter duration. Adequate alternatives are thus needed, particularly in light of the HIV pandemic. The investigation of alternative preventive therapy regimens is mandatory. There is also urgent need to evaluate multiple drug regimens for prevention, especially of combination pills using shortened duration and possibly on an intermittent basis.

Investigation and development of immunotherapy techniques have already created a challenging conceptual model and offer an interesting opportunity for further scientific investigation.

**BCG**

It was noted that various BCG products have been adopted in the Expanded Programme of Immunization (EPI) and that BCG vaccines may differ in their protective efficacy and in the frequency of producing adverse reactions. Because good protection may be achieved by potent vaccines with few adverse reactions, it is recommended that the most suitable vaccines be identified and recommended.

**Intervention strategies and HIV infection**

Standard short-course chemotherapy appears to be effective in the treatment of tuberculosis in acquired immune deficiency (AIDS) patients but the frequency of adverse reactions appears to be higher, and failure to deliver an effective programme is also a greater problem in reports available to date. There are enormous challenges in the delivery of successful preventive programmes in this group.

Environmental mycobacteria that usually only cause disease in the immunocompetent, frequently cause disease in HIV infected patients and contributes to the urgent necessity to identify more effective therapeutic agents against these organisms.

The development of standardization of antigens from opportunistic environmental mycobacteria, so that epidemiologists may be provided with a reliable surveillance tool for these mycobacteria, is also a major challenge.

**Basic research**

Research is being carried out in the field of genetic engineering which could play an important role for the development of new techniques in the diagnosis of mycobacterial disease. No immediate practical applications for diagnosis or monitoring of treatment have so far been developed. However, one of the exciting benefits of such research has been the formation of
research links with workers outside the field of mycobacterial disease and this is considered important for the future development and support of such research. This is particularly so in the field of polymerase chain reaction (PCR) technology. The results so far suggest that gene amplification for diagnosis, deoxyribonucleic acid (DNA) probes for typing and the use of plasmids and mycobacteriophages for genetic engineering offer the most promising prospects. There is hope that molecular biology will change our understanding of the disease and expand the tools available for control programmes. The possibility to clone genes for specific antigens, offers the possibility of leading to more potent vaccines, provided that specific protective antigens can be recognized. These investigations are leading to a better understanding of the immune status in individuals infected with tubercle bacilli and offer the possibility of manipulating the immune response in vaccinated people or in patients with tuberculosis. For instance there is some evidence that the tissue damage by tuberculosis is mediated at least in part by the release of tumour necrosis factor from macrophages. These advances in our understanding offer a rational basis for the possibility of combining chemotherapy and immunotherapy with vaccines derived from killed environmental bacteria. It is felt that further basic research in this field should be encouraged and supported.

Recommendations from the working group

National tuberculosis services

A nationwide information and data collection system should be established to facilitate the prompt and accurate reporting of cases and to quantify the incidence of tuberculosis. Ideally these data collecting systems should be computer-based and should remain under the direct supervision of epidemiologists with expertise in tuberculosis, thereby facilitating the recognition of deficiencies in control programmes and their correction. Monitoring of programme outcomes would be facilitated and the systems could also be extended to offer advice on individual patient supervision or treatment.

Each country should maintain a central (national) tuberculosis programme unit. Responsibilities of this unit should, in addition to surveillance, include:
1. development and revision of a National Tuberculosis Control Programme;
2. monitoring of programme effectiveness;
3. training and provision of an adequate number of personnel with specialized tuberculosis expertise.

There should be direct governmental responsibility for the provision of a comprehensive tuberculosis service including the implementation of the control programme.

Surveillance

A nation-wide information and data collection system should be established to facilitate the prompt and accurate reporting of cases and to quantify the incidence of tuberculosis. Ideally these data collecting systems should be computer-based and should remain under the direct supervision of tuberculosis experts, thereby facilitating the recognition of deficiencies in control programmes and their correction. Monitoring of programme outcomes would be facilitated and the systems could also be extended to offer advice on individual patient supervision or treatment.

Parameters for monitoring tuberculosis in the elimination phase

The limitations of the traditional epidemiological parameters need to be recognized and new methods formulated for low incidence countries. The basic parameters, namely incidence of active tuberculosis mortality from tuberculosis, and incidence of tuberculosis meningitis in children should continue to be monitored but must be reviewed by a tuberculosis expert who understands the inherent limitations of these indices. The incidence of active tuberculosis in young people and tuberculin conversion in contacts reflects the current transmission of tuberculosis in a more precise way and should also be useful. The annual risk of infection and its trend over time is the most sensitive parameter of the epidemiology of tuberculosis in the community but has particular limitations where BCG has been widely used and is a difficult index to derive in countries who do not have a well established data base or where the prevalence of infection with M. tuberculosis has become very low.

The desirability of adhering to the WHO standard tuberculin Mantoux test with 2 tuberculin units (TU) of purified protein derivative (PPD) RT23 is reaffirmed (WHO/TB/Techn. Guide/3/1963) for both clinical and epidemiological purposes.

Case finding in the elimination phase of tuberculosis

It is recommended that the national tuberculosis control programme should formulate plans based on local epidemiological conditions. Special plans are needed in industrialized countries with large numbers of displaced people. It is recognized that the best approach to preventing spread to individuals or groups with special susceptibility to tuberculosis remains the early identification of patients with bacteriologically positive disease, particularly of the respiratory tract, and appropriate chemotherapy, coupled with contact tracing and preventive therapy for infected contacts. Preventive chemotherapy must play a major role in high risk groups.
**Treatment**

Short-course chemotherapy is recommended for all forms of tuberculosis in all patients. The prevalence of drug resistance especially in immigrants should always be considered. Supervised regimens are needed to overcome compliance problems.

**Preventive chemotherapy**

It is recommended that the identification of high risk groups be given priority and that preventive therapy be provided to those infected with *M. tuberculosis*. Evaluation by cohort analysis and efficiency of preventive intervention must form part of any such strategy.

**BCG vaccination**

Low incidence countries should consider discontinuing routine universal BCG vaccination of children. Countries with an incidence greater than 10 per 100,000 active cases of tuberculosis should also consider discontinuation but may have to contend with increases in the incidence of tuberculosis in non-vaccinated cohorts, which will usually be non-infectious but may include a small number of cases of tuberculosis meningitis. Modified BCG vaccination programmes could then be focused on groups considered to be at increased risk of infection. It is felt that these decisions can only be made with safety in countries with effective national tuberculosis control programmes which provide accurate contact investigation, preventive chemotherapy, data collection and programme monitoring facilities.

It is also recommended that the most suitable type and dosage of BCG be identified and that only those should be recommended.

**HIV infection**

The greatly increased risk of progression of tuberculosis from latent infection with *M. tuberculosis* is well-established. Screening of HIV infected persons for tuberculosis and infection with *M. tuberculosis* is recommended—but the limitations of the tuberculin skin test among immunosuppressed persons are recognized. Preventive chemotherapy with isoniazid should be used, but there is urgent need for trials to establish the most effective regimens.

Standard short-course chemotherapy is recommended in HIV infected patients with tuberculosis. The need for a longer continuation phase or the value of using a single agent chemotherapy after completion of treatment is unknown but these measures are practised in some circumstances. Follow-up of patients after completion of treatment may be maintained by close monitoring.

**Mycobacterial laboratory services**

It is recommended that mycobacterial laboratory services recognize the problems in assuring quality.

It is recommended that a Level I (local) laboratory would undertake only microscopic smear examinations for mycobacteria. Level II (1 million inhabitants) would perform smear (Ziehl-Neelsen (ZN) or fluorescence), culture and standard identification test for *M. tuberculosis* only. Level III (5–10 million inhabitants or national) would perform Level II work plus more elaborate identification tests and drug sensitivity tests. National drug resistance should be monitored to assure confidence in treatment regimens. Inter-laboratory quality control validation is recommended.

**Research**

New epidemiological parameters need to be formulated and the existing parameters need to be re-evaluated in low incidence conditions. The search for a more specific tuberculin test substance should continue as the problems of differentiating reactions to tubercle bacilli from those due to opportunistic mycobacteria will become even more important as the incidence of tuberculosis decreases.

The role of preventive therapy urgently needs further evaluation and is likely to be helped by the development of multiple-drug regimens used for short durations.

The continued investigation of drug combinations and the development of new anti-mycobacterial medication are highly recommended.

Immunotherapeutic techniques should be further investigated. Basic research in genetic engineering is exciting but has little tangible benefit at present. The possibilities are, however, enormous and therefore such research should be encouraged.

L’elimination de la Tuberculose dans les pays d’Europe et d’autres pays industrialisés. D’après un colloque tenu à Woluwe (Pays-Bas) 4–9 Mars 1990, sous les auspices de la région Europe de l’UIT-MR et ceux de l’O.M.S.

RÉSUMÉ: Le groupe de travail a résumé les conclusions de l’atelier dans le but de définir les grandes lignes pour la préparation de plans nationaux pour l’élimination de la tuberculose.

Les stratégies fondamentales ayant prouvé leur efficacité peuvent être dé écrites comme suit:

1. Le service public a la responsabilité directe du diagnostic, du traitement et de la prévention de la tuberculose (l’Etat est légalement responsable de l’identification précoce de la tuberculose et de la guérison des malades).
2. Renforcement ou mise en place d’un système efficace de la surveillance de la maladie et de suivi du programme.
3. Existence au niveau régional et provincial de personnel spécialisé en tuberculose, ayant la responsabilité de maintenir la qualité du diagnostic et d’assurer que les tuberculeux reçoivent l’attention nécessaire dans les centres de santé.

En ce qui concerne la recherche, le sentiment général est qu’aucune des innovations diagnostiques, thérapeutiques ou vaccinologiques ne peuvent pour le moment être introduites dans la pratique générale. La recherche fondamentale en mycobactériologie doit cependant être encouragée et soutenue.

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Case-finding in the elimination phase of tuberculosis: tuberculosis in displaced people

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Canada is a nation of displaced people. Even its earliest inhabitants were immigrants (from Asia). Thus, the impact of migration of human populations on the tuberculosis problem is well illustrated in this country. For the past century, approximately one in four Canadians were born in another country and moved to Canada. There have been several phases in the migration of people to Canada. The earliest phase (many thousands of years ago) was the movement of people across the Bering Strait (at that time, a land bridge) from Asia to establish the earliest settlement of Canada. The first wave of settlement moved south with the ice age and then returned to repopulate the north as the ice receded. These are known as "Inuit". The later wave probably came by boat from Asia and developed a lifestyle adapted to ice and snow. These are known as "Indians". The later wave was largely composed of the Inuit and a lifestyle adapted to living in the arctic and discontinuous habitats. These are known as "Indians". The later wave probably came by boat from Asia and developed a lifestyle adapted to ice and snow. These are known as "Inuit". Apart from a brief encounter with Scandinavians in the ninth and tenth centuries, there was no further contact between these groups and the remainder of the world until the arrival of Europeans in the sixteenth and seventeenth centuries. Shortly after this contact (which was initially, mutuallly friendly), the local populations were rapidly decimated by common illnesses introduced by the Europeans, such as tuberculosis, smallpox and measles. It is estimated that the population was reduced to 50% of its original size within a short time. The impact of this change is horribly illustrated by a study by Ferguson in Saskatchewan in the 1880's. The death rate from tuberculosis in Saskatchewan Indians in 1881 was one in one hundred persons per year. This rose to almost one in ten persons per year by 1886, after the establishment of residential reserve lands and only slowly declined to one in one hundred persons per year by 1900. The effect of this epidemic is still seen today where the rates of tuberculosis in aboriginal people are inversely related to the time since these people first came into contact with Europeans.

After an initial period of growth, immigration was balanced by emigration until the end of the nineteenth century when Canada participated in the latter phase of the great European migration, between 1880 and 1920, which populated western Canada. Immigrants came from all countries of Europe but non-Europeans were restricted. Immigration virtually stopped between 1930 and 1950 after which it began again. After 1965, restrictions were eased and an increasing proportion of immigrants came from Asia. Since that time, the impact of immigration on tuberculosis rates has become increasingly noticeable as the rates of disease in Canadian-born persons have substantially declined.

In a study in 1970-1974 (4) we showed the wide variation in rates of tuberculosis by country of birth, among Canadians. The highest rates were in those born in Asia, the lowest were in immigrants from northwest Europe with intermediate levels in those from southeast Europe. The rates in these immigrant groups (Figure 1) in every instance were similar but slightly lower than rates among their countrymen who had not immigrated.

The apparent higher rates in the first five years after immigration were shown to be due to the inclusion of cases of tuberculosis among non immigrants (visitors, students, seamen, etc.) in calculating the rates while considering only those with landed immigrant status in the denominator, and when these were excluded, there was no evidence of higher rates in the first few years.

We further investigated the association of rates with country of birth by comparing tuberculosis incidence in Canada, and in the country of origin, of immigrants from Scandinavia and from Finland (5). We chose to study these groups because their social characteristics were similar but incidence rates of tuberculosis were much different.

In addition, almost all of them had come to Canada before 1930. We found that, within age cohorts (Figure II), the incidence of tuberculosis in the immigrants was lower but parallel the incidence in their country of origin in spite of the fact that they had lived, on average, in Scandinavia for 15 years while in Canada for 10 years.

Figure 1. Average annual incidence of active tuberculosis by country of birth (on the x axis) and country of residence, 1980-1982 (solid bar indicates residence in country of birth, hatched bar indicates residence in Canada).

Figure II. Age-specific annual incidence of active tuberculosis in persons born in Finland and Scandinavia according to country of residence, 1970-1972. SK/SK-born and residing in Scandinavia; F/F-born and residing in Finland; SK/CD-born in Scandinavia and residing in Canada; F/CD-born in Finland and residing in Canada.
average, in Canada for over 40 years. We concluded that the incidence of tuberculosis in this group was determined by their experience prior to the age of 20 and probably reflected the likelihood of having become infected with tuberculosis.

We determined the trend in tuberculosis by country of birth for immigrants in Canada (Figure III). The incidence declined over this period in all groups except those born in southeast Asia. In this group, the rate rose between 1979 and 1981. This rise coincided with the entry to Canada of refugees from Indochina and was shown to be related to the much higher rate of tuberculosis in this group. We studied this group, in detail, by following approximately 9,000 refugees coming to British Columbia between 1979 and 1981 (6). These refugees were examined prior to coming to the province and, again, immediately upon arrival. We found that the incidence was highest in the first 3 months after arrival and included a high proportion of minimal pulmonary cases whose sputum was negative on culture for M. tuberculosis. Subsequent to the initial 3 months the incidence was lower (although still considerably higher than in the general population) and remained stable. We concluded that the higher incidence in the early period was, in part, related to overdiagnosis due to screening.

All immigrants to Canada require a chest X-ray examination prior to immigration to identify abnormalities due to tuberculosis. In the presence of such abnormalities, prospective immigrants must be further examined to ensure that the disease is not active prior to being allowed to immigrate. This is accomplished either by repeating the X-ray at a 6-month interval to ensure that the abnormality is stable or by demonstrating negative sputum cultures. Such immigrants are required to be re-examined on arrival to Canada. Because we were aware that the prevalence of lung scars indicating previous active tuberculosis was greater in some immigrant groups than in the general population and that the incidence of tuberculosis in patients with evidence of previous disease was much higher than in the general population, we wondered to what extent this subgroup accounted for the higher overall rate in some immigrant groups.

To answer this question, we studied all 24,000 immigrants to British Columbia, between 1982 and 1985, from China, Taiwan, Hong Kong, Japan, Korea, Philippines and India (7). We determined that 1,400 had evidence of previous tuberculosis and the remainder had normal chest X-rays (8). We then determined how many immigrants had active disease on arrival to the province and how many subsequently developed the disease over the period of follow-up. We found that 1% of those with evidence of previous disease had active disease on the first examination after arrival. No cases were reported in the group who had normal X-rays. All the cases were negative for acid-fast bacilli on direct microscopy prior to immigration and, in all cases, there was no apparent change in the X-ray. The patients all denied symptoms.

On follow-up, one-half of new cases arose in the group with evidence of previous disease and the other half in those with normal X-rays. The incidence rate of active disease was more than ten times higher in those who had evidence of previous disease than in those who had normal X-rays at the time of immigration. Moreover, the incidence of active disease in immigrants with previous disease was only slightly higher than in those in the general population of the province who had previous disease, and the difference between the incidence in immigrants and the general population, who had normal X-rays, was much reduced, to a level which was not considered to allow active case-finding to be cost effective. We concluded that immigrants with evidence of previous disease form a substantial proportion of the potential tuberculosis problem in immigrants from high prevalence countries, they are easily identified on pre-immigration screening and they are amenable to preventive therapy, reducing the likelihood of developing active tuberculosis and, thus, the incidence of disease in the group.

In summary, studies of immigrants to our country have shown that the tuberculosis problem is a reflection of the situation from which the immigrants come, the problem appears to be decreasing in all groups of immigrants to our country and a substantial proportion of the problem arises in those who have evidence of previous disease, who can be easily identified by screening and are amenable to preventive therapy, provided they are examined after landing in Canada.

REFERENCES


Figure III. Trend in annual incidence of active tuberculosis by place of birth in immigrants to Canada, 1970-1981. SEA-southeast Asia; SEE-southeast Europe; NWE-northwest Europe.
BCG VACCINATION ISSUES

a. Old BCG replaced by new vaccine?

Human leukocyte antigens (HLA) and mycobacterial disease*

R. DE VRIES**

The immunogenetic approach to mycobacterial disease

In most individuals extensive exposure to mycobacteria does not result in disease. Many factors are involved in this apparent successful parasitism of mycobacteria. For instance, most mycobacterial species rarely or never cause disease. In this short review I will only discuss generic host factors that play a role in the outcome of an infection with potentially pathogenic mycobacteria. To this purpose I will confine myself to the two most important pathogenic mycobacteria, namely Mycobacterium tuberculosis (M. tuberculosis) and Mycobacterium leprae (M. leprae). Of these two mycobacterial species M. leprae is by far the less virulent and toxic and, therefore, makes host factors particularly apparent.

Certainly in leprosy, but probably also tuberculosis, the immune response of the host to the bacillus is responsible for the disease symptoms rather than direct damage by the mycobacterium. Virtually everybody has an intact immune system, but only few sufficiently exposed to and infected with M. tuberculosis or M. leprae develop a clinically relevant disease. Particularly during the last two decades it has become clear that subtle differences in immune reactivity exist between individuals and that these differences are genetically controlled and biologically relevant. The study of genetically controlled differences in immune reactivity and their relevance for disease susceptibility historically belongs to a discipline called immunogenetics.

Immunogenetics was born as the ABO blood groups and is thus 88 years old. Because several blood group antigens also appeared to be transplantation antigens, immunology became not only a tool but also a subject of study for immunogenetics. This led to the discovery of the major histocompatibility complex (MHC)-linked immune response (Ir-) genes and the role of their products in the regulation of the immune response, which is the main subject of this short review.

Regulation of T cell responsiveness against mycobacterial antigens by HLA class 2 immune response genes

Helper T lymphocytes can only recognize mycobacterial antigens when they are presented by HLA class 2 molecules. Thus these molecules may play an important role in the regulation of the immune response against mycobacteria. In this review it is demonstrated that the T cells from individuals with different HLA class 2 molecules react to different mycobacterial antigens. These data indicate that HLA class 2 molecules are the products of immune response (Ir) genes for mycobacteria.

Such genetically controlled differences in antimycobacterial T cell reactivity may explain the association of certain HLA class 2 alleles with a different course of mycobacterial infections and may have implications for vaccine development.

A better understanding of T cell reactivity against Mycobacterium tuberculosis and of its regulation might aid in the development of rational approaches to the production of an effective vaccine against tuberculosis. In the past few years, the tools for studying T cell reactivity have improved dramatically: well-defined protein and nonprotein antigens as well as monoclonal T cell reagents have become available, and novel cellular-immunologic techniques have been developed. With the use of these tools, it has now become possible to define exactly and produce the epitopes on M. tuberculosis that are recognized by functionally different types of T cells. These epitopes are presented to T cells by HLA class 2 molecules, which thus have an important role in the regulation of T cell reactivity against M. tuberculosis.

In this short review I will discuss the role of immune response (Ir) genes in the pathogenesis of mycobacterial diseases and the implications for vaccine development. Ir genes are genetic host factors that code for interindividual differences in antigen-specific immune reactivity. The best-defined human Ir genes are the...
extremely polymorphic HLA class 2 genes that code for the above-mentioned HLA class 2 molecules. Data will be presented indicating that interindividual qualitative differences between HLA class 2 molecules result in (1) presentation of different mycobacterial epitopes to T cells; (2) activation of functionally different T cell subsets and thus (3) differences in the course of an infection with Mycobacterium leprae or M. tuberculosis. The molecular basis for these genes effects will be discussed, as well as its implications for vaccine development.

**HLA system**

The HLA system is the major histocompatibility complex (MHC) of humans. It contains two different sets of very polymorphic genes : class 1 and class 2 genes. These two sets of genes are the human MHC-linked Ir genes. Several genes coding for factors of the complement system (C2, C4 and factor B) are situated between the class 1 and class 2 genes. These genes are neither structurally nor functionally related to the HLA class 1 and 2 genes; we therefore do not consider them to belong to the HLA system, although this does not mean that these genes may not be relevant to the differential susceptibility to or the course of mycobacterial infections. However, in this review I will focus on the HLA class 1 and 2 Ir genes. There are three functional class 1 genes (A, B and C) and at least three sets of class 2 genes (DP, DQ and DR) coding for class 2 products. Except for DP, these genes are so close (recombination frequency < 2 %) that they are usually inherited together or as a so-called haplotype.

The HLA system is by far the most polymorphic genetic system known in humans. This implies that individuals will have a unique set of HLA class 1 and 2 alleles unless they are closely related genetically. Apart from the fact that this extreme polymorphism provides us with a powerful tool for genetic studies, it is probably also essential for the function of the system.

The virtually infinite number of possible combinations is restricted to some degree by so called linkage disequilibria : certain combinations of alleles of different loci occur more (or less) often than would be predicted from their respective gene frequencies. These linkage disequilibria may be (or have been) functionally important. Moreover, they have practical relevance for the demonstration of disease susceptibility genes, because products of genes linked to a particular disease susceptibility gene may serve as genetic markers.

**HLA and tuberculosis**

Much less attention has been paid to the relationship between tuberculosis and HLA than to that between leprosy and HLA. Some associations have been reported between HLA class 1 alleles and tuberculosis but these vary among populations. One of these studies suggested that disease severity is associated with HLA type. A similar observation was made in China, where tuberculosis meningitis was associated with a particular HLA antigen (Jiang Zaifang, personal communication). A family study in India showed significant co-segregation of pulmonary tuberculosis with HLA-DR2. In a recent large population study in Indonesia carried out in collaboration with J. Ivanyi (London), we observed a significant association between tuberculin-positive tuberculosis and (also) DR2. In that study a strong association was noted between DR2 and a high antibody titer to an epitope on a 38-kilodalton (kDa) protein of M. tuberculosis, a finding indicating that a DR2-associated immune response gene may be the mechanism for this association.

**Old BCG coming to an end – a new vaccine coming too late for Europe ?**

P.E.M. FINE

Concerning this important item, we suggest that the reader refers to 3 main articles from Dr Paul Fine which give an overall view of the current thinking and field studies under way relating to the protection against tuberculosis and/or tuberculosis and leprosy:

b. First experience with BCG discontinuation in Europe

Experience in Sweden 15 years after stopping general BCG vaccination at birth

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Fifteen (15) years ago, in April 1975, routine BCG vaccination of newborns was abandoned in Sweden. Previous analyses of the consequences of the changed BCG policy were reviewed by the end of 1980, 1984 and 1987 (1,2, 3). The present analysis includes the period between April 1975 and December 1989, i.e. nearly 15 years.

Target population

In 1975 to 1989 the population in Sweden included on average 8.4 million inhabitants, of whom 8% were immigrants. The annual number of newborns ranged between 92,000 and 116,000 during the same period. In total 1.5 million children were born in Sweden after the changed BCG policy in April 1975 up to the end of 1989. About 11% of them were of foreign origin, i.e. the one or both parents were foreigners.

Tuberculosis in the whole population

The development of tuberculosis in Sweden during 15 years before and 15 years after the changed BCG policy is shown in Figure 1. The annual incidence rate per 100,000 population of all ages decreased from 60 in 1959 to a level around 6 in 1987, 1988 and 1989 respectively.

More details on the background situation as recorded in the year before the changed BCG policy (1974) and 14 years later (1988) are given in Table 1. The current low risk of tuberculosis exposure in Sweden is demonstrated by the declining rate of smear-positive patients per 100,000 inhabitants from 4.5 in 1974 to 1.7 in 1988 (Table 1). On the other hand the increasing proportion of cases confirmed by culture among all new cases of active tuberculosis (Table 2) might indicate that tuberculosis nowadays is diagnosed at later stages possibly due to lack of knowledge of how to establish the clinical diagnosis by radiological findings. The age specific incidence rate decreased in all age groups, except in children, both among Swedes and among the foreign population (Table 2).
Table 3. New cases of active tuberculosis in Sweden. Age-specific incidence rate per 100,000 population of Swedes and foreigners respectively in 1974 and 1988

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>0-14</th>
<th>15-24</th>
<th>25-44</th>
<th>45-64</th>
<th>&gt; 65</th>
<th>All ages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swedes</td>
<td>1974</td>
<td>0.3</td>
<td>4.6</td>
<td>11.3</td>
<td>29.0</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>1988</td>
<td>0.2</td>
<td>0.7</td>
<td>1.3</td>
<td>5.4</td>
<td>20</td>
</tr>
<tr>
<td>Foreigners</td>
<td>1974</td>
<td>18</td>
<td>32</td>
<td>44</td>
<td>42</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>1988</td>
<td>23</td>
<td>19</td>
<td>21</td>
<td>11</td>
<td>23</td>
</tr>
</tbody>
</table>

3). However the risk of tuberculosis is still considerably higher in foreign born than in Swedes especially among children and young adults.

Tuberculosis in children

Considering the child population in its entirety the annual incidence rate of tuberculosis per 100,000 population aged 0-14 years has been between 0.5 and 2 right from the end of the 1960's and no apparent change could be observed after 1975 (Figure I). Restricting the analysis to the youngest age groups, and furthermore to those children who were born in Sweden and therefore influenced by the Swedish BCG policy for newborns, a slight increase could be observed after 1975. Among children aged 0-4 years the maximum level (1.9/100,000) was reached in 1979, to be compared with children aged 5-9 years among whom the peak incidence (1.1/100,000) was notified in 1985, when all cohorts included in this age group belonged to those mainly non-BCG-vaccinated (Figure II). If the foreign born child population is also included the recorded level is slightly higher (the non-interrupted line in Figure II), while the annual tuberculosis incidence rate estimated among the foreign born child population separately ranges between 7 and 70 cases per 100,000 children aged 0-4 years and between 0 and 16 cases per 100,000 children aged 0-9 years.

Selective BCG vaccination of risk groups after April 1975

The higher risk of tuberculosis recorded in the immigrant population supported the recommendations to continue selective BCG vaccination of children at increased risk of tuberculosis exposure also after April 1975. In this risk group were included children in families immigrated from countries with high prevalence of tuberculosis, also those children who were born in Sweden, and furthermore foreign and Swedish children who planned to travel to such countries as well as Swedish children with a family history of previous or recent tuberculosis.

BCG vaccination coverage

Since the 1950's up to 1975 at least 95 % of all newborns were BCG-vaccinated at the maternity wards. After stopping routine vaccination the recorded vaccination rate among cohorts born from 1976 to 1980 was below 5 %, which was not sufficient to cover the population at risk. For this reason the medical staff at maternity wards and at child health centres were encouraged to follow the current recommendations and to intensify their efforts to identify and BCG vaccinate children at increased risk of tuberculosis exposure. Consequently the vaccination rate increased up to 17 % of cohorts born in 1984. Most children are vaccinated during their first years of life.

According to approximate calculations, based on reports in January 1988, BCG coverage of children born in Sweden increased among those born of Swedish parents from 2 % of cohorts born in 1981 up to 9 % of those born in 1984 and among those born of foreign parents from 35 to 79 %.

BCG vaccine used in Sweden

The BCG vaccine used from the 1940's was produced at the bacteriological laboratory in Gothenburg from the BCG strain named "Gothenburg". In the beginning of the 1970's the vaccine production was moved to Denmark—but the same Swedish BCG strain was used until the end of 1978. Since 1979 vaccine produced from the Danish BCG strain named "Copenhagen 1331" has been used in Sweden.

Serious vaccine complications

The reason for stopping routine vaccination at birth in 1975 was the high rate of complications presenting as osteitis recorded in cohorts born from 1972 to 1974 (29 cases per 100,000 children born in Sweden). Another 3 cases of BCG osteitis were reported among approximately 5,500 children who were born in Sweden and BCG-vaccinated between April 1975 and December 1978. The approximate number of children who were born and BCG-vaccinated from 1979 to 1988 amounts to 95,000. During this period no case of osteitis has been reported. However 4 children born in the period between 1984 and 1988 have suffered from serious vaccine complications with generalized lesions of BCG infection. One previously healthy child developed BCG meningitis and 3 children with severe combined immune deficiency syndrome developed disseminated BCG-itis, 2 of whom died.

Tuberculosis in BCG-vaccinated and non-BCG-vaccinated children born in Sweden

The influence of the varying degree of BCG vaccination coverage was studied among children born in Sweden before and after April 1975. The cumulative incidence rate of tuberculosis before 5 years of age was estimated to 1.0 per 100,000 children born from January 1969 to March 1975 and to 6.2 per 100,000...
Table 4. Tuberculosis in children born in Sweden from 1969 to 1985. Cumulative incidence rates before 5 years of age per 100,000 children born of Swedish and foreign parents respectively. Comparison between children born during periods of high, low and moderate BCG-vaccination rates

<table>
<thead>
<tr>
<th>BCG vaccination rate all children</th>
<th>Children born in Sweden</th>
<th>Cumulative incidence rate of tuberculosis below 5 years of age</th>
<th>Relative risk Foreign/Swedish</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Period of birth</td>
<td>No.</td>
<td>Swedish parents</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No./100,000</td>
</tr>
<tr>
<td>A.</td>
<td>Jan. 1969-</td>
<td>5</td>
<td>0.8 (0.3,1.9)</td>
</tr>
<tr>
<td></td>
<td>March 1975</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B.</td>
<td>April 1975-</td>
<td>19</td>
<td>3.9 (2.3,6.1)</td>
</tr>
<tr>
<td></td>
<td>Dec. 1980</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C.</td>
<td>Jan. 1981-</td>
<td>12</td>
<td>2.9 (1.5,5.1)</td>
</tr>
<tr>
<td></td>
<td>Dec. 1985</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative risk</td>
<td>B/A</td>
<td>4.9</td>
<td>(1.7,16)</td>
</tr>
<tr>
<td></td>
<td>C/A</td>
<td>3.6</td>
<td>(1.2,13)</td>
</tr>
</tbody>
</table>

The relative risk of tuberculosis in children born of foreign parents compared with those of Swedish origin was estimated to 4.9 (95% confidence interval 1.7, 16).

The incidence of tuberculosis was compared in 3 groups of children belonging to cohorts with high, low and moderate BCG vaccination rates (Table 4). Among mainly non-BCG-vaccinated children born of Swedish parents from 1975 to 1980 the relative risk of tuberculosis compared with those BCG-vaccinated born from 1969 to 1974 was estimated to 4.9 (95% confidence interval 1.7, 16).

Epidemiological/clinical findings in children born in Sweden after April 1975 and diagnosed as having tuberculosis to the end of 1989

In total 84 children who were born in Sweden between April 1975 and December 1989 contracted tuberculosis during the same period. Forty-five (45) of them, who were born of Swedish parents, were all non-BCG-vaccinated. Among 39 children, who were born of foreign parents, 32 were non-BCG-vaccinated and 7 had been BCG-vaccinated at birth (Table 5).

Clinical illness usually presented as high fever and coughing had developed in 38 of 84 children (45%) at the time when the diagnosis was established. Three (3) children suffered from serious illness; one boy with neonatal miliary tuberculosis died; one 2-year old boy with meningitis developed serious chronic sequelae, while one 18-month old boy with meningitis recovered after treatment. All these 3 serious cases occurred within the first 5-year period after the changed BCG policy (1).

The reason for detection of tuberculosis was contact screening in 58 of 84 children (69%), while 24 children were diagnosed only because of their illness. The diagnosis was unnecessarily delayed in several of these children because of the following reasons: the source of infection was not yet diagnosed; the child developed illness shortly after normal findings at contact screening and there-

Table 5. Tuberculosis from 1975 to 1989 in children born in Sweden from 1975 to 1989

<table>
<thead>
<tr>
<th>Period of birth</th>
<th>Years of observation</th>
<th>Born of Swedish parents Total (BCG)*</th>
<th>Foreign parents Total (BCG)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>April 1975-Dec. 1979</td>
<td>14.5-10.5</td>
<td>22 (0)</td>
<td>26 (0)</td>
</tr>
<tr>
<td>1980-1984</td>
<td>9.5-5.5</td>
<td>20 (0)</td>
<td>8 (3)</td>
</tr>
<tr>
<td>1985-1989</td>
<td>4.5-0.5</td>
<td>3 (0)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Total number</td>
<td>45 (0)</td>
<td>39 (7)</td>
<td></td>
</tr>
</tbody>
</table>

*number of whom BCG-vaccinated at birth
fore tuberculosis was excluded as possible cause of the illness; or the consulting doctor was not aware of the recent exposure to tuberculosis. Furthermore there were difficulties in interpreting clinical symptoms and/or the tuberculin skin test reaction in children who were BCG-vaccinated previously.

The source of infection was found within the family or in close relatives (grandparents or parents' siblings) in 58 of 84 children (69 %) and in more distant contacts in 16 children (19 %). However in 10 children (12 %) the source of infection could not be identified.

Conclusions

Fifteen (15) years after stopping general BCG vaccination at birth, tuberculosis is still a rare disease in Swedish children. Serious illness has not been reported in any non-BCG-vaccinated child born in Sweden during the last 10-year period. Therefore general BCG-vaccination at birth is not justified.

The decreased occurrence of tuberculosis recorded among children born of foreign parents from 1981 to 1985 compared with those born from 1975 to 1980 suggests a beneficial effect of the improved BCG coverage of the population at risk which might be an effect of the declining risk of infection. However despite the selective BCG vaccination of risk groups the recorded incidence of tuberculosis was still higher among children born of foreign parents than among those of Swedish origin by the end of 1989.

The high proportion of BCG vaccinated children found among those children who were born of foreign parents from 1980 to 1989 and who contracted tuberculosis (Table 5) cannot be definitely explained, but might reflect the increasing BCG coverage of these cohorts or might even suggest a poor protective efficacy of the vaccine used or perhaps poor vaccination technique.

The recent occurrence of serious disseminated BCG infection in children with severe combined immune deficiency syndrome calls for attention and demands careful individual assessment before BCG vaccination at birth. Would it be reasonable to postpone BCG vaccination of risk groups to the age of 6 months or later?

In any case, other methods to prevent childhood tuberculosis than BCG vaccination should be intensified:

- Case-finding. Special attention should be paid to the tuberculosis history and the present health of becoming parents and the family around the newborn child.
- Contact tracing. Children in contact with TB patients, also more accidental close contacts, should be traced and examined without delay. We want to find the infected child before developing illness. However also long term surveillance of exposed children is necessary as regard to possible onset of illness after normal examination.
- Doctors' delay of diagnosis has to be prevented by education and information.

The recorded increase of childhood tuberculosis after stopping BCG vaccination at birth was predicted and it tallies with the prognosis made by Ingela Sjögren in 1975 (4).

Non-tuberculous mycobacterial lymph node disease


During the last 10-year period the annual number of bacteriologically confirmed cases in children below 15 years of age has ranged between 20 and 40; to be compared with only 2 cases found in the same age group during the whole period from 1969 to 1976. The majority of patients are between 1 and 4 years of age.

Mycobacterium avium-intracellulare was identified in most cases. (Preliminary data 1990, to be published. V. Romanus in cooperation with P. Wahlén, K. Wickman & I. Juhlin.) Non-tuberculous mycobacterial lymph node disease caused by Mycobacterium avium-complex is today a more common disease than tuberculosis among Swedish children. The role of the changed BCG policy in this development has not been established.

Acknowledgement. Data from the Central Tuberculosis Register were kindly made available by Pr. Ake Hångreen, of the Swedish National Association Against Heart and Chest Diseases.

My sincere gratitude to Pr. Gunnar Dahlström for his valuable views on the manuscript, to Dr. Ake Svensson who gave advice on the statistical analyses and to First technician Gun Sandzelius for valuable help.

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REFERENCES

Project on discontinuation of BCG vaccination in newborns in Czechoslovakia

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*Institute of Hygiene and Epidemiology, 10000 Prague 10, Czechoslovakia.
**Institute of Respiratory Diseases Research Institute, 18071 Prague 8, Czechoslovakia.

Mass BCG vaccination has been carried out in Czechoslovakia since 1953. Actually about 98 % of all newborns are BCG-vaccinated and tuberculin negative subjects aged 7, 13 and 18 years are revaccinated.

Since April 1, 1986 a project has been established in which mass BCG vaccination of infants born in an area with an annual birth rate of approximately 35,000 has been discontinued. Compulsory BCG vaccination is applied in the rest of the country.

The aim of the project was to check possibilities to adapt the BCG vaccination policy to the actual tuberculosis situation, based on objective data on the transmission of tuberculosis in infants and detailed cost/benefit analysis. The methodology and the first results of the project were published in the IUATLD Bulletin in 1988 (1).

In the period from April 1, 1986 to December 31, 1989 102,079 children were not BCG-vaccinated (86 % out of 118,776 infants born in the project area). Out of them 18 % are at the present time more than 3 years old, 50 % between 1-3 years of age and 32 % of unvaccinated children are less than one year old.

A total of 3.5 % (4,023) of infants born in the project area were vaccinated because of presumed high risk of tuberculosis and only 1.8 % (2,112) parents of newborns asked for BCG vaccination. The remaining children were vaccinated mainly because they were born outside the project area.

The number of children moving out of the area during the course of the project and thus vaccinated did not exceed 2 %.

All unvaccinated children were checked at yearly intervals by skin tuberculin tests (2 TU PPD RT 23). The frequency and distribution of tuberculin reactions are given in Table 1. There was no significant difference in the distribution of reactions in the respective age groups of 1, 2 or 3 year-old children. Numbers of children with repeatedly verified reactions of 6 mm or more (positive tuberculin reaction) were small in all 3 cohorts: 20-1 year-olds, 32-2-year-olds and 24 3-year-olds. They were thoroughly examined and were followed up at the specialized chest clinic.

Taking these children as being infected by mycobacteria, the risk of tuberculosis infection amounted to 0.03 % for children aged 0-1 year; the respective values for children 1-2 years old were 0.07 % and 0.09 % for children 2-3 years old.

The transmission of tuberculous infection was followed in cohorts of unvaccinated children (born in 1986, 1987 and 1988) (Table 2). In the first year of life the risk of infection was only approximately half of that in the second and third years of life (with a significant difference of 1 %). There was no change in the risk of infection in children of the same age in different cohorts.

Primary lung tuberculosis was detected in 9 unvaccinated children; 5 of them were aged under 1 year, 3 were

---

Table 1. Frequency and results of tuberculin testing

<table>
<thead>
<tr>
<th>Children aged (years)</th>
<th>No.</th>
<th>%</th>
<th>No.</th>
<th>%</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>2</td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>No. of unvaccinated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- eligible</td>
<td>69,297</td>
<td>100.0</td>
<td>43,464</td>
<td>100.0</td>
<td>17,919</td>
<td>100.0</td>
</tr>
<tr>
<td>- examined</td>
<td>66,950</td>
<td>96.6</td>
<td>41,333</td>
<td>95.4</td>
<td>15,924</td>
<td>88.9</td>
</tr>
<tr>
<td>Results of testing:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>induration (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-3</td>
<td>66,517</td>
<td>99.4</td>
<td>40,903</td>
<td>99.0</td>
<td>15,716</td>
<td>98.7</td>
</tr>
<tr>
<td>4-5</td>
<td>413</td>
<td>0.6</td>
<td>398</td>
<td>1.0</td>
<td>184</td>
<td>1.2</td>
</tr>
<tr>
<td>6+</td>
<td>20</td>
<td>0.32</td>
<td>32</td>
<td>0.68</td>
<td>24</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Table 2. Risk of tuberculosis infection in unvaccinated children (tuberculin test 6 mm and more) ; percentage out of all unvaccinated children

<table>
<thead>
<tr>
<th>Year of birth</th>
<th>Age at time of infection (months)</th>
<th>0-12</th>
<th>13-24</th>
<th>25-36</th>
</tr>
</thead>
<tbody>
<tr>
<td>1986 No.</td>
<td>5</td>
<td>0.028</td>
<td>0.039</td>
<td>0.056</td>
</tr>
<tr>
<td>%</td>
<td>1987 No.</td>
<td>13</td>
<td>19</td>
<td>14*</td>
</tr>
<tr>
<td>%</td>
<td>1988 No.</td>
<td>2</td>
<td>6*</td>
<td>-</td>
</tr>
<tr>
<td>%</td>
<td>Total No.</td>
<td>20</td>
<td>32</td>
<td>24</td>
</tr>
<tr>
<td>%</td>
<td>* preliminary data, all results not yet available</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

Table 3. Incidence of tuberculous disease in unvaccinated children

<table>
<thead>
<tr>
<th>Year of birth</th>
<th>Age at time of disease (years)</th>
<th>0-1</th>
<th>1-2</th>
<th>2-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1986</td>
<td>No. rate</td>
<td>2</td>
<td>11.16</td>
<td>2</td>
</tr>
<tr>
<td>1987</td>
<td>No. rate</td>
<td>2</td>
<td>7.83</td>
<td>-</td>
</tr>
<tr>
<td>1988</td>
<td>No. rate</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1989</td>
<td>No. rate</td>
<td>1*</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Rate: per 100,000 unvaccinated children
*examined because of contact with tuberculous mother

The incidence of tuberculous disease was compared in children in contact with tuberculosis sources in comparable unvaccinated and vaccinated groups. In the unvaccinated group the rate of tuberculosis was 3.4%, whereas in the vaccinated group the estimated rate was only 1.3%. The higher incidence in the former group could be however influenced by protocol examinations.

The results of our project were compared with those in Sweden, where mass BCG vaccination was discontinued in 1975 (2). The incidence of tuberculosis in Swedish children born 1975-1980, was 6.5/100,000 unvaccinated children, whereas in vaccinated children born 5 years before (1969-1974) the incidence was only 0.95/100,000. Our figures in 1990 thus correspond well to those in Sweden from 1975-1980.

Table 4. Risk of tuberculous disease per 100,000 children

<table>
<thead>
<tr>
<th>Risk of BCG side-effects</th>
<th>Children</th>
<th>Unvaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculous disease</td>
<td>8.7</td>
<td>1.3</td>
</tr>
<tr>
<td>BCG side-effects:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>local serious reactions</td>
<td>-</td>
<td>109.0</td>
</tr>
<tr>
<td>osteomyelitis</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>BCG-itis</td>
<td></td>
<td>1.7</td>
</tr>
</tbody>
</table>

The discontinuation of BCG vaccination of newborns in the project area has been well accepted by parents. Already 100,000 children have been allocated to the project.

The observed risk of infection in children aged 1-3 years did not exceed 0.1% and was below the limit of expected values calculated at the time of project preparations (Table 5). On the other hand the risk of tuberculous disease (breakdown to tuberculosis) was above (15% of the infected children) expected values.

In unvaccinated children the incidence of tuberculosis has so far been higher than in vaccinated children. The difference is minimized if the incidence of serious BCG side-effects is taken into account. Cost of BCG vaccination is another factor which has to be taken into account. Cost evaluation together with late results of the project will offer a reasonable basis for sound decision making.

Table 5. Expected and observed risk of infection and tuberculosis in unvaccinated children

<table>
<thead>
<tr>
<th>Risk of</th>
<th>Expected (estimation)</th>
<th>Observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>0.06</td>
<td>0.13 %</td>
</tr>
<tr>
<td>Breakdown to tuberculosis</td>
<td>5</td>
<td>10 %</td>
</tr>
</tbody>
</table>

REFERENCES

BCG vaccination and HIV infection*

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Introduction

HIV infection among children has been a matter of concern for BCG vaccination programmes because children with immunodeficiency syndromes are known to be prone to developing persistent or disseminated BCG disease when vaccinated at birth. In fact, in countries where BCG vaccination is given routinely to the newborn, the risk of persistent or disseminated BCG infection closely reflects the incidence of severe combined immunodeficiency, cellular immunodeficiency and chronic granulomatous disease. Up to now HIV infection and AIDS have been relatively rare among young children in developed countries. In the USA it is estimated that 1.4 % of the cases of AIDS occurred in children. In developing countries the proportion is far higher: over 6 % of AIDS cases and over 3 % of HIV infections in Uganda occurred in children (over 25,000 infections).

A related matter of concern has been acceptability with regard to lymphadenitis. Lymph node involvement is an integral part of the BCG immunization process, but is regarded as an untoward side reaction, both by parents and the medical profession, when suppuration occurs in more than one or two percent of the vaccinated children. If its incidence were much increased in HIV-infected children, the entire vaccination programme might suffer in terms of coverage since BCG vaccination is the "gateway" to EPI.

For HIV-infected infants any benefit of BCG vaccination only could be marginal because the prognosis is very poor: 50 % will develop AIDS in the first year and over 80 % within three years after birth (2). Unfortunately it is not possible to exclude HIV-infected children at birth. When born to HIV-infected mothers, infants are not necessarily HIV-infected, even when HIV-seropositive. The uninfected infants born to HIV-infected mothers are at a greatly increased risk of tuberculosis infection since in dualy infected women the risk of tuberculosis after childbirth is very high. Dual infection may be very common, not only in developing countries. In Argentina about 50 % of HIV-infected women (mainly intravenous drug users) are also infected with tuberculosis. Even the question of whether or not to exclude from BCG vaccination infants born to known or suspected HIV-infected mothers is therefore not answered easily.

Observations

A number of published reports refer to the safety of BCG vaccinations in HIV-infected individuals. The total number of observations is still small and most refer to lymphadenitis (although this is sometimes described as dissemination).

In several African countries the matter of safety in HIV-infected infants was precipitated by observed increases in lymphadenitis. A study of an outbreak in Zimbabwe (7) showed that among 185 HIV-infected infants the lymphadenitis rate was similar to that in other children. A study in Zaire (8) among 223 HIV-seropositive children showed that 9 % had lymphadenitis and 2 % fistulae. In other children these proportions were 5 % and 1 %. Whereas the risk of lymphadenitis in HIV-seropositive children may be somewhat increased, it certainly is not alarming. When an outbreak of lymphadenitis was observed, 19 cases examined were all HIV-negative (9). The sudden increase in lymphadenitis could be ascribed to the introduction of BCG from the Institut Pasteur. A similar association has been reported recently from Uganda.

Adenopathy and local abscesses have been described. Among 67 HIV-seropositive infants vaccinated with BCG within 2 months of birth, 7 developed axillary adenopathy. The evolution was benign in 5 cases without treatment, in one with rifampicin and in one with isoniazid (10). The incidence may seem excessive, but in the absence of controls it is difficult to draw any conclusion.

A 22-year-old man with AIDS who did not react to tuberculin was BCG-vaccinated. A few days later a fistulized abscess developed at the injection site. The lesion responded quickly to treatment with isoniazid and rifampicin (11). This may well have been a case of accidental subcutaneous injection of the vaccine.

On the other hand the fact that BCG may multiply as a result of HIV infection is strongly suggested by the case of a 36-year-old man with AIDS who developed axillary lymphadenitis that showed Kaposi’s sarcoma and acid-fast bacilli upon examination of biopsy material. BCG was found on culture. The BCG infection was controlled with a regimen of isoniazid, rifampicin, ethambutol and pyrazinamide. The special feature is that the man had been vaccinated at the age of 6 years (12).

Disseminated BCG disease, unfortunately, has been observed as well. In Argentina a girl BCG-vaccinated after birth started developing multiple infections as from the second week of life. She was hospitalized and treated with various antibiotics but remained febrile. She showed adenopathies and acid-fast bacilli were recovered from the liver, the spleen, lymphnodes and bone marrow. She died at the age of 8 months. BCG was isolated from cultured material. The child’s parents were HIV-seropositive (I. Miceli, personal communication).

A boy from Zaire born to a mother with ARC developed lymphadenitis 4 months after BCG vaccination (13). BCG was recovered from the lymph node and the cerebrospinal fluid. The child was very ill on admission but improved dramatically, in three days, upon treatment with isoniazid, rifampicin and ethambutol.

A 3.5-month-old Amerindian girl who
had received BCG at three weeks of age presented with an oozing BCG vaccination lesion and symptoms of AIDS. Two weeks later she developed Pneumocystis Carinii Pneumonia. BCG was recovered from blood, gastric aspirate, tracheal aspirate and lung biopsy material. The child improved clinically upon intravenous treatment with isoniazid and rifampicin (14).

A 31-year-old man with AIDS was given BCG in Mexico. The local lesion healed normally but started to ulcerate 4 months later when he also developed axillary lymphadenitis. BCG was found in blood culture and a culture from the local lesion. He responded favourably to treatment with isoniazid and ethambutol (15).

Recommendations

Whereas these, mainly anecdotal, observations indicate that the risk of complications in HIV-infected infants may be increased, the incidence appears to be very low. Recommendations for vaccination programmes have been based mainly on these considerations. The WHO Special Programme on AIDS and the Expanded Programme on Immunization issued a joint statement in 1987 (3):

- for asymptomatic HIV-infected individuals where the risk of tuberculosis is high, BCG is recommended at birth or as soon as possible thereafter in accordance with standard policies for immunization of non-HIV-infected children;
- in a limited number of areas, the risk of tuberculosis is low but BCG is recommended as a routine immunization; in these areas, BCG may be withheld from individuals known or suspected to be infected with HIV;

- for symptomatic HIV-infected individuals BCG should be withheld.

A joint WHO/UNICEF statement (4) and a joint GPA/TUB statement (5) in 1989 more specifically recommended that "BCG should be administered to infants as early in life as possible, including when the mother is known to be or suspected of being HIV-infected. BCG should be withheld from individuals with symptomatic HIV infection".

Advisory bodies in the USA had less problems since BCG is not recommended for the newborn. In 1989, the Advisory Committee for the Elimination of Tuberculosis (6) stated that it "agrees with WHO that BCG should not be administered to persons with HIV infection in countries where the risk of infection is low, such as the USA."

Protective effect

So far no experimental data have become available on the effectiveness of BCG given to HIV-infected individuals, but as mentioned above the benefit for infants cannot be high. The matter is different as regards BCG vaccination given early in life to individuals at a high risk of tuberculosis infection and who contact HIV infection during adulthood. Such persons have a very high risk of developing tuberculosis. It is therefore of tremendous importance to determine whether the increase in the tuberculosis problem can be reduced by BCG (re-) vaccination (e.g. at school age). In a number of ongoing studies it is attempted to solve the question provisionally by the case-control method. Of relevance in this connection is that AIDS patients in Sweden (where BCG has been used extensively) rarely show disease caused by mycobacteria of the avium complex. In the USA (where BCG has not been used) these disorders are common. Yet, MAC infection appears to be more common in Sweden than in the USA. Thus, BCG vaccination, by protecting against MAC disease, may protect against AIDS (though this is a question of definition) and against tuberculosis (16).

Further research and monitoring

As the information is still very scarce, especially as regards the relatively rare events that may be associated with BCG vaccination, efforts are being made to collect further data from different parts of the world. WHO's Expanded Programme on Immunization is in contact with 15 studies, 10 of which in Africa, relative to vaccination of children born to HIV-infected mothers. A recently set up joint TUB/GPA (Global Programme on AIDS) research programme has initiated a monitoring programme in Uganda. All children reporting to 15 vaccination clinics will be systematically followed up.

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AIDS, IV DRUG USE AND MYCOBACTERIAL DISEASE: THE DUBLIN EXPERIENCE

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+ Fiona M. Mulcahy, MD, FRCPi
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ABSTRACT/SUMMARY

In the period 1980-1985 we treated 1641 patients for tuberculosis of whom 2 were known to be intravenous drug users and none had HIV infection. Of the next 1000 patients treated for tuberculosis (January 1986 – December 1989), 6 were HIV -ve intravenous drug users (IVDU), 18 patients were HIV +ve (12 IVDU; 6 homosexual/bisexual).

Statistical analysis (X²) showed a numerically small but statistically significant (p<0.00001, DF = 1, X² = 20.38) increase in intravenous drug users with a diagnosis of tuberculosis.

The HIV +ve patients who completed treatment responded well to antituberculous drugs.

The importance of tuberculosis in the context of HIV infection is that it is preventable, treatable and is the only bacterial infection to which HIV subjects are prone which can be readily transmitted to a non-HIV infected subject.
INTRODUCTION

Tuberculosis (TB) is well recognised as one of the most common bacterial infections in patients infected with Human Immunodeficiency Virus (HIV). While the lifetime risk of active disease following primary infection is said to be the order of 10% in an immuno-competent subject, the risk of active disease is believed to be up to 30% in a HIV +ve subject.

It is possible that tuberculosis, even if successfully treated, may accelerate the progression of HIV infection to AIDS. Tuberculosis in otherwise normal individuals has a number of immunosuppressive effects including increased production of acute phase reactants some of which may suppress certain lymphocytic functions and even induction of CD4 lymphopenia. Immunological mediators produced during infection may augment the replication of HIV virus in lymphocytes and monocytes.

A steady increase in the incidence of tuberculosis in the United States of America has been attributed to the AIDS epidemic. The question is whether tuberculosis among HIV +ve subjects is due to recent infection and early progression of disease or due to reactivation of previous latent infection. In their study in New York, Selwyn et al suggested that in HIV infected persons tuberculosis most often resulted from reactivation of latent disease. It is possible however, that in HIV +ve subjects, because of declining immunocompetence, that tuberculosis may become rapidly progressive to active disease following recent infection.
We have previously noted the occurrence of tuberculosis in patients infected with HIV in the Republic of Ireland. We have also reported the incidence of disease due to mycobacteria other than tuberculosis (MOTT) as 8 per 1000 positive mycobacterial cultures. In a retrospective study covering the period January 1980 to December 1985, only 2 out of 1641 patients treated for tuberculosis were known intravenous drug users (IVDU). Their HIV status is unknown.

Tuberculosis in HIV+ve subjects may be difficult to diagnose as the typical radiological appearances may not occur. Indeed many of the features are more consistent with primary infection. The tuberculosis is not confined to the apices, cavitation may be absent, there may be widespread pulmonary involvement and frequently there is hilar or mediastinal gland involvement. There is also frequently extrapulmonary disease.

We treat all patients with tuberculosis, including patients who are HIV+ve with standard anti-tuberculous regimens.
AIMS

The aims of the study were to determine the number of cases of mycobacterial disease, both TB and MOTT, in HIV +ve patients and in intravenous drug users (IVDU) treated in the period January 1986 to December 1989 inclusive in the Department of Genito-Urinary Medicine, St. James' Hospital and Peamount Chest Hospital, Dublin. We considered the organisms involved, clinical presentation, radiological extent of disease, response to therapy and relapse rate.

METHODS

We made a record of the chest X-ray appearances, bacteriological status, tuberculin status and response to treatment of all patients with mycobacterial disease known to be HIV +ve and also patients who were known to be IVDU. Tuberculin skin hypersensitivity is routinely tested using PPD-RT23 (Staten Serum Institute, Copenhagen) and the Mantoux technique.

All chest X-rays are read and classified in accordance with the recommendations of the National Tuberculous Association of the USA.
RESULTS

On the 1st January 1990 there were 10 known cases of HIV infection in the Republic of Ireland. One hundred and twenty-four cases of AIDS had been diagnosed of whom 58 had died.

In the study period we treated 1000 cases of tuberculosis and 11 cases of MOTT. Eighteen patients were HIV +ve. We are aware of 2 further HIV +ve patients (both haemophiliacs) who were diagnosed as having TB but who were not admitted under our care and are not included in this study.

Of the 18 patients (15 male, 3 female) who were HIV +ve; 12 were IVDUs of whom 1 was also a prostitute and 1 a bisexual; 6 HIV +ve patients were homosexual/bisexual. Six patients with TB (3 male, 3 female) were known IVDUs and HIV -ve.

Six of the HIV +ve patients had other features of CDC stage IV disease at the time tuberculosis was diagnosed - PCP pneumonia and oral candidiasis (1); PCP pneumonia (1); oropharyngeal candidiasis (3); recurrent bacterial pneumonia and anaemia (1). Three patients were receiving Zidovudine (AZT) at the time mycobacterial disease was diagnosed.

Seven HIV +ve patients and 3 HIV -ve patients were known to have received previous BCG vaccination. The chest X-ray appearances, tuberculin skin test results and organisms isolated are shown in Table 1. All strains of Mycobacterium tuberculosis isolated were fully

Patients with TB were treated with standard therapy unless contraindicated by associated hepatic disease or drug intolerance. The patients with MOTT were treated with other drug combinations (Cycloserine 500mg bd, Clofazamine 100mg tds, Rifabutin 300mg-600mg daily, Clarithromycin 500mg bd).

Seven patients, (6 HIV +ve and 1 HIV -ve IVDU) were lost to follow-up before completion of treatment. Four of these patients were positive on direct staining and culture for tuberculosis at the time they were lost to follow-up. Three HIV +ve patients died before completing treatment (1 Mycobacterium Kansasi, 2 non mycobacterial causes). Two HIV patients, both with MOTT have had no response to treatment. The remaining 12 patients (7 HIV +ve, 5 HIV -ve) have responded to treatment and completed their anti-tuberculous drug regimen.

Table 2 shows the time for patients to become consistently direct smear (S) and culture (C) negative for all patients. This is not significantly different from the conversion rates we have seen in trial protocols with standard anti-tuberculous treatment. The 6 patients who were smear negative were unproductive of sputum. Three of these patients were positive on culture of broncho-alveolar lavage; 1 was positive on urine culture; 1 had a strongly positive 1TU Mantoux with chest X-ray.
appearances consistent with tuberculosis and 1 had therapy initiated in the U.K. where he had been positive on culture of pleural fluid for fully sensitive M.TB. This last patient relapsed with fully sensitive Mycobacterium tuberculosis three months after completion of chemotherapy. He admitted ongoing drug abuse and poor compliance after 10-12 weeks of therapy. He has since become consistently negative on direct staining and on culture with supervised chemotherapy.

Statistical analysis using the X technique comparing our experience between 1980 and 1985 with 1986 to 1990 showed that there were statistically significantly more IVDUs treated for tuberculosis in the latter period ($p < 0.00001; DF 1, X = 20.38$). Analysis of patients admitted to Peamount in the latter period showed no significant geographical shift in referral pattern and we continued to treat 28-32% of all reported cases of tuberculosis in the Republic of Ireland. Consultation with the drug addiction treatment centres in Dublin have shown that all known IVDUs with TB attending the centres were treated by us.

DISCUSSION

Twelve of the 24 patients described in this study were intravenous drug abusers. This shows a statistically highly significant increase in tuberculosis in IVDUs in Dublin since our previous study. Six of these patients were HIV +ve and these results suggest that the AIDS epidemic is contributing to an increased incidence of TB in the IVDU population in Dublin.
The numbers remain small but form a significant percentage of the total patients with AIDS and a significant workload because of the difficulty of managing patients, particularly those with manifestations of AIDS. Tuberculosis is also important in that it was the first indicator of Stage IV disease in 11 of 18 patients who were HIV +ve.

While advice with respect to safe sex and needle exchange programmes may help reduce the transmission of HIV, it will have no effect on the transmission of tuberculosis. One feature of the problem is that 4 patients (all IVDU) were lost to follow-up at a time when they were still positive on direct staining and culture. The organism will remain pathogenic and because compliance in these patients is likely to be poor, they must be regarded as a serious ongoing source of transmission of tuberculosis.

While it has been suggested that patients with tuberculosis should perhaps be considered for HIV screening, experience in the Republic of Ireland to date suggests that this would not be appropriate or necessary at this time. It has been suggested that patients who are infected with HIV and have a positive skin test should be offered chemoprophylaxis or definitive treatment for tuberculosis to prevent them developing active disease. This may also help prevent the associated immunosuppression seen with tuberculosis and perhaps prevent acceleration of progression to AIDS.

A difficulty in interpreting tuberculin skin test status in the Republic of Ireland is that the majority of young adults will have had BCG
vaccination either as infants or at 12-14 years of age. In their study 6 Selwyn et al could regard the Mantoux test as indicative of previous infection as routine BCG vaccination is not the practice in the United States. A further difficulty is deciding on the significance of skin anergy (negative 10 TU Mantoux) in patients infected with HIV as the negative test could indicate deteriorating T cell function and progression towards AIDS. HIV+ve patients with chest symptoms or pyrexia of unknown origin and positive tuberculin skin tests must be assessed for active tuberculosis.

The duration of chemotherapy for patients with HIV/AIDS for tuberculosis is not clear. These patients seem to respond equally well to therapy but there are problems with IVDUs particularly with compliance and other disease processes particularly hepatitis B. We have had a policy of isoniazid prophylaxis indefinitely following completion of therapy because of possible reactivation and/or reinfection. Special procedures to ensure compliance with chemotherapy by IVDUs who have active tuberculosis are necessary and ideally they should receive fully supervised therapy.

Our study does not suggest that BCG gave useful protection against tuberculosis in these HIV+ve subjects but it was not designed to detect protection against tuberculosis from BCG. We have previously reported the protective effects of BCG on younger subjects in the Republic of Ireland but there is no reason to believe that this finding may be extrapolated to HIV+ve individuals.
TABLE 1: RADIOLOGICAL APPEARANCES, EXTENT OF DISEASE, MANTOUX STATUS AND MYCOBACTERIA ISOLATED IN ALL PATIENTS

<table>
<thead>
<tr>
<th>CHEST X-RAY</th>
<th>HIV +ve</th>
<th>HIV -ve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Miliary</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Pleural Effusion</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Minimal</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Moderate</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Advanced</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Not Available</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Extrapulmonary TR</td>
<td>10</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MANTOUX RESULT</th>
<th>HIV +ve</th>
<th>HIV -ve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive 1TU</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Positive 10TU</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Positive 100TU</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Negative 100TU</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Incomplete</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mycobacterium tuberculosis</th>
<th>HIV +ve</th>
<th>HIV -ve</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>M.O.T.T.</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>No mycobacteria cultured</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>
TABLE 2: TIME FOR SPUTUM TO BECOME BACTERIOLOGICALLY NEGATIVE FOR M. TUBERCULOSIS

<table>
<thead>
<tr>
<th>DURATION OF TREATMENT (WEEKS)</th>
<th>HIV +ve</th>
<th>HIV -ve/IVDU</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 12</td>
<td>6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>S-</th>
<th>C-</th>
<th>S-</th>
<th>C-</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>8</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
<td>8</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>12</td>
<td>7</td>
<td>8</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>26</td>
<td></td>
<td></td>
<td>9</td>
<td>9</td>
</tr>
</tbody>
</table>

4 patients (3 of whom were HIV positive) were positive on direct staining and culture at the time they were lost to follow up.

S- = Direct Smear Negative  C- = Culture negative
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GLOBAL PROGRAMME ON AIDS AND TUBERCULOSIS PROGRAMME

STATEMENT ON AIDS AND TUBERCULOSIS

GENEVA
MARCH 1989

WORLD HEALTH ORGANIZATION
IN COLLABORATION WITH
INTERNATIONAL UNION AGAINST TUBERCULOSIS AND LUNG DISEASES
Statement on AIDS and tuberculosis*

Tuberculosis (TB) has already been recognized as one of the most frequent opportunistic infections in persons with HIV infection in developing countries. In some HIV affected developing and industrialized countries, the number of reported cases of TB is increasing. In addition to an increasing number of new cases of TB in some areas, health programmes face new problems related to unusual clinical presentations of TB and proper management of *M. tuberculosis* and HIV-infected persons.

This statement is based upon collaboration* between the World Health Organization's Global Programme on AIDS (GPA) and the Tuberculosis Unit (TUB) of the Division of Communicable Diseases and the International Union against Tuberculosis and Lung Diseases (IUATLD).

This joint statement is addressed to all health care personnel engaged in TB and AIDS control activities worldwide for the purpose of providing technical direction and guidance to national and local efforts for AIDS/TB control and research.

**Summary**

In a number of developing countries, particularly in Sub-Saharan Africa, infection with both *M. tuberculosis* and human immunodeficiency virus (HIV) is highly prevalent. HIV infection results in an impairment of the immune system and entails a substantial risk of TB in those individuals who are or become infected with the tubercle bacillus. Because persons with both infections have an increased risk of developing clinical TB and further transmitting *M. tuberculosis* infection, some of these countries are facing, or will have to face, a rapid upsurge of the TB problem.

The interaction between HIV and *M. tuberculosis* infection poses a serious health problem which will result in a major increase in disease, death and health care service needs in many countries. Immediate action at the global, national and local levels is needed to address this problem. In their national plans of action, national AIDS and TB control programmes should include coordinated activities to reduce the impact of the problem and international organizations and donor countries should be encouraged to support them technically and financially.

Control of this TB epidemic linked with HIV infection will depend largely on the availability of prompt diagnosis and adequate treatment for TB, and possibly of effective chemoprophylaxis, not just for HIV-infected persons but for other groups as well. To deal with this problem, a number of issues need to be studied urgently. In addition, a number of immediate steps can be taken by control programmes.

**Background**

**The AIDS pandemic**

WHO estimates that at least five million persons in the world are already infected with HIV-1. As of 1 February 1989, approximately 140 000 cases of AIDS had been reported to WHO by 144 countries. Owing to underdiagnoses, underreporting, and delays in notification, this represents only part of the global cumulative total which is estimated at about 400 000 cases.

* Joint WHO/IUATLD working group on HIV infection and tuberculosis, Geneva, 18-19 January 1988;
WHO technical advisory meeting on research on AIDS and tuberculosis, Geneva, 2-4 August 1988.
Statement on AIDS and tuberculosis

The pandemic started in the 1970's with a period of unrecognized spread of the virus. The first cases of AIDS were recognized in 1981. During the following years the virus was identified, the modes of spread defined and laboratory methods to detect HIV antibodies developed. The infection is transmitted by sexual intercourse, by blood (transfusions, needles, organ transplants) or from mother to infant before, during or shortly after birth. The risk of transmission varies with the mode of transmission. Transfusions of infected blood have a probability of transmission of over 90%, perinatal transmission from an infected mother of 25-50%; and each needle puncture from an infected source of less than 1%. A single episode of penile-vaginal sexual intercourse with an HIV-infected individual carries an estimated transmission risk of from 1/100 to 1/1000 but this risk may be increased by the presence of genital ulcerative disease. The HIV-infected individual becomes a potential source of infection for life even in the absence of symptoms. Clinical AIDS may not appear for many years, but nearly half of infected individuals appear to develop AIDS within 10 years. Death almost invariably occurs within two years of the diagnosis of AIDS.

HIV infection is not evenly distributed around the world. In general, urban areas are more affected than rural areas. Three patterns of HIV/AIDS can be recognized depending on when HIV began to spread extensively in the population and the socio/sexual risk factors/behaviours in the community.

In pattern I areas, most cases occur in homosexual men and there are relatively few HIV-infected women and children. Transmission through blood has been virtually eliminated since HIV-antibody testing began in 1985. Transmission through needles is frequent among intravenous drug users. This pattern is seen in North America, Western Europe, Oceania and parts of Latin America and the Caribbean.

In pattern II areas transmission is mainly heterosexual, with almost equal numbers of male and female cases. Transmission via blood transfusions is not controlled or is only partially controlled; the use of unsterilized syringes and needles and other skin piercing instruments outside health services represents a potential risk and perinatal transmission is relatively common. In some countries the prevalence of infection in the sexually active population in the cities reaches 10-25% and in certain high risk groups over 50%. This pattern is seen in Sub-Saharan Africa and increasingly in parts of Latin America and especially in the Caribbean.

In pattern III areas the infection has been introduced more recently (1980s) and most of the initial cases have been infected through exposure in other countries or by international travellers. In most countries in these areas, there has not yet been sufficient indigenous spread to determine what will be the predominant forms of transmission. This pattern is presently seen in Eastern Europe, Asia, the Middle East and the Pacific.

These patterns can be seen simultaneously in a single country or areas of the same country, and there is a general trend towards pattern II (heterosexual transmission) in some pattern I areas.

No vaccine or cure is yet available for HIV infection; it is not expected that a vaccine will be available in the near future (5-10 years). The main strategies for prevention and control of HIV infection are therefore information and education to reduce the risk of sexual transmission through behavioural changes - reduction and selection of sexual partners, use of condoms; control of blood and blood products (including reduction of unnecessary transfusions); information and training to reduce the risk of transmission by syringes and other skin piercing instruments; and information and counselling to reduce the social, familial and individual impact of infection and disease. Even if these strategies are effective, they will not alter the number of AIDS cases anticipated in the next several years, because most of these will arise from existing infections.
Statement on AIDS and tuberculosis

The tuberculosis pandemic

It is estimated that 30-60% of adults in developing countries are infected with *M. tuberculosis*. Approximately 8-10 million individuals develop clinical TB and 3 million die of TB each year.

Infection with *M. tuberculosis* is transmitted through droplet nuclei suspended in the air as a result of the cough of persons with pulmonary TB. About half of the close contacts of an infectious patient will become infected. Patients are infectious only after developing pulmonary disease and in proportion to the number of bacilli expectorated. An untreated smear-positive case may infect on average 10-20 individuals in two years.

The risk of acquiring infection depends on the prevalence of infective sources - smear-positive cases - in the community. Males are more commonly infected than females. Household contacts of an infectious patient are at especially high risk of infection. Infection with *M. tuberculosis* may last for life and disease may appear soon after infection or after a long time. The risk of disease among infected persons is highest in the first few years following infection. The average lifetime risk of progression to active disease is about 10%, and varies with age and immunological status. Half the cases develop infectious pulmonary disease; children usually develop non-infectious types of tuberculosis. Case fatality in the absence of treatment is over 60% in five years. With prompt diagnosis and adequate chemotherapy it may be reduced to 3% or less.

Disease control methods include case finding and chemotherapy of patients, Bacille Calmette-Guerin (BCG) vaccination for those not yet infected and preventive therapy for infected individuals at a high risk of progression of clinical TB.

The most common strategy used in developing countries is case detection through direct sputum smear examination of persons with symptoms suggestive of TB and ambulatory chemotherapy.

At present there is a reduction of the risk of infection of over 10% per year in industrialized countries, a reduction of 5% to 10% in some developing countries with good control programmes and general health service structures, and a reduction of 0-4% in other developing countries. Due to the fact that the last group comprises most of the world population and has the highest prevalence of TB as well as a population growth of 2-3% per year, the general reduction of the global TB problem in absolute numbers of cases is very small.

Overall, the world TB situation is thought to be improving very little despite the existence of effective therapy and a partially effective vaccine. This may be due in part to the need for more effective application of existing strategies as well as the need for improved technology.

Association of HIV and tuberculosis

Individuals infected with *M. tuberculosis* have a high risk of progression to TB if they are also infected with HIV. Therefore, the proportion of AIDS patients with TB will be high where *M. tuberculosis* infection is highly prevalent. In many instances these patients may present to the health service as TB patients so that the proportion of HIV seropositive cases among TB patients is also increased. Overall, the number of TB patients will also be increased where *M. tuberculosis* and HIV infection are highly prevalent.

It is possible that TB may also accelerate the evolution from HIV infection to overt disease (AIDS) in dually infected individuals.

The possibility also exists for transmission of HIV among TB patients through the use of inadequately sterilized syringes used in the treatment of TB (eg., for streptomycin injections).
Statement on AIDS and tuberculosis

Interactions of mycobacteria and HIV infections include interactions with non-tuberculosis mycobacteria. This was first observed in North America where a high incidence of disease with Mycobacterium avium-intracellulare (MAI) complex was noted in AIDS patients who commonly had several other opportunistic infections. However, it was soon discovered that in populations with a high prevalence of M. tuberculosis infection, TB is the predominant mycobacterial infection in HIV-infected persons. Tuberculosis, in contrast to MAI-related disease, generally occurs as an early, and often the first, clinical manifestation of AIDS.

In Florida (USA) the prevalence of TB among AIDS patients was about 10% among non-Haitians, and over 60% among Haitians. These percentages are very similar to the estimated prevalence of M. tuberculosis infection in these populations. This suggests that persons infected with both M. tuberculosis and HIV have a very high risk of developing TB.

Several studies in Sub-Saharan Africa, the Caribbean and in some urban areas of the United States (USA) have shown from 20-60% of TB patients to be HIV seropositive. The most likely explanation for this finding is an accelerated progression to TB among persons who harbour infection with M. tuberculosis and are also infected with HIV. This interaction of HIV and M. tuberculosis infections poses serious problems for TB control programmes in these countries. An upsurge of the TB problem must be expected if measures are not immediately taken to reduce transmission of M. tuberculosis, perhaps including steps to reduce progression to TB among dually infected persons.

Increases in the incidence of TB that are thought to be caused at least in part by the effects of the HIV/AIDS epidemic have been noted in several countries, including the USA, Tanzania, Burundi, Uganda, and Zaire.

TB programmes face other new problems in addition to an increase in the number of patients. TB patients usually present with symptoms characteristic for pulmonary disease, such as chronic cough, and can be readily diagnosed by direct sputum smear-microscopy. In HIV-infected patients, however, the clinical picture is often different from that usually seen in adult-type tuberculosis, and includes unusual extra-pulmonary manifestations, from widespread lymphatic involvement to intracranial tuberculomas. In addition, low or midzone pulmonary infiltrates are more common and sputum smears are less likely to be positive. Case-finding and diagnosis by health workers at all levels is therefore more difficult.

When the diagnosis of TB is established at an early stage of HIV infection the response to intensive treatment with rifampicin containing regimens is usually fairly good. In most developing countries, the more effective regimens that include rifampicin and pyrazinamide have not yet been introduced generally because of their high cost. However the optimal duration and adverse reaction rate of such treatment in HIV-infected TB patients is still unknown. In addition, at the more advanced stages of HIV infection adverse drug reactions may be a problem, in particular with thiacetazone.

M. tuberculosis is more infectious than other opportunistic infections associated with AIDS, and is therefore of additional concern to the general population. It is transmitted by air and therefore untreated cases of pulmonary TB pose a potential risk to health personnel caring for patients with AIDS, as well as to family contacts. As TB is curable and treatment renders infectious cases non-infectious, prompt detection and treatment are important to prevent transmission in the community.

All of these factors emphasize the need both to strengthen the TB control capacity at national and local levels, and to take immediate action as regards a number of epidemiological, clinical and preventive research questions and issues.
Statement on AIDS and tuberculosis

Recommendations for control programmes

Although research is needed to answer many questions regarding the interaction of TB and HIV, TB and AIDS control programmes can take immediate steps to better control the TB problem. These recommendations will need periodic revision as new information becomes available.

At the national level, programmes for control of AIDS and TB should be coordinated to provide consistent high-quality care to patients with both diseases and to advise infected individuals regarding the risk of disease and methods to prevent transmission to others. To facilitate this coordination, the inclusion of an expert on TB control in the national committee on AIDS is strongly encouraged.

The experience of TB experts and staff in integration of their activities within health services, in programme organization and management, and in the training and motivation of health personnel may all be extremely useful to AIDS-pro grammes. Several special aspects of disease control are common to both programmes, such as the need to ensure confidentiality, case notification and reporting, patient and family counselling, and in some programmes strategies for evaluation of household contacts (for TB) or sexual and needle sharing partners for HIV i.e., partner notification.

Hospitals and clinics that are treating AIDS patients need to be vigilant regarding possible concurrent TB to ensure accurate diagnosis and prompt therapy to prevent further spread of M. tuberculosis to contacts. As M. tuberculosis can also be spread in hospitals, it is important for health workers to be prompt to begin anti-TB therapy.

TB in HIV-infected individuals or AIDS patients should be treated according to national policy, preferably with short course regimens. Since the optimal duration of treatment in such cases is not known, patients should be followed up bacteriologically whenever possible. Treatment should be continued for six months after sputum conversion. Drug intake should be fully supervised, at least in the initial phase with intensive daily therapy.

The indications for hospitalizing patients for TB are the same whether they are infected with HIV or not. As it is expected that cases with simultaneous AIDS and TB will increase, and that they may pose special clinical problems, hospitals treating TB cases must be prepared to provide adequate care. This includes training health personnel in the management of cases of AIDS and providing diagnosis and treatment for the most common opportunistic infections associated with HIV infection and AIDS. Training is also needed in the diagnosis and treatment of extrapulmonary TB in HIV-infected persons.

Prevention of HIV transmission is based mainly on information and health education, which should be provided systematically to all TB patients. Access to voluntary serological tests for detection of HIV infection including pre- and post-test counselling should be offered wherever HIV infection is known to occur. As HIV is transmitted through sexual contact and through blood and, as appropriate chemotherapy rapidly renders persons with TB non-infectious, there is no reason to isolate HIV-infected persons or AIDS patients (with or without TB). Discrimination in dealing with HIV-infected patients, as with TB, should be absolutely avoided.

Adequate safety procedures involving injections, blood, blood products or other body fluids when caring for TB patients should be enforced regardless of a patient's HIV status (Guidelines for nursing management of people infected with human immunodeficiency virus [HIV]). The Guidelines on sterilization and high-level disinfection methods effective against human immunodeficiency virus (HIV) should be promoted and followed. Where sterility of needles and syringes cannot be ensured, an entirely oral medication regimen should be used.

Prevention strategies for TB control include immunization with BCG and chemoprophylaxis. BCG should be administered to infants as early in life as possible, including when the mother is known to be or suspected of being HIV-infected (Joint WHO/UNICEF statement on early immunization for HIV-infected children). Evidence remains inconclusive regarding the rate of adverse reactions after BCG immunization among asymptomatic HIV-infected individuals. BCG should be withheld from individuals with symptomatic HIV-infection.

Individuals infected with *M. tuberculosis* and HIV have a high risk of developing TB. In countries where the national TB programme strategies include chemoprophylaxis, dual infection with HIV and *M. tuberculosis* should be considered as an indication for chemoprophylaxis.

**Recommendations for research**

The long term objective of the proposed research activities is to curb the anticipated increase in TB in developing countries where both *M. tuberculosis* and HIV infection are highly prevalent. The immediate objectives are to obtain information on the magnitude of the problem and its trend, to develop appropriate diagnostic techniques, and to identify effective treatment and preventive regimens and strategies. Explicit recommendations for both epidemiological and clinical research can be found in the Report of the WHO Technical Advisory Group on research in AIDS and TB, Geneva, 2-4 August 1988 (WHO/GPA/BVIR/S9.3).

Epidemiological studies should be undertaken by the national TB and AIDS programmes of countries that have a high prevalence of *M. tuberculosis* and HIV infection, especially African countries south of the Sahara and countries in the Caribbean. They should first determine the prevalence of HIV infection in a sample of newly detected TB patients. (For more precision the prevalence of HIV infection could also be determined in matched controls or by comparison with serologic information from sentinel surveillance groups in the same district. A sentinel surveillance system should then be set up to monitor trends in HIV prevalence among new TB patients by periodic sampling.)

An immediate research priority is the determination of the risk of TB among dually infected persons in order to determine if the risk is sufficiently high to immediately begin intervention (chemoprophylaxis) trials. This requires further studies in developing countries.

Further epidemiological studies should determine trends in the incidence of TB and of the risk of *M. tuberculosis* infection in the general population according to the level of HIV infection, the infectiousness of *M. tuberculosis* in HIV-infected TB patients, and the effectiveness and safety of BCG vaccination in HIV-infected persons.

1. Published by World Health Organization in collaboration with the International Council of Nurses (ICN), Geneva, 1988 (WHO AIDS Series No. 3).
Clinical studies should focus on the symptoms and signs of TB in HIV-infected persons, on the effectiveness of the routinely used tests (smear examination, culture, tuberculin tests, chest X-ray, CSF examination) and on the value of new, especially serological, tests for screening and diagnosis of TB. Alternative treatment regimens should be compared in terms of effectiveness and toxicity in HIV-infected and non-HIV infected TB patients, as regards both pulmonary and extra-pulmonary disease. Whereas it will not be necessary to carry out the proposed clinical studies in all countries concerned, it will be necessary to include different settings (e.g., including HIV-2 affected areas).

Short-course chemoprophylactic regimens should be evaluated in persons found to have both HIV and M. tuberculosis infection.

For some studies, detailed protocols will be best prepared jointly by GPA and TUB in cooperation with the national programmes and technical consultants. General guidance will be obtained from experts selected by WHO, IUATLD and national TB and AIDS programmes.

Strengthening of national TB programmes in the countries concerned will require consultant services as well as equipment and supplies (notably for drugs, including short-course chemotherapy). In some countries surveillance and research activities will be undertaken in conjunction with the Mutual Assistance Programme already in operation under guidance of the IUATLD. In some countries the national TB programmes will require considerable support, both managerial and technical, to strengthen case-finding and treatment and to undertake or strengthen epidemiological surveillance and research.
A REVIEW

Tuberculosis and the acquired immune deficiency syndrome

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1. INTRODUCTION: HISTORICAL ASPECTS

A review of tuberculosis and the acquired immune deficiency syndrome (AIDS) would be incomplete without reference to the history of both conditions. Tuberculosis was known in antiquity; characteristic lesions of spinal tuberculosis have been described in the skeleton of a neolithic man and acid-fast bacilli have been seen in pre-Columbian Peruvian mummies with lesions compatible with tuberculosis (Clark et al. 1987). The aetiological agent, however, remained in doubt until the early 19th century when Villemin's earlier work supporting the theory of infection was confirmed by Koch's discovery of the tubercle bacillus in 1882. This gave impetus to the search for an effective remedy for the disease as, for centuries, treatment had been merely palliative (Keers 1978). Hippocrates (460-355 BC) had advocated rest, baths, attention to the bowels and a liquid diet in the acute phase, and mild exercise, a diet of rich, easily digested food with milk taken liberally, for the chronic case. Drugs, which were mainly purgatives and expectorants, were used sparingly. Galen's (131 AD) treatment consisted of rest, restraint of cough and a ban on visitors to eliminate the strain of conversation. Good food was considered important and fresh milk was a specific in pulmonary ulceration. Patients suffering from scrofula, a term applied to tuberculosis of the neck glands, could, from the time of Clovis the Frank (496 AD), attend the ceremony of touching for 'The King's Evil' which was based on the belief in the royal power to heal (Crawford 1911). In England the practice began with Edward the Confessor and continued with interruptions to the reign of Queen Anne who was encouraged to practise the art to demonstrate the divine right of the Stuarts. The ceremony was conducted for the last time in England on 27 April 1714, three months before her death.

By the time of Koch's discovery, the sanatorium regimen had already been conceived, but greater energy was directed both to general measures, with emphasis on fresh air, good food, rest for the body and mind and, specifically, to rest for the diseased lung in the form of collapse therapy. This had first been introduced by the physician John Carson who, in 1881, presented a paper on 'Lesions of the Lung' in which he described his experimental work on induced artificial pneumothorax in rabbits which had subsequently recovered. The work had been based on his belief that the elasticity of the lung, which kept it permanently stretched, was the cause of the difficulty observed in the healing of parenchymal lesions. The difficulty could be overcome by reducing the lung to a state of collapse. For those patients in whom pneumothorax was indicated but technically impossible owing to adhesions, the problem was solved by the introduction of adhesion section thoracoscopy and cautery, a technique devised in 1913 by Hans Christian Jacobaeus of Stockholm who had invented the thoracoscope. Other techniques of collapse therapy followed over the succeeding years including pneumoperitoneum, phrenic paralysis and thoracoplasty, leading up to the 1940s when lung resection was introduced. Initially, morbidity and mortality was high but after the introduction of effective anti-tuberculosis drugs, the operative risks were reduced considerably. By 1955 collapse therapy, including the multiple-staged, deforming thoracoplasties, had been...
largely replaced by resection surgery. By the end of the 1950s, surgery in its turn had, for the most part, been replaced by long-term chemotherapy. The drug era had been heralded by Waksman's discovery of streptomycin in 1943 followed by PAS in 1947 and isonicotinic acid hydrazide (isoniazid, INAH) in 1950. All three drugs were used as a standard regimen to prevent the emergence of resistant strains of mycobacteria but streptomycin was usually stopped after the first two months of treatment and PAS and INAH, in a combined form as PAS/INAH, were continued for a total of 18–24 months. In 1962 PAS was replaced by ethambutol. In the same decade the routine use of streptomycin was phased out after rifampicin was introduced in 1969 and found to be a potent bactericidal and sterilizing drug which produced rapid sputum conversion. Pyrazinamide, formerly a reserve drug which tended to cause liver damage in the dosage prescribed at the time, was subsequently noted to have excellent sterilizing qualities even on a lower and more easily tolerated dose. With pyrazinamide taken in combination with rifampicin, INAH and ethambutol it has been possible to shorten the duration of treatment from 18 months to six months with little danger of relapse. It is possible to eliminate ethambutol from the regimen and in some centres the current practice is to give pyrazinamide, rifampicin and INAH for two months and then to continue on the latter two for a total of six months.

The UK was slow to respond to Koch's discovery of the tubercle bacillus and it was not until 1887 that practical preventive measures against tuberculosis were attempted. It was then that the Edinburgh physician Robert (later Sir Robert) Philip succeeded with the help of friends in establishing the Victoria Dispensary for Consumption in Edinburgh (Smith 1888). This became a centre for the reception, examination and selection of patients for domiciliary or hospital treatment, depending on the severity of their condition. Systematic examination of close contacts, family friends and workmates was arranged in the course of domiciliary visits by dispensary nurses or 'volunteer' health visitors whose duties also included instruction of the patient and his family in basic hygiene. The dispensary also helped towards the relief of the financial distress which commonly accompanied the disease by putting the family in touch with a charitable or public fund. Philip's scheme ultimately served as a model for a national scheme of tuberculosis dispensaries on the recommendation, in 1913, of the Astor Departmental Committee on Tuberculosis. During the same period, 15 years after the concept of notification was first proposed, notification of all forms of tuberculosis was made compulsory by the Public Health (Tuberculosis) Regulations 1912–1913.

A link between diseased cows and abdominal tuberculosis and other forms of tuberculous disease in children had been established by German scientists during the late 1870s when it was suspected that the 'virus' was contained in the tuberculous matter in abscesses on the udder which fell into the pail during milking or was coughed up by the cow into the atmosphere and thence into the milk. The bovine bacillus was later isolated and studied by Theobald Smith (1898) who, at the Harvard Medical School, clearly differentiated the organism from the human variety. Preventive measures were later directed to tuberculin testing of cattle, the slaughtering of infected animals and to the pasteurisation of milk. The elimination of bovine tuberculosis since the end of the Second World War by means of the area eradication scheme achieved considerable success. Finally, the introduction of BCG vaccination of secondary school children in the 1950s has since contributed greatly to the control of tuberculosis in the UK.

In contrast to tuberculosis, the first cases of AIDS were not reported until 1981; the pandemic, however, started in the 1970s with a period of unrecognized spread of the primary cause, the human immunodeficiency virus (HIV) which was discovered in May 1983 by Professor Luc Montagnier of the Pasteur Institute in Paris (Barre-Sinoussi et al. 1983). The infection is transmitted by anal and vaginal sexual intercourse, by contaminated blood and blood products, organ transplants, needles, and from mother to infant before, during or shortly after birth.

Infection with Mycobacterium tuberculosis and HIV have certain features in common. In both cases it is possible to be infected but clinically healthy—overt disease may not commence until many years after the initial infection. During the interval before illness commences, the only signs of infection are, respectively, a positive tuberculin test and circulating antibodies (HIV positivity). A person infected with M. tuberculosis only becomes infectious if he or she develops sputum smear-positive pulmonary tuberculosis. Although HIV-positive persons are not infectious in the normal day-to-day social and working contact they are, nevertheless, potential sources of infection for life even in the absence of symptoms, although clinical AIDS may not appear for many years (Report 1989a). Nearly half of infected individuals appear to develop AIDS within 10 years.

Unlike tuberculosis, which can be treated and cured, there is as yet no known cure for HIV infection and once AIDS is established the prognosis is poor. The burden of illness is increased by the fear or bigotry generated by ignorance and resulting in distressing social and occupational problems. Of the many AIDS-associated opportunistic diseases tuberculosis is unique as it poses a serious risk of transmission of infection to the general population. It is generally agreed that the impact of HIV infection and AIDS on the global aspects of tuberculosis is an exceedingly worrying one. Indeed, in view of this problem, Styblo
inhale. The site of implantation and multiplication of the bacilli is the lung. Resulting from the inhalation of bacilli in the cough spray of infected individuals. The inhaled bacilli multiply at the site of implantation and induce a localized inflammatory lesion termed the Ghon focus. Some bacilli pass to the lymph nodes at the root or hilum of the lung where additional foci of infection cause node enlargement. The Ghon focus and the enlarged hilar lymph nodes form the primary complex of Ranke. Some bacilli are more widely disseminated via the lymphatic or blood stream and, in a minority of individuals, these cause serious complications such as meningitis, bone and joint lesions and renal tuberculosis. In most cases, however, the rapid onset of an effective cell-mediated immune response causes the tubercle bacilli to be contained within compact aggregates of activated macrophages termed granulomas and the disease process subsides. For reasons that are still poorly understood, not all the tubercle bacilli within the granulomas are destroyed by the host immune response: some, termed persisters, remain viable for years or even decades.

About eight weeks after infection the phenomenon of tuberculin conversion occurs and the infected individual reacts with characteristic dermal induration to an intracutaneous injection of tuberculin. This reaction, also known as a Type IV, cell-mediated or delayed hypersensitivity reaction, is analogous to the necrotic Koch phenomenon elicited by injection of tuberculin into the skin of infected guinea pigs. The necrotic component of tuberculin reactivity appears to be due to vascular changes secondary to the release, by macrophages activated by gamma interferon and vitamin D₃ metabolites, of an immunological mediator termed tumour necrosis factor (TNF) (Rook et al. 1987; Beck et al. 1989). This name is derived from the ability of TNF to induce haemorrhagic necrosis of tumours but this factor has many other biological effects, some beneficial and some harmful. In acute inflammation it is a mediator of various immune responses and it induces the acute phase response and the release of cytokines. In severe infections with septicemia, bacterial endotoxins trigger the release of excessive amounts of TNF from macrophages and this is responsible for endotoxic shock and associated intravascular thrombosis. Also, TNF is the mediator responsible for the wasting, phthisis, consumption, or cachexia characteristic of advanced tuberculosis and also of other chronic infections. Thus an alternative name for TNF is cachectin. (For further details of TNF/cachectin see Beutler & Cerami 1986; Tracey & Cerami 1989.)

About 10% of newly infected persons will develop clinically apparent tuberculosis during their life time; half during the first few years after infection and the other half many years, often decades, later. In the other 90%, effective host defences are sufficient to prevent progression from infection to disease (Hopewell 1989; Murray & Mills 1990). With the depression of immunity by HIV infection, latent infection is much more likely to progress to clinically significant disease. Individuals infected with tubercle bacilli may, later in life, develop post-primary tuberculosis. This
is attributed to a re-awakening of the dormant bacilli although some cases are the result of exogenous re-infection. The occurrence of exogenous re-infection has been the subject of some controversy but the prevalence of tuberculosis reactivity among close contacts of infectious cases suggests that new infection occurs about 50% of the time (Rouillon et al. 1976). Post-primary lesions often develop in the upper parts of the lung and are characterized by extensive tissue necrosis due to the release of large amounts of TNF from activated macrophages (Rook et al. 1987). This necrotic or caseous material (so named on account of its cheese-like appearance) is softened or liquefied by protease enzymes released from activated macrophages. If, as often happens, this necrotic mass erodes into a bronchus, the liquefied caseous matter escapes and a bronchus, the liquefied caseous matter escapes and a cavity is formed. Being freely supplied with oxygen, the cavity wall becomes an ideal breeding ground for the tubercle bacillus.

4. EPIDEMIOLOGY

The connection between HIV infection and tuberculosis has been reviewed in a comprehensive leading article by Watson & Gill (1990). Tuberculosis is a well-recognized complication of immunosuppression and HIV infection with its resultant impairment of the immune system incurs a substantial risk of this disease in those individuals who have been previously infected, or become infected, with the tubercle bacillus.

According to estimates by the World Health Organisation (WHO) (Report 1989b; Kochi 1991), a third of the world’s population is, or has been, infected with M. tuberculosis; most of these infected people reside in the developing countries. Each year, around 8 million individuals develop clinical tuberculosis and 2.9 million die of this disease each year. The impact of HIV infection upon the incidence of tuberculosis world-wide has been revealed by the WHO Global Programme on AIDS in their statement on the AIDS and tuberculosis pandemics (Report 1989b). It was also estimated that at least five million individuals in the world are already infected with HIV. As of February 1989, approximately 140,000 cases of AIDS had been reported to the WHO by 144 countries. As a result of under-diagnosis, under-reporting and delay in notification, this represents only part of the cumulative total which is estimated at about 400,000 (Report 1989b). Since then, the WHO Weekly Epidemiological Record (April 1990) has published an increase of AIDS cases to 237,110 as reported by 177 countries up to 31 March 1990. The impact of HIV infection on the global epidemiology of tuberculosis has been reviewed and analysed by Styblo (1990). The increase in numbers of tuberculosis resulting from HIV infection will certainly lead to an increase in transmission of M. tuberculosis, thereby causing a further deterioration of the tuberculosis problem. This is dependent upon the following: (1) the prevalence of HIV infection and co-existing prevalence of tuberculosis, particularly in the young and middle-aged groups, i.e. 15–49 years; (2) the breakdown rate of tuberculous infection to overt disease; (3) the level of risk of tuberculous infection and its trend and (4) the detection rate of sputum smear-positive cases of tuberculosis and their cure.

In the USA there have been recent increases in the incidence of tuberculosis in areas where there were corresponding high numbers of AIDS cases. Studies in New York City showed that almost two-thirds of patients with both tuberculosis and AIDS had developed tuberculosis within six months of AIDS being diagnosed (Report 1987a; Laroche et al. 1989). Tuberculosis preceded the conditions that establish the diagnosis of AIDS by a median of two months and the findings of other studies are similar (Pitchenik et al. 1984; Report 1986; Louie et al. 1986). A follow-up study of a cohort of injecting drug-users provided evidence that patients infected with HIV develop tuberculosis from a latent tuberculous infection (Selwyn et al. 1989). The Advisory Committee for the Elimination of Tuberculosis (Report 1989a) has therefore recommended that patients in whom tuberculosis is diagnosed should be offered HIV testing and that all people reacting to tuberculin should be questioned about any risk of HIV infection.

Nationwide information on tuberculosis and AIDS in the USA is available from two surveillance methods—the matching of AIDS and tuberculosis registries in each state and reporting of AIDS cases with extrapulmonary tuberculosis to the Centers for Disease Control (Bloch & Snider 1990). Matching of tuberculosis and AIDS registries for 94% of the AIDS cases reported during 1988 indicates that 4% of the reported AIDS cases had tuberculosis. From October 1987 until September 1989, 2.6% of the AIDS cases reported during this period had extrapulmonary tuberculosis. Of these, 53% were black, 29% white, 17% Hispanic and included the following risk categories: 38% reported intravenous drug use, 36% had male homosexual/bisexual contact, and 9% were in both risk groups. It is
vital to identify HIV-positive individuals in these categories who are infected with *M. tuberculosis* and to treat them prophylactically, thereby avoiding tuberculosis morbidity and mortality. In addition, in order to prevent tuberculosis mortality and transmission of tubercle bacilli, tuberculosis must be included in the diagnostic assessment of HIV-infected persons. These two surveillance methods, although they provide useful information, do not measure the full magnitude of the HIV-related tuberculosis problem since they exclude most HIV-infected patients with associated pulmonary tuberculosis who form the majority of patients with both infections.

In his presentation of the epidemiology of tuberculosis and HIV infection in New York at the World Conference on Lung Health, Boston 1990, Stoneburner (unpublished) indicated that the 25000 AIDS cases in New York City formed 25% of the total AIDS population for the USA. Race, ethnicity and socio-economic factors contributed to this high incidence. Blacks and Hispanics ran six times the risk of developing tuberculosis and were at a higher risk of HIV infection than the indigenous Caucasian population. Many of these persons were socially and economically disadvantaged, many were drug abusers, homeless and less likely to have access to health services. The relationship between tuberculosis and socio-economic conditions is mentioned in three recent independent reviews (Pitchenik et al. 1988; Hopewell 1989; Murray & Mills 1990). Poverty, with its associated overcrowding, poor nutrition and hygiene, is an important factor in the spread of tuberculosis. The black group formed 52% of the total AIDS cases including 14% female, 61% of the total were drug abusers, and 41% were partners of HIV cases. From 1980 to 1989, in the non-white population of New York, there has been an increase in the tuberculosis rates amongst the 20-54 year age group by over 100% in the males and 70% in the females. This increase has been in line with an increase in AIDS figures. In addition, over the same period, there has been an increase in the tuberculosis rates amongst non-white children in the 0-4 year age group. Of the cases of tuberculosis without AIDS, 36% were HIV-positive and 84% were drug abusers. It was therefore suggested that pulmonary tuberculosis should be included in the AIDS definition in addition to extrapulmonary tuberculosis (Report 1987b). An abstract on the current impact of AIDS on tuberculosis in the USA (Block & Snider 1990) also drew attention to the omission of HIV-associated pulmonary tuberculosis from the AIDS case definition.

In Great Britain, the likely incidence of tuberculosis in patients with HIV infection will depend on any overlap between the population infected with HIV and the population with previous tuberculosis infection. Although tuberculosis in patients with AIDS in Britain is well recognized (Watson & Gill 1990; Helbert et al. 1990), the tuberculosis notification rates in England and Wales up to 1988 have continued to decline. In addition, no association has been observed between increases in tuberculosis notifications and cases of AIDS in London Health Districts (Watson & Gill 1988). The reason for this may be due to only a small overlap between the population infected with HIV and the population previously infected with *M. tuberculosis*. Almost two-thirds of the patients with AIDS reported by the end of September 1989 were white men aged 25-44 years, while only 9% of patients with tuberculosis in the 1983 Medical Research Council Survey were in this group (J. Darbyshire, personal communication). The highest rates of tuberculosis in England and Wales are amongst patients from the Indian sub-continent, while only 1% of AIDS cases have been reported in Asian or Oriental ethnic groups. The tuberculosis notification rates for Scotland up to 1988 have also shown no increase (J. Emslie, personal communication) although in Edinburgh, where intravenous drug abuse is a particular problem, one in 100 males in the age range 15-44 years is reported to be HIV positive (Report 1988). This is in contrast with the USA where drug abusers have been at increased risk of developing tuberculosis (Hewlet et al. 1988; Selwyn et al. 1989). In Great Britain, two other factors may affect the overlap between the two infections in the population. First, about 80% of the indigenous population in the 15-40 year age group has received BCG vaccination. Secondly, there is under-reporting both of tuberculosis and HIV/AIDS individuals.

Estimates of the prevalence of HIV infection in the UK have, until recently, shown that the majority of patients belonged to established 'risk groups', i.e. homosexual/bisexual and intravenous drug abusers. The spread of HIV infection to the heterosexual community has since been noted with some concern (Skegg 1989; Adler 1990). Pregnant women as a stable sub-group of the total homosexually active population should, if tested, mirror any trend in HIV infection of that in the heterosexual population. In March 1990 the results of anonymous testing for HIV infection among pregnant women by use of Guthrie cards from neonatal screening were published (Peckham et al. 1990). This was a pilot study to establish methods for anonymous testing of anti-HIV-1 in blood routinely collected from newborn babies and preparatory to a planned series of large multicentre surveys of unlinked anonymous testing that will include the newborn. The study covered three of the four Thames Regions in Britain over a one year period to June 1989. Approximately 113000 samples were tested. The results showed marked contrasts: in inner London 0·49 per thousand women were positive, outside London the rate was twelve times lower, at 0·04 per thousand, while in outer London intermediate rates were observed. A total of 28 positives were identified, but antibodies to HIV in the serum of the newborn infant does not
imply that the infant is infected. Such antibody is acquired transplacentally from the mother antibody and is therefore an indirect measure of maternal infection. About 1 in 4 seropositive newborn babies will, however, be infected. Thus the neonatal HIV-1 infection rate in London over the study period would be 6 per 100,000 live births.

Although the prevalence of anti-HIV-1 infection in newborn babies or pregnant women can effectively monitor the prevalence of HIV infection in the heterosexual population, it provides no information on risk factors: many sexually active women intend never to become pregnant. Termination of pregnancy will be missed and the lack of risk factor information becomes a drawback once prevalence becomes appreciable (Anon. 1990). In some areas of London it would seem appropriate to conduct named, with consent, testing in parallel with anonymous testing. The former provides risk factor information, the latter provides lack of bias. The risk of acquiring AIDS among heterosexuals who do not belong to a recognized high risk group will not be known until the completion of a few years of anonymous testing for HIV, although the number of cases of AIDS in this category has more than doubled in the UK from 8 as of 30 June 1989 to 21 by the end of June 1990 (Dela mothe 1990; Report 1990).

Increases in the incidence and prevalence of tuberculosis have been particularly evident in regions, notably sub-Saharan Africa, where there is a high prevalence of both M. tuberculosis and HIV infection (Report 1989b; Harries 1990). In October 1990, WHO estimated that 3.9% of all cases of tuberculosis worldwide are HIV-associated but that in sub-Saharan Africa the figure is 17% (Kochi 1991). Styblo (1990) reported a marked increase in notified tuberculosis cases in Tanzania from an average of 13,000 in the period 1979–1987 to 18,000 cases, including 9800 smear-positive cases, in 1988. An increase in all forms of tuberculosis associated with HIV infection was also observed in Malawi. At the 1990 World Conference on Lung Health in Boston, USA, Eriki (unpublished) showed that, in the developing countries, more than 80% of tuberculosis cases occurred in the sexually active groups. The situation was becoming worse owing to the HIV epidemic and, in some of these countries, the tuberculosis figures had doubled, and 40–60% of adults were infected with M. tuberculosis.

In Kampala, the capital city of Uganda, the tuberculosis notification rate, which had been falling, started rising in the 1980s and was associated with an annual increase in AIDS figures of 10–20%. In Uganda as a whole, by December 1 1989, 790,322 Ugandans, the majority of whom were either under the age of 5 years or in the 15–44 year age group, were reported as HIV-positive. The figures are now in excess of one million, and 50% of these also have tuberculosis.

Heterosexual transmission of HIV and perinatal infection of the newborn is most important and of greatest concern in high prevalence countries: in sub-Saharan Africa, more than half of the large numbers of people with HIV infection or AIDS are women and children (Chin 1990).

5. CLINICAL FEATURES OF HIV/AIDS-ASSOCIATED TUBERCULOSIS

Tuberculosis is the most pathogenic of the HIV-associated opportunistic infections and therefore tends to occur early on, often within the first six months, in the HIV infection. The disease usually arises as a result of reactivation of an endogenous tuberculous lesion or following recent exogenous infection. When tuberculosis occurs in the early stages of HIV infection before the patient’s immunity is compromised, the clinical features are generally characteristic and diagnosis is straightforward. Thus the patient usually reacts strongly to tuberculin and the chest radiographic appearances are typical, with parenchymal lesions, which may be cavitating, in one or both upper zones of the lung. Enlarged intrathoracic lymph nodes may also be seen on X-ray.

In the later stages of HIV infection or AIDS, the chest radiographic appearances are generally atypical: the disease is often confined to the lower zones, although more diffuse infiltration may occur, and cavities are not present. Enlarged intrathoracic lymph nodes are often seen. Extra-pulmonary lesions and unusual disseminated forms of tuberculosis are also common. The patients do not react to tuberculin and microscopic examination of sputum for acid-fast bacilli is often negative although respiratory tuberculosis in an HIV-infected individual may be as infectious as in a non-HIV-infected person and therefore of equally important public health concern.

Generalized symptoms of tuberculosis such as malaise, anorexia, weight loss, fever and night sweats may also be caused by other conditions associated with AIDS and cough, productive or non-productive with or without haemoptysis, may also occur in other common chest conditions. These symptoms therefore pose serious diagnostic problems and the physician should accordingly maintain a high index of suspicion for tuberculosis and bronchoscopy is advised. Conversely, in patients with proven tuberculosis, the physician should have a high index of suspicion for associated HIV infection if the patient belongs to a high risk group, has an unusual presentation of tuberculosis or has symptoms or signs commonly associated with HIV infection or AIDS, e.g. unexplained persistent diarrhoea, thrush, hairy leukoplakia of the tongue and/or generalized enlargement of the lymph nodes.

Tuberculosis tends to occur earlier in the course of HIV infection than disease due to other opportunistic mycobacteria such as M. avium-intracellularare (MAI) and, as outlined
in Section 8, may accelerate the evolution from HIV infection to overt AIDS. (For details of MAI infection in AIDS patients see Grange et al. 1990.)

6. CONTROL, NOTIFICATION AND CONTACT TRACING

Owing to the association between HIV infection and tuberculosis, it necessarily follows that a programme of tuberculosis control, if not of eradication, must include identification of the HIV-infected individual, ideally at an early stage of infection when evidence of associated infection with *M. tuberculosis* may still be obtained by tuberculin testing before the development of anergy. If the tuberculin test is found to be positive, chemoprophylaxis with isoniazid is recommended to prevent progression from tuberculous infection to clinical disease (see Section 4). Early identification of HIV infection also provides an opportunity to offer the patient chemoprophylaxis with zidovudine (AZT) which could possibly delay progression to AIDS, thereby prolonging survival (Fischl et al. 1987; Weller 1988; Anon. 1989). It would therefore appear greatly to the patient’s advantage to be tested for HIV, particularly if a diagnosis of tuberculosis is already suspected. Testing for HIV in the UK, however, requires the patient’s express consent and must be accompanied by pre-test counselling (d’Eca 1989). As a positive HIV test has serious implications, further counselling must be offered if the test proves positive. The British Medical Association gave guidance that doctors are expected to obtain the patient’s consent to investigative procedures or invasive techniques (Dyer 1983). This is especially important in the case of testing for HIV infection. Only in the most exceptional circumstances when a test is imperative to secure the safety of persons other than the patient, can testing without explicit consent be justified. In the case of a child whose parent may have been the source of infection and who is not old enough to give consent, and it is in the best interest of the child, it is considered proper to test without parental consent.

The following resolution was adopted by the British Medical Association at its 1988 conference (see d’Eca 1989).

‘HIV testing should be performed only on clinical grounds and with the specific consent of the patient. There may be individual circumstances where a doctor believes that in the best interest of a particular patient it is necessary to depart from this general rule, but if the doctor does so he or she must be prepared to justify this action before the courts and the General Medical Council.’

Notification of HIV infection is not compulsory in Great Britain but a voluntary system of notification is available for doctors to report cases of AIDS under strict confidentiality to the AIDS Unit of the Public Health Laboratory Service Communicable Disease Surveillance Centre (CDSC). Results of serological tests for HIV infection are reported under strict confidentiality direct to the CDSC from the respective laboratories (HIV Surveillance). It would, on the other hand, be helpful if the physician who is directly involved in the screening of contacts could be informed if the index case is dually infected. With this additional knowledge, the physician would be better prepared to give appropriate advice and treatment to his or her patients. Thus an HIV-infected individual who is newly infected with tubercle bacilli may already have become immunologically anergic as a result of the viral infection and the tuberculin test, which otherwise is regarded as an important tool in contact tracing, could, by its negative response, mislead the physician who has been kept in ignorance of the dual infection. Furthermore, BCG vaccination may unwittingly be given to an HIV-infected contact (see Section 7). If, on the other hand, the dual diagnosis of the index case is known, immunological anergy in the contacts would be anticipated and additional tests could be carried out including, with consent, serological tests for HIV infection while BCG vaccination would be withheld. (It may be appropriate to refer children who are contacts to specialized pediatric units.)

In view of the unfortunate stigma and taboo overshadowing the disease, there are some doctors who are reluctant to ‘notify’ the condition for fear of breach of confidentiality and there are patients who are too frightened to submit to having the test itself. Thus serosurveillance of HIV infection in England and Wales is limited. This view was supported by Heptronstall & Gill (1989) in a paper presenting the legal and ethical justification for unlinked anonymous HIV testing. The public health and direct health advantages of detecting HIV infection as early as possible are presented by Rhame & Maki (1989) in their exposition of the case for wider testing. Allowing for under-reporting of diagnosed HIV infection, it has been estimated that only a small proportion of the general population who are infected with this virus know of their infection. Allowing for the endorsement by the Centers for Disease Control of routine testing of persons who may have a sexually transmitted disease, intravenous drug abusers and others who consider themselves to be at risk (Report 1987c) current efforts to make persons infected with HIV aware of their infection are failing. Many of those at greatest risk of infection choose not to be individually tested and all are encouraged not to donate blood. This results in data bias with subsequent inaccurate estimates of prevalence of HIV infection. The published figures which are produced in accordance with the requirements of the Secretary of State under the AIDS Control Act 1987 are consequently an
underestimate of the incidence of HIV infection and AIDS.

Identification of the source of transmission of the HIV infection is vital to the control of the AIDS epidemic. Anonymous testing as a means of obtaining seroprevalence rates in the community was therefore recommended by the Royal Statistical Society in its meeting on the statistical aspects of HIV infection in 1987 (Black et al. 1987). Good prospective data are particularly needed on patterns of sexual activity in addition to social and behavioural studies on representative groups including heterosexuals other than those in the high risk groups (Altman 1987). Although six years had already elapsed since the onset of the epidemic, the introduction of a long awaited national programme in Britain was delayed by several years to the detriment of public health control of the disease owing to considerable criticism and prolonged argument on the ethical aspects of anonymous testing (Anon. 1990). In November 1989 the Department of Health announced plans for extensive testing for HIV of unlinked anonymous blood samples taken from patients in England and Wales. The aim of the proposed programme was to provide estimates of the prevalence of HIV infection in the population and in particular the rate of change of the prevalence estimates over time, thus improving understanding of the evolving epidemic (Gill et al. 1989) while reducing uncertainties resulting from lack of information on changing seroprevalence (Anon. 1990).

In contrast to HIV infection and AIDS, tuberculosis is a notifiable disease in many countries. As soon as a diagnosis of tuberculosis is made, irrespective of the site of disease or degree of infectivity, the patient must be notified as suffering from tuberculosis as decreed by the regulations of the country. In Great Britain, the completion of the official Notification of Infectious Diseases Certificate and dispatch of it to the District Medical Officer (Director of Public Health), is a statutory duty imposed on all medical practitioners under the Public Health (Tuberculosis) Regulations of 1912. On receipt of the notification the District Medical Officer sends a copy to the chest physician in charge of the chest clinic serving the patient’s home address for appropriate action to be taken. Thus the main purpose of notification is to set in motion the machinery for tracing and examining contacts as this is an important procedure in the control and prevention of tuberculosis. This applies equally to contacts of dually infected patients as to those of patients suffering from tuberculosis only. In the former there is a possibility of close contacts also being infected with HIV and therefore being at greater risk, through subsequent loss of immunity, of developing tuberculosis. Notification is also of statistical and epidemiological importance as the incidence of tuberculosis in any area may be assessed from the notification figures which are collected by the local boroughs and sent to the Office of Population Censuses and Surveys for analysis and publication. There are now, unfortunately, some doctors who are ignorant of the need for, or purpose of, notification. Failure to notify a patient may have serious consequences for two reasons. First, contact tracing is impeded and new cases may be missed as such tracing has a potential yield of 3-4% and 3-6% respectively in Asian and non-Asian close contacts rising to 9% of Asian, and 12% of non-Asian, close contacts of smear-positive patients (Report 1978). Many of these contacts are children who are at risk of tuberculous meningitis and in whom early diagnosis and treatment are therefore particularly important. Secondly, the accuracy of the tuberculosis statistics is affected and, as government policy concerning tuberculosis control is influenced by changes in the incidence of the disease, the consequences could be far-reaching.

7. PREVENTIVE CHEMOTHERAPY AND VACCINATION

Preventive anti-tuberculosis therapy is advocated for all HIV seropositive persons with evidence of *M. tuberculosis* infection (Report 1987a). There is evidence that a 12 month course of isoniazid will prevent progression from a latent *M. tuberculosis* infection to active tuberculosis. The Advisory Committee for the Elimination of Tuberculosis in the United States recommends tuberculin testing of all people infected with HIV so that preventive treatment may be offered to those who react to tuberculin, while recognizing that in some patients with HIV-related anergy, the tuberculin test will be falsely negative (Report 1989a; see also Pitchenik 1988; Pitchenik et al. 1986; Theuer 1989; Murray & Mills 1990). Pitchenik et al. (1986) also recommended that all persons in risk groups for AIDS, particularly Haitians and intravenous drug abusers, whose HIV infectious status is either negative or unknown should also receive a tuberculin test. If they have significant reactions they should at least be managed according to the preventive therapy guidelines for the general population (Report 1987a). Since infection by *M. tuberculosis* appears to be particularly high among Haitian immigrants in the USA (30-60%), a case was made for treating all HIV-immunosuppressed, tuberculin-ergic Haitians with isoniazid, provided that active tuberculosis is excluded (Pitchenik et al. 1982, 1984; Pitchenik & Fischl 1983; Report 1986).

The vaccine against tuberculosis, BCG (Bacille Calmette-Guerin), is a living vaccine and, if it is given to immunosuppressed HIV-infected individuals, there is a danger that it will cause disseminated infection (Ninane et al. 1988). Thus the American Thoracic Society cautions against the use of BCG and other live attenuated vaccines
in HIV-infected individuals (Report 1987a) although the WHO and the International Union against Tuberculosis and Lung Disease (Report 1989b) continue to recommend widespread BCG vaccination in developing countries where there is a high prevalence of both HIV infection and tuberculosis but they state that the vaccine should not be given to any symptomatic HIV-infected children or adults.

8. EFFECT OF TUBERCULOSIS ON THE PROGRESSION OF AIDS

Tuberculosis occurring in HIV-infected patients usually responds well to standard anti-tuberculosis therapy. The question has, however, been raised as to whether tuberculosis, even if successfully treated, might accelerate the progression of HIV infection to AIDS (Hopewell 1989; Report 1989b). Tuberculosis, in otherwise normal individuals, has a number of suppressive effects on the immune system, including elevated production of acute phase reactants, some of which suppress certain lymphocyte functions (Caplin et al. 1989) and the induction of a CD4 lymphopenia (Beck et al. 1985). Successful treatment of the tuberculosis, however, causes these changes to revert to normal. More worrying is the apparent ability of immunological mediators produced during intercurrent infections, including tuberculosis, to augment the replication of HIV in lymphocytes and monocytes. As discussed in Section 2, the HIV provirus may become incorporated in the host chromosome DNA and lie dormant for a long period of time. In the asymptomatic HIV-positive individual active viral replication occurs in less than 1 in 10⁴ lymphocytes. Zagury et al. (1986) showed that stimulation of HIV-infected T-cells with phytohaemagglutinin led not only to their activation with production of interleukin 2 (IL-2) and expression of the IL-2 receptor but also to replication of the HIV and cell death. This raised the possibility that activation of lymphocytes in vivo would have a similar effect.

The replication of many viruses, including HIV, is inhibited by gamma interferon (INFg). Some viruses are also inhibited by TNF and this cytokine augments the inhibitory effect of INFg on HIV replication (Wong et al. 1989). It has, however, been shown in several studies that TNF (large amounts of which, as described in Section 3, are produced in post-primary tuberculosis) induces HIV replication in HIV-infected CD4 cell lines in vitro (Matsuyama et al. 1988; Ito et al. 1989; Folks et al. 1989; Israel et al. 1989). Evidence that this phenomenon might also occur in vivo was provided by Michihiko et al. (1989) who found that the addition of recombinant TNF augmented the replication of HIV in the peripheral blood mononuclear cells from three of four individuals infected with HIV-1. This augmentation was blocked by the reverse transcriptase inhibitor zidovudine (AZT) and also by the simultaneous addition of INFg.

The first step in the active replication of the HIV is the transcription of the provirus DNA into viral RNA. The activation of transcription (transactivation) of the provirus requires a DNA-binding protein termed nuclear factor kappa B (NF-kB) which is the same factor that induces transcription of the gene for the kappa light chain of immunoglobulin B-cells (Nabel & Baltimore 1987). The transcription factor NF-kB is itself induced by infectious agents and other stimuli that activate T-cells to secrete lymphokines. Thus Nabel & Baltimore (1987) remarked that infection of HIV-positive individuals by viral, bacterial and protozoal organisms would therefore pose a risk beyond the immediate infection. It was subsequently found that TNF is a principal mediator involved in the induction of NF-kB in lymphocytes (Osborn et al. 1989). It also leads to the differentiation and maturation of monocytes and the expression of NF-kB within these cells (Griffin et al. 1989).

Following replication, the newly-formed HIV particles escape by budding from the cell membrane rather than by bursting the cell. Nevertheless, active replication leads to cytopathic effects and cell death. The mechanism of such cell death is not fully understood, nor is it clear whether the profound CD4 T-cell depletion seen in AIDS is solely due to such killing. Likely causes of cell death include increased cell membrane permeability due to viral budding (Fauci 1988), direct or antibody-dependent cellular cytotoxicity (Wright et al. 1988; Jewett & Bonavida 1990) and altered lipid synthesis secondary to elevated intracellular calcium levels induced by the HIV, TNF or both (Lynn et al. 1989).

There is therefore strong evidence that opportunist infections in individuals infected with HIV may, by generating TNF, lead to transactivation and replication of HIV with associated destruction of lymphocytes in the CD4 subset and the onset of AIDS. In this respect, post-primary tuberculosis, with its protracted course and associated high TNF production, is a particular cause for concern. Once the patient has developed AIDS, repeated infections, including those due to opportunist mycobacteria, especially M. avium-intracellulare, may lead to a chronic elevation of TNF levels which may not only contribute to the continuing decline in immune reactivity but may, as in other chronic infections including tuberculosis, lead to cachexia. (In Africa, the descriptive name for AIDS-associated cachexia is 'slim disease'.) The levels of TNF/cachethin in sera from all of eight asymptomatic HIV-positive individuals and from 11 of 13 patients with HIV-related lymphadenopathy syndrome were within the range found in healthy individuals. On the other hand, elevated levels were found in sera from five of nine patients with AIDS-related
complex and from all of nine patients with AIDS (Laldevirta et al. 1988). Similar findings were reported by Reddy et al. (1988) who also found that intravenous drug abusers, irrespective of their HIV status, had elevated serum TNF levels, probably as a result of repeated infections.

9. CONCLUSIONS

There can be no doubt that the very serious public health problems of AIDS and tuberculosis are greatly compounded when the two diseases co-exist. Indeed, Chretien (1990) has aptly termed them 'the cursed duo'. Currently, 3-9% of all cases of tuberculosis world-wide are HIV-related. Tuberculosis is the only AIDS-related opportunistic disease that can infect healthy members of the community.

Not only is HIV infection having a dramatic effect on the incidence of tuberculosis in the individual patient and in the community but tuberculosis may, by generating large quantities of TNF, hasten the onset of AIDS in otherwise asymptomatic HIV-infected individuals, possibly by several years. Hence, there is an urgent need to control the spread of tuberculosis and AIDS world-wide, but particularly in regions, such as sub-Saharan Africa, where the two infections frequently coincide and where, currently, 17% of cases of tuberculosis are HIV-related.

There are many advantages in detecting HIV infection as early as possible. One obvious advantage of wider testing is the prevention of active tuberculosis by targeting high risk groups who may be infected with M. tuberculosis. By focusing on the testing of apparently asymptomatic persons, preferably based within the health care system, it would be possible to detect HIV infection as early as possible before, for example, the loss of dermal reactivity to tuberculin. At this stage, tuberculin testing could still identify those individuals with dormant tuberculous foci who have a high risk of developing active disease and can be treated prophylactically with isoniazid.

The early detection of asymptomatic HIV infection would also provide an opportunity to make the patients aware of the hazardous signs and symptoms of HIV-related disease and to encourage them to seek prompt medical advice when such signs and symptoms appear. Early prophylactic therapy with zidovudine is recommended in addition to the specific treatment of opportunistic infections. A recommendation to undergo HIV testing as part of routine health care would also reduce the reluctance of persons who know that they are at an increased risk of infection to be tested. Taking the test would enhance appreciation of the fact that HIV infection and AIDS are problems that society at large must face. In spite of efforts by governments and voluntary agencies to educate the public, ignorance and fear of HIV infection and AIDS remain widespread and the conditions have become taboo subjects. Physicians, microbiologists and other care workers must endeavour, by continuing education and example, to change community attitudes to this potentially fatal infection.

10. ACKNOWLEDGEMENTS

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11. REFERENCES


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Tuberculosis and human immunodeficiency virus infection in developing countries

A. D. Harris

World Health Organization (WHO) estimates indicate that at least 5 million people are infected with the human immunodeficiency virus (HIV) world wide. By Dec 31, 1989, 203 599 AIDS cases had been reported to the WHO by 152 countries, because of under-diagnosis, under-reporting, and delays in notification this probably represents less than half of the actual cumulative total, which has been estimated at over 400 000. In the tropics reported AIDS cases on Dec 31, 1989, were 38 248 in 48 Asian countries; with more than 2000 cases each reported from Burundi, Kenya, Malawi, Tanzania, Uganda, and Zambia. In Latin America, Brazil has reported 664 cases, Mexico 2663, and Haiti 2215. By contrast, only 494 AIDS cases have been reported from 25 Asian countries, 108 in Japan.

In many developing countries, human immunodeficiency virus (HIV) transmission is principally by heterosexual intercourse, with nearly equal numbers of men and women affected: in parts of sub-Saharan Africa, 30-50% of sexually active adults aged 20-40 are thought to be infected. Transmission at birth or by blood transfusion is also common that in developed countries, and the use of unsterilised needles and ritual skin piercing represent other potential routes of infection. In some parts of Latin America and the Caribbean, however, virus transmission is related more to homosexuality and intravenous drug abuse.

Recent WHO and International Union against Tuberculosis and Lung Disease (IUATLD) estimates indicate 8-10 million new cases of tuberculosis occur each year world wide, with 3-5 million deaths. Over three-quarters of these cases occur in the tropics; the highest smear-positive pulmonary tuberculosis rates in the world occur in Africa, followed by Asia and Latin America. Skin test surveys on children in sub-Saharan Africa and southeast Asia show infection rates of 1-3% per year of age. Thus, in some countries, about half the adult population aged 30-40 years have been infected with Mycobacterium tuberculosis, which may reactivate when cell-mediated immune defences decline. There has been a dramatic fall in the incidence of tuberculosis in most developed countries in the last few decades, but in many developing countries they have changed little despite BCG vaccination of children, active case-finding, and chemotherapy of patients known to be infected. The failure of many such programmes to control tuberculosis is largely because only a small proportion of smear-positive cases, who transmit disease, are routinely diagnosed, and the success rate of standard chemotherapy regimens in those who are diagnosed is often below 50%. Improved case detection and the introduction of short-course chemotherapy with initial intensive treatment in hospital may be the key to more effective tuberculosis control in the tropics.

Association of tuberculosis and HIV

Tuberculosis was not mentioned as a manifestation of AIDS in early descriptions of the disease from the USA and Europe; the association with tuberculosis was first recognised in Haitians and intravenous drug abusers. In developing countries, however, tuberculosis is now recognised as one of the most common opportunistic infections in patients seropositive for HIV-1. In Zimbabwe, tuberculosis is found at presentation in approximately one-third of patients infected by HIV-1. Positive serology is also found in 15-55% of tuberculosis patients in several central and east African countries. The studies summarised in table 1 are heterogeneous, and include populations with bacteriologically proven disease or with suspected disease; with newly diagnosed disease or who have been inpatients in TB sanatoria; and from urban or rural areas. This heterogeneity may partly explain the variations in HIV seropositivity. Many of the studies in table 1 were done in urban areas where 5-15% of the general population may be HIV seropositive. In rural areas, HIV seroprevalence rates are much lower than in towns and cities, and rural patients with tuberculosis have lower HIV infection rates than their urban counterparts. Nevertheless, in all areas patients with tuberculosis have significantly higher HIV infection rates than the healthy population.

It is unclear whether HIV-associated tuberculosis is usually a primary, reactivated, or secondary exogenous infection but, whatever the source, people infected by both HIV and Mycobacterium tuberculosis have an accelerated progression to overt tuberculosis. A prospective study in intravenous drug users in USA found the rate of active tuberculosis was 8% per year in those with dual infection, but in Africa the rate of progression is unknown. However, one likely consequence is an upsurge of tuberculosis: several

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countries, including Tanzania, Burundi, Uganda, and Zaire, have reported increases in tuberculosis incidence.\textsuperscript{14,15} Associated HIV infection may greatly influence these figures, although caution is needed in such interpretation; for example, in Tanzania, the reporting system for tuberculosis became national in 1979 and complete by 1982; short-course chemotherapy was introduced in 1983, and the subsequent increase in tuberculosis since then may also be a result of increased attendance for short-course chemotherapy. Increased sex and health services in Burundi may also account for some of the increase in reported pulmonary tuberculosis.

In Latin America a high proportion of Haitian AIDS patients present with tuberculosis,\textsuperscript{16} and in Haiti itself high HIV seroprevalence rates are found in patients with tuberculosis—similar findings to those in sub-Saharan Africa. There are urban rural differences of HIV infection in the general population (3% to 33%); this is reflected in patients with tuberculosis, in whom urban patients have HIV seroprevalence rates of 48%, compared with 15% for patients from rural areas.\textsuperscript{17} In Brazil, despite a large number of reported AIDS cases and high tuberculosis notification rates, the association is much less striking: HIV seropositivity rates of 3.1% are found in patients with pulmonary tuberculosis\textsuperscript{18} and of 2.3% in patients with extrapulmonary tuberculosis.\textsuperscript{19} A high proportion of these with dual infection are homosexual or use intravenous drugs.

**Clinical features**

In Africa, surveys in Kenya and Tanzania between 1964 and 1983\textsuperscript{20-26} provide reliable information on the pattern of tuberculosis before the AIDS epidemic. The pattern of disease and types of extrapulmonary disease in 8741 patients with tuberculosis are shown in table II. Almost 90% had pulmonary disease; of these with extrapulmonary tuberculosis, 85% had lymphadenopathy (mainly cervical), bone and joint disease, or pleural effusion. (In Kenya, pericardial or peritoneal involvement was seen in 5% of patients with extrapulmonary disease.) In adults and children older than 15 years with pulmonary tuberculosis, 75% had positive sputum smears for acid-fast bacilli on Ziehl-Neelsen stain and 66% had cavitation on chest radiography (these findings were strongly associated). Excessive lung disease was observed in 30%; but miliary tuberculosis was uncommon (eg, in Kenyan adults it was observed in 1.7% of 1722 patients with pulmonary tuberculosis). What has happened since the advent of AIDS?

Patients with both HIV infection and tuberculosis can present in various ways, but while many have typical clinical and radiographic signs of tuberculosis, some clinicians in central Africa have noticed a change in the pattern of disease. More patients seem to produce no sputum, or have negative sputum smears; chest radiography may show little change, or there may be diffuse pulmonary infiltrates without cavitation. Many African hospitals do not have facilities to culture mycobacteria and rely on sputum smears or plain radiography for rapid diagnosis. Extrapulmonary disease also appears to be more common—especially in forms that were previously uncommon, such as pericarditis, peritonitis, and miliary tuberculosis. This change in disease pattern has made diagnosis of tuberculosis more difficult—although a high index of suspicion usually means that these patients are thought to have tuberculosis and receive empirical antituberculosis chemotherapy, usually with good effect. These clinical impressions are confirmed by the few published African studies of the clinical interaction between tuberculosis and HIV infection. In Bangui, Central African Republic,\textsuperscript{27} 30% of patients with pulmonary tuberculosis were HIV seropositive; many had atypical findings on chest radiography and, in those with classic upper lobe cavitation without extrapulmonary involvement, the HIV seropositivity rate (7.5%) was similar to that found in the general population. Extrapulmonary tuberculosis and mediastinal lymphadenopathy were significantly more common in HIV-positive (60-85%) compared with HIV-negative (25%) patients with tuberculosis. Studies from Zaire and Zambia also showed that patients with suspected tuberculosis and with extrapulmonary tuberculosis had higher HIV seropositivity rates than patients with smear-positive tuberculosis (table II). In Uganda, tuberculous lymphadenopathy used to be uncommon: in 1983, only 6 of 170 new patients with tuberculosis seen at Mulago hospital, Kampala, over 6 months had lymphadenopathy;\textsuperscript{28} whereas in 1986, 16 patients with tuberculous lymphadenopathy were diagnosed over 6 weeks\textsuperscript{29}—all of whom were HIV seropositive. Histological examination of lymph-node biopsy specimens from these 16 patients revealed gaseating lesions with scanty or no visible acid-fast bacilli in 7 and poor cellular reactivity with numerous bacilli in 9. This anergic

**TABLE I—HIV AND TUBERCULOSIS IN AFRICA**

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Patients with tuberculosis</th>
<th>% HIV-positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>1985</td>
<td>Zaire\textsuperscript{a}</td>
<td>231</td>
<td>40</td>
</tr>
<tr>
<td>1985</td>
<td>Zaire\textsuperscript{b}</td>
<td>159</td>
<td>33</td>
</tr>
<tr>
<td>1985</td>
<td>Burundi\textsuperscript{c}</td>
<td>326</td>
<td>54</td>
</tr>
<tr>
<td>1985</td>
<td>Uganda\textsuperscript{d}</td>
<td>152</td>
<td>43</td>
</tr>
<tr>
<td>1987</td>
<td>Zaire\textsuperscript{e}</td>
<td>235</td>
<td>50</td>
</tr>
<tr>
<td>1985</td>
<td>Central African Republic\textsuperscript{f}</td>
<td>55</td>
<td>35</td>
</tr>
<tr>
<td>1985</td>
<td>Central African Republic\textsuperscript{g}</td>
<td>165</td>
<td>34</td>
</tr>
<tr>
<td>1985</td>
<td>Zambia\textsuperscript{h}</td>
<td>54</td>
<td>50</td>
</tr>
<tr>
<td>1985-86 \textsuperscript{i}</td>
<td>Total</td>
<td>1917</td>
<td>39</td>
</tr>
</tbody>
</table>

**TABLE II—TUBERCULOSIS IN EAST AFRICA, 1964-86**

<table>
<thead>
<tr>
<th>Year</th>
<th>n</th>
<th>Pulmonary</th>
<th>Pulmonary and extrapulmonary</th>
<th>Extrapulmonary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kenya</td>
<td>1964-1967</td>
<td>858</td>
<td>25</td>
<td>100</td>
</tr>
<tr>
<td>1974</td>
<td>1974</td>
<td>855</td>
<td>10</td>
<td>102</td>
</tr>
<tr>
<td>1968-1970</td>
<td>854</td>
<td>25</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>1980-1986</td>
<td>855</td>
<td>25</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1974</td>
<td>854</td>
<td>25</td>
<td>100</td>
</tr>
</tbody>
</table>

**TABLE III—HIV SERONEGATIVITY AND PATTERN OF TUBERCULOSIS IN AFRICA**

<table>
<thead>
<tr>
<th>Region</th>
<th>Smear-positive</th>
<th>Smear-negative</th>
<th>Extrapulmonary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zaire\textsuperscript{a}</td>
<td>250</td>
<td>152</td>
<td>16</td>
</tr>
<tr>
<td>% HIV-positive</td>
<td>33</td>
<td>45</td>
<td>37</td>
</tr>
<tr>
<td>Zambia\textsuperscript{b}</td>
<td>18</td>
<td>38</td>
<td>37</td>
</tr>
<tr>
<td>% HIV-positive</td>
<td>44</td>
<td>56</td>
<td>16</td>
</tr>
</tbody>
</table>
non-reactive histology is also reflected in an anergic response to tuberculin in Zaire and the Central African Republic, a higher proportion of HIV-positive patients with tuberculosis (20-57%) had cutaneous anergy to 5 tuberculin units compared with HIV-negative patients with tuberculosis (19-22%).

Haïtians show a similar disease pattern to that seen in Africa; approximately 70% of patients with both tuberculosis and AIDS had extrapulmonary disease compared with only 20% of HIV-negative patients with tuberculosis.3 Again, the pattern of extrapulmonary disease differed: in HIV-negative patients, pleural effusion, lymphadenopathy, and bone and joint disease were most common (54% of the total); in those with AIDS, lymphadenopathy and myelitis TB were most common, and pericardial, peritoneal, and meningeval disease accounted for most other extrapulmonary disease. In Brazil,12 of 19 HIV-positive tuberculosis patients had either disseminated or extrapulmonary disease; of the 7 with pulmonary disease, only 3 had optical radiographic features of tuberculosis.

Treatment

The efficacy of antituberculous chemotherapy in African patients with combined tuberculosis and HIV infection is underachieved, although improvements usually suggest that the tuberculosis responds well to conventional treatment. However, a study in central Africa,16 which examined outcome 12 months after the start of standard chemotherapy, found mortality to be 33.3% in HIV-seropositive patients compared with 19.5% in HIV-seronegative patients. In Haiti17 and Brazil,12 the response of tuberculosis to chemotherapy was found to be good. However, HIV-positive patients may have an increased risk of relapse after the end of antituberculous treatment. Several African countries now use short-course chemotherapy.5 months total; 2 months streptomycin, rifampicin, isoniazid, and pyrazinamide; 6 months isoniazid and thiacetazone for smear-positive pulmonary tuberculosis and reserve the standard regimen (1 month streptomycin, thiacetazone, and isoniazid; 11 months thiacetazone and isoniazid) for smear-negative and extrapulmonary tuberculosis. All regimens used in Africa include daily intramuscular injections of streptomycin for 1-2 months at the start of treatment. Epidemiological evidence from central Africa has implicated use of injections with increased transmission of HIV infection.8 Although the validity of this association has been questioned,9 the use of daily injections in patients with a high prevalence of HIV is a cause for concern; if streptomycin is considered to be essential because of its low cost and effect on patient compliance, it is vital to ensure an adequate supply of syringes and needles for control of tuberculosis in African countries. The alternative, but more expensive, solution would be to replace the use of streptomycin by oral regimens alone.

Another new trend since the increased prevalence of HIV is the increased incidence of cutaneous hypersensitivity reactions to standard chemotherapy regimens. Previously they were unusual (2-4%), in Africa18 and Melenckis from Papua New Guinea,19 and thiacetazone was the drug most often implicated. Severe reactions, such as exfoliative dermatitis and Stevens-Johnson syndrome, were very rare (0-5%). More recently there have been signs of an increase in severe cutaneous hypersensitivity reactions, particularly Stevens-Johnson syndrome—almost all in HIV-seropositive patients, with some deaths; these reactions usually occur in patients on standard chemotherapy regimens, and are very unusual in patients on short-course chemotherapy, so thiacetazone may again be a factor.

BCG immunisation is an important element in attempts to control tuberculosis in many African countries, often administered to infants as early in life as possible. There have been isolated reports of disseminated Mycobacterium fortin in HIV-infected infants after BCG vaccination,1,2 and in Zaire.3 However, in the study of infants born in Zaire, none of the children with BCG abscesses was HIV seropositive and local adenitis after BCG was found with similar frequency in HIV-seropositive and HIV-seronegative children.3 In the absence of clear evidence of an adverse effect of BCG vaccination, WHO guidelines are to withhold BCG only from HIV-seropositive individuals with symptoms.

Discussion

The strong association of HIV and tuberculosis in some developing countries has important implications. There is evidence of an increased incidence of tuberculosis, and strategies for effective control of tuberculosis may have to be re-examined. In particular, the following questions must be answered. Is BCG vaccination safe for infants born to HIV-seropositive mothers? What extra investigations or diagnostic facilities may be needed in view of the increase in smear-negative, pulmonary, and extrapulmonary, tuberculosis? What is the safest and most effective treatment of tuberculosis in patients with dual infections? Are there differences in the course of tuberculosis in patients infected by HIV-1 compared with HIV-2? What will be the effect on the incidence of tuberculosis in HIV-seropositive people if a large proportion of the HIV-positive population have tuberculosis? And where will the money to investigate and to treat these patients come from? The combination of a bacteria identified in the 1880s and a virus isolated a century later will be an important challenge for medicine in the years ahead.

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An estimate of the future size of the tuberculosis problem in sub-Saharan Africa resulting from HIV infection

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SUMMARY. The impact of the human immunodeficiency virus (HIV) on tuberculosis is well documented. Its effect in populations with a high proportion of dually infected individuals is likely to be significant. Sub-Saharan Africa is one such region and to better document the effect of HIV infection on tuberculosis there we developed a mathematical model to predict the likely extra numbers of tuberculosis cases due to it.

A mathematical model was developed using a variety of scenarios giving a range of risks for the period 1980–2000. The four scenarios included (1) a low rate of 1% risk of tuberculosis infection in year 0 (1980) with 45% tuberculosis infection prevalence, and an HIV prevalence of 2% in 1989; (2) a 2% risk of tuberculosis infection in year 0 with 60% tuberculosis infection prevalence, and a 2% HIV prevalence in 1989; (3) a 2% risk of tuberculosis infection in year 0 with 60% tuberculosis infection prevalence, and a 10% HIV prevalence in 1989; and (4) a 2% risk of tuberculosis infection in year 0 with 60% tuberculosis infection prevalence and a 20% HIV prevalence in 1989.

Under scenarios 1 and 2, a 50–60% increase in smear-positive rates in the subpopulation (15–45 years old) is predicted for the year 2000, under scenario 3, smear-positive rates in the subpopulation in the year 2000 are expected to increase four-fold from the 1980 baseline. Under scenario 4, a 10-fold increase in smear-positive rates in 2000 is expected in the subpopulation. Under this scenario, total disease will have increased 12-fold in the subpopulation.

These data suggest that there will be a dramatic increase in the number of cases of tuberculosis due to HIV infection in sub-Saharan Africa. This increase is likely to strain the already fragile health care system in this region.

RESUMÉ. L’impact du virus de l’immunodéficience humaine (HIV) sur la tuberculose est bien documenté. Son effet sur les populations avec une proportion élevée d’individus atteints d’une double infection apparaît important. L’Afrique sub-saharienne se situe dans ce groupe, et pour mieux documenter l’effet de l’infection HIV sur la tuberculose dans cette région nous avons développé un modèle mathématique pour calculer les cas futurs de tuberculose due à l’HIV.

Un modèle mathématique a été développé utilisant une variété de scénarios donnant un ordre de risques au cours de la période 1980–2000. Les quatre scénarios incluent (1) une faible dette de risque à 1% d’infection pour la tuberculose à l’année 0 (1980) avec une prévalence de 45% d’infection tuberculeuse, et une prévalence de 2% d’infection par le HIV en 1989; (2) un risque à 2% d’infection pour la tuberculose à l’année 0 avec une prévalence de 60% d’infection tuberculeuse, et une prévalence de 2% d’infection par le HIV en 1989; (3) un risque à 2% d’infection pour la tuberculose à l’année 0 avec une prévalence de 60% d’infection tuberculeuse, et une prévalence de 10% d’infection par le HIV en 1989; et (4) un risque à 2% d’infection pour la tuberculose à l’année 0 avec une prévalence de 60% d’infection tuberculeuse, et une prévalence de 20% d’infection par le HIV en 1989.

Dans les scénarios 1 et 2, une augmentation de 50–60% des taux frottis positifs dans la sous-population (âgée de 15 à 45 ans) est prévue pour l’an 2000; dans le scénario 3, les taux de frottis positifs dans la sous-population dans l’an 2000 sont appelés à se multiplier par 4 à partir du taux de base de l’an 1989; dans le
INTRODUCTION

Human immunodeficiency virus (HIV) infection profoundly influences tuberculosis resulting in a substantial increase in the number and rate of cases of this disease. This has been documented in particular age groups and ethnic minorities in the USA. The increase is even more apparent in countries of sub-Saharan Africa where tuberculosis rates have been rising since the mid-1980s, whereas previously there had been a small but steady decline. In Tanzania, for instance, there were about 8,000 smear-positive cases diagnosed in 1984. This number increased to 10,000 by 1989. An even more dramatic picture is seen in Uganda with the annual number of confirmed cases doubling from 1984 to 1987.

In this paper we briefly review the literature documenting the impact of HIV infection on tuberculosis and, based on these data and previous data on the epidemiology of tuberculosis, we develop a model which describes the interrelationship between these two infections and predicts the future impact of HIV infection on tuberculosis.

REVIEW OF THE LITERATURE: HIV AND TUBERCULOSIS INTERRELATIONSHIPS

Prevalence of HIV seropositivity in patients with tuberculosis

A number of studies show a significant association between HIV infection and tuberculosis in African patients. Recent data from Zaire and Zambia show HIV seropositivity rates of 36% (85 of 234 cases) and 60% (206 of 346 cases) respectively in patients hospitalized with tuberculosis. Extrapulmonary tuberculosis was common. The proportion of positive smears is generally somewhat lower among HIV-positive patients than among HIV-negative patients. In the Zambia study, 82% of HIV-negative patients were smear-positive while in HIV-positive tuberculosis cases this proportion was 63%. These relatively high smear-positive rates reflect the hospital-based population studied, and contrast with lower levels found in the community of approximately 40% in HIV-positive cases of tuberculosis and 50% in HIV-negative cases of tuberculosis. HIV-positive and negative patients with positive smears show a similar proportion of infected contacts. Fatality among HIV-positive patients is high: in the Zaire study it was 36% (60 of 155) at 1 year after diagnosis, as compared with 5.5% (26 of 476) for HIV-negative subjects.

Risk of tuberculosis in dually infected individuals

The risk of tuberculosis in individuals infected with both tubercle bacilli and HIV is extremely high. Data from Selwyn indicate that some 50% of individuals who have been infected with tubercle bacilli prior to their infection with HIV develop overt tuberculosis. The major risk of disease occurs late in the course of HIV infection, either when they develop AIDS (about one-
third of tuberculosis cases) or during the previous 2 years or so (about two-thirds of cases). As most of these individuals have been infected with tubercle bacilli many years before, the impairment of cellular immunity must indeed be profound to convert the risk of less than 1% to that of 50%. There are no well-documented studies concerning the risk of developing tuberculosis in individuals in whom infection with tubercle bacilli occurs following HIV infection. A recent study by de Perri suggests the risk may be very high. In this study, 18 HIV-infected inpatients were exposed to cases of tuberculosis and active tuberculosis developed in 8 of them (in 7 of them within 60 days of the diagnosis of the index case). Unfortunately previous tuberculin status of these patients was not known.

Incidence and prevalence of tuberculous infection

Surveys of school children in sub-Saharan Africa indicate that the risk of infection by tubercle bacilli is between 1 and 2% per annum. From this risk, prevalence of infection in different age groups can be estimated. It appears that some 45% of adults between the ages of 15 and 49 have been infected with tubercle bacilli in populations with 1% risk, and 60% when this risk rises to 2%. In Uganda, positive tuberculin tests have been reported in 60–80% of BCG unvaccinated adults. Styblo has shown that 1% of annual risk of infection is equivalent to the incidence of smear-positive cases of 50 per 100 000.

Risk of tuberculosis following infection (HIV-negative individuals)

The risk of active tuberculosis following infection has been studied by a large number of investigators. Chiba in Japan and Nissen Meyer in Scandinavia have presented extensive data; the risk is high during the first 12–24 months following infection and then steadily diminishes but never completely disappears. The disease appears in two forms: extrapulmonary complications of which particularly serious forms are miliary tuberculosis and tuberculous meningitis and progressive pulmonary tuberculosis. The extrapulmonary complications usually occur early following infection in newly infected individuals independent of age, though they are particularly common in infants and young children. Progressive pulmonary tuberculosis tends to occur in the first year or two following primary infection in adolescents and adults, but in infected children it is usually delayed until the age of puberty.

THE MATHEMATICAL MODEL

Assumptions

Using the information reviewed above, a mathematical model based on the reported HIV and tuberculosis rates of infection in sub-Saharan Africa was constructed. This model predicts the annual rate of development of new cases of tuberculosis, in HIV-positive and HIV-negative individuals.

The model followed cross-sectionally a sexually active sub-Saharan population aged 15–49 from 1980 (year 0) to 2000 (year 20). A stationary age distribution was assumed, based on the UN data for Tanzania in 1985. The model followed cross-sectionally a sexually active sub-Saharan population aged 15–49 from 1980 (year 0) to 2000 (year 20). A stationary age distribution was assumed, based on the UN data for Tanzania in 1985.

The model was calculated separately for four scenarios of tuberculosis and HIV rates: (1) a low rate of 1% risk of tuberculosis infection in year 0 (1980) with 45% tuberculosis infection prevalence, and an HIV annual incidence rate of 0.66; (2) a moderate rate of 4% risk of tuberculosis infection in year 0 (1980) with 60% tuberculosis infection prevalence, and an HIV annual incidence rate of 1.26; (3) a high rate of 10% risk of tuberculosis infection in year 0 (1980) with 65% tuberculosis infection prevalence, and an HIV annual incidence rate of 1.86; and (4) a very high rate of 20% risk of tuberculosis infection in year 0 (1980) with 69% tuberculosis infection prevalence, and an HIV annual incidence rate of 2.46.

To obtain a range of prediction values reflecting the geographic variations in sub-Saharan Africa, two initial (pre-HIV) levels of annual risk of infection by tubercle bacilli (TB infection) (1% and 2%) were analyzed in the model, in combination with corresponding infection prevalences of 45 and 60%

<table>
<thead>
<tr>
<th>Year</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980</td>
<td>0.42</td>
</tr>
<tr>
<td>1981</td>
<td>0.42</td>
</tr>
<tr>
<td>1982</td>
<td>0.66</td>
</tr>
<tr>
<td>1983</td>
<td>0.88</td>
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<td>1991</td>
<td>1.92</td>
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<tr>
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<td>1.96</td>
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<tr>
<td>1993</td>
<td>1.98</td>
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<td>1999</td>
<td>1.68</td>
</tr>
<tr>
<td>2000</td>
<td>1.56</td>
</tr>
</tbody>
</table>
prevalence of 2% in 1989; (2) a 2% risk of tuberculosis infection in year 0 with 60% tuberculosis infection prevalence, and a 2% HIV prevalence in 1989; (3) a 2% risk of tuberculosis infection in year 0 with 60% tuberculosis infection prevalence, and a 10% HIV prevalence in 1989; and (4) a 2% risk of tuberculosis infection in year 0 with 60% tuberculosis infection prevalence and a 20% HIV prevalence in 1989.

Breakdown rates to active tuberculosis in successive years following tuberculosis infection were assumed to follow the patterns shown in Table 3.

Children (≤ 12 years) were assumed to be HIV-negative and to follow breakdown rates at 50% of those of HIV-negative adults, until reaching age 13, at which point adult rates were applied. Finally, individuals infected with tubercle bacilli prior to HIV infection were assumed to follow HIV-negative adult breakdown rates for the first 7 years following HIV infection. Breakdowns in the final 3 years (years 8, 9, and 10) were assumed to total 30%, equally divided (16.7%) among the 3 years. Previously tuberculosis-uninfected adults who became infected with tubercle bacilli following HIV infection were assumed to break down with rates proportional to those of HIV-negative adults, but were scaled up to total 80% breakdown in the first 10 years after tuberculosis infection.

It was assumed that 50% of HIV-negative individuals who broke down with pulmonary tuberculosis were smear-negative, and 50% smear-positive. Of HIV-positives, 60% of breakdowns were assumed to be smear-negative, and 40% smear-positive.

To update the risk of tuberculosis infection over time, the growing yearly rate of smear-positives was cumulatively added to the stationary risk at year 0, according to Styblo's formula, which states that 50/100,000 smear-positives are equivalent to a 1% risk of infection per year.

The rates predicted by this model are applicable to the population studied (15-49 years old). To estimate corresponding rates for the total population, an adjustment was introduced. This was derived as a weighted average, based on annual (1981-1989) age-specific smear-positive tuberculosis case (IUATLD data on file) detection rates and on age-specific population data.23

The prediction equations

The equations were developed recursively. It was assumed that initially, in year 0 (1980), no HIV infections were present, and that cases of smear-positive and smear-negative tuberculosis were present in equal numbers. The magnitudes of these two groups relative to the population were derived in analogy with life-table (actuarial) calculations, using products of conditional probabilities. Each age-group was analyzed in turn. Thus, for example, the 12.46% of the population in the 30-34 year age group (Table 1) were followed back as a cohort. For any individuals in this cohort to end up in year 0 in one of the groups with tuberculosis, they must have been infected j years previously, 0 ≤ j ≤ 34, according to the stationary risk of infection assumed in the model, failed to break down for j-1 subsequent years (with probabilities derived from the age-specific rates in columns 1 and 2 of Table 3), and then broken down in the final year (Table 3). These products of probabilities were summed over j for each age group and over the 7 age groups to yield total estimated rates for the tuberculosis smear-positive and smear-negative groups in the year 0 (1980).

For each of the subsequent years (1981-2000), four groups with tuberculosis were identified and estimated: smear-positive HIV-positive; smear-positive HIV-negative; smear-negative HIV-positive; and smear-negative HIV-negative. According to the assumptions made earlier, the HIV-negative groups were taken to be of equal size; the HIV-positive groups were taken to be in the ratio of 40:60 of smear-positive to smear-negative.

To derive the annual sizes of the HIV-negative groups with tuberculosis, the current HIV-negative population (from Table 2 and the assumption of 10-year survival following HIV infection) was analyzed. Analogous actuarial computations were again applied to the various age groups, with the added complication that the annual tuberculosis risk of infection after year 0 had increased year by year by the cumulative presence of the smear-positive HIV-positive groups, so that in each of the years 1, 2, 3, ..., an increasing risk of tuberculosis infection, followed by breakdown in the current year, was accounted for, using Styblo's conversion formula.

To derive the annual sizes of the HIV-positive groups with tuberculosis, the current HIV-positive population (from Table 2 and the 10-year survival assumption) was analyzed. Individuals infected by HIV first and by tubercle bacilli later were stratified by their year (and incidence rate) of HIV infection, and by the year (and cumulated risk) of tuberculosis infection, and then actuarially followed to breakdown in the current year (using Table 3, column 3). Individuals dually infected (infected by tubercle bacilli first, then by HIV) were followed back in time as cohorts, in the description for year 0 above, to account for their tuberculosis infection according to the stationary pre-HIV risk, and followed to breakdown in the current year. They were

Table 3. Breakdown rates (in % per year) for each year following tuberculosis infection *

<table>
<thead>
<tr>
<th>Year</th>
<th>HIV-negative adults (≥ 13 years)</th>
<th>HIV-negative adults (≤ 12 years)</th>
<th>HIV-positive adults (tuberculosis infection following HIV infection)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.0</td>
<td>2.50</td>
<td>42.1</td>
</tr>
<tr>
<td>2</td>
<td>2.0</td>
<td>1.00</td>
<td>16.8</td>
</tr>
<tr>
<td>3</td>
<td>0.5</td>
<td>0.25</td>
<td>4.2</td>
</tr>
<tr>
<td>4</td>
<td>0.5</td>
<td>0.25</td>
<td>4.2</td>
</tr>
<tr>
<td>5</td>
<td>0.5</td>
<td>0.25</td>
<td>4.2</td>
</tr>
<tr>
<td>6</td>
<td>0.2</td>
<td>0.10</td>
<td>1.7</td>
</tr>
<tr>
<td>7</td>
<td>0.2</td>
<td>0.10</td>
<td>1.7</td>
</tr>
<tr>
<td>8</td>
<td>0.2</td>
<td>0.10</td>
<td>1.7</td>
</tr>
<tr>
<td>9</td>
<td>0.2</td>
<td>0.10</td>
<td>1.7</td>
</tr>
<tr>
<td>10</td>
<td>0.2</td>
<td>0.10</td>
<td>1.7</td>
</tr>
<tr>
<td>≥11</td>
<td>0.1</td>
<td>0.05</td>
<td>0.0</td>
</tr>
</tbody>
</table>

* For 'dually infected' individuals (tuberculosis infection prior to HIV infection), see text for breakdown rates.
stratified by their year of HIV infection (and corresponding incidence rate), and breakdown rates were calculated using the values described in the text following Table 3.

RESULTS

The rates of smear-positive cases for the 15-49 year subpopulation, calculated by this model for the period 1980-2000, are given in Table 4 under four scenarios.

Table 5 compares the incidence rates between 1980, 1989 and 2000, under the four scenarios, for the subpopulation (15-49 years), and the adjusted rates for the total population. Under scenarios 1 and 2, a 50-60% increase in smear-positive rates in the subpopulation is predicted for the year 2000, (36-40% increase for the total population). Under scenario 3, smear-positive rates in the subpopulation in the year 2000 are expected to increase four-fold from the 1980 baseline (three-fold for the total population). Under scenario 4, a 10-fold increase in smear-positive rates in 2000 is expected in the subpopulation (seven-fold in the total population). Under this scenario, total disease will have increased 12-fold in the subpopulation (nearly nine-fold in the total population).

Table 4. Estimated incidence rates (per 100 000) of smear-positive pulmonary tuberculosis for the 15-49 year old subpopulation in sub-Saharan Africa under four scenarios

<table>
<thead>
<tr>
<th>Year</th>
<th>Scenario 1</th>
<th>Scenario 2</th>
<th>Scenario 3</th>
<th>Scenario 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Smear+ HIV-</td>
<td>Smear+ HIV+</td>
<td>Smear+ HIV-</td>
<td>Smear+ HIV+</td>
</tr>
<tr>
<td>1980</td>
<td>89 0</td>
<td>179 0</td>
<td>179 0</td>
<td>179 0</td>
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<tr>
<td>1983</td>
<td>89 1</td>
<td>179 1</td>
<td>177 5</td>
<td>175 11</td>
</tr>
<tr>
<td>1986</td>
<td>89 2</td>
<td>178 3</td>
<td>174 13</td>
<td>170 29</td>
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<tr>
<td>1989</td>
<td>90 4</td>
<td>180 5</td>
<td>182 30</td>
<td>182 71</td>
</tr>
<tr>
<td>1991</td>
<td>93 14</td>
<td>185 26</td>
<td>207 138</td>
<td>224 304</td>
</tr>
<tr>
<td>1992</td>
<td>96 17</td>
<td>190 31</td>
<td>228 168</td>
<td>258 377</td>
</tr>
<tr>
<td>1993</td>
<td>98 20</td>
<td>194 36</td>
<td>243 197</td>
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<td>1994</td>
<td>100 22</td>
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<td>301 533</td>
</tr>
<tr>
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<td>201 45</td>
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<tr>
<td>1996</td>
<td>104 26</td>
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<td>2000</td>
<td>110 32</td>
<td>214 58</td>
<td>325 356</td>
<td>410 1359</td>
</tr>
</tbody>
</table>

* Scenario 1 represents the combination of 1% risk of tuberculosis infection in year 0, 45% tuberculosis infection prevalence, and a 1989 HIV prevalence of 2%. Scenario 2 represents, correspondingly, 2%, 60% and 2%. Scenario 3 represents 2%, 60% and 10%. Scenario 4 represents 2%, 60% and 20%.

† In each scenario, smear-, HIV- cases will occur at the same rate as that of smear+, HIV- for the same year; also, smear-, HIV+ cases occur at a rate of 0.5 times the rate of smear+, HIV+ given, for the same year. These figures are not included in the table in order to simplify the presentation.

Table 5. Estimated incidence rates (per 100 000) of tuberculosis in sub-Saharan Africa in the years 1980, 1989 and 2000 under four scenarios

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Smear-positive cases</th>
<th>Total cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 2 3 4</td>
<td>1 2 3 4</td>
</tr>
<tr>
<td>15-49 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1980 Adjusted for total population</td>
<td>55 110 110 110</td>
<td>110 220 220 220</td>
</tr>
<tr>
<td>1989 % increase since 1980</td>
<td>6 3 18 41</td>
<td>190 372 438 541</td>
</tr>
<tr>
<td>1990 Adjusted for total population</td>
<td>57 112 124 142</td>
<td>115 226 254 298</td>
</tr>
<tr>
<td>1999 % increase since 1980</td>
<td>3.5 2 13 29</td>
<td>4.5 3 15 35</td>
</tr>
<tr>
<td>2000 % increase since 1980</td>
<td>142 272 681 1,769</td>
<td>300 573 1,540 4,218</td>
</tr>
<tr>
<td>Adjusted for total population</td>
<td>95 52 280 888</td>
<td>67.5 60 330 1,078</td>
</tr>
<tr>
<td>% increase since 1980</td>
<td>77 150 325 792</td>
<td>162 312 727 1,875</td>
</tr>
<tr>
<td>% increase since 1980</td>
<td>40 36 195 620</td>
<td>47 42 230 752</td>
</tr>
</tbody>
</table>

* Scenario 1 represents the combination of 1% risk of tuberculosis infection in year 0, 45% tuberculosis infection prevalence, and a 1989 HIV prevalence of 2%. Scenario 2 represents, correspondingly, 2%, 60% and 2%. Scenario 3 represents 2%, 60% and 10%. Scenario 4 represents 2%, 60% and 20%. 
DISCUSSION

A very large increase in the tuberculosis problem is already occurring in the countries of sub-Saharan Africa. In this analysis we have considered four scenarios, one based on recently reported findings in Kampala, Uganda, where up to 20% of the general adult population are infected with HIV and more moderate scenarios applicable to the situation in most areas in the countries of sub-Saharan Africa in which the current prevalence rates of HIV infection are assumed to be 2% and 10%, and risks of infection by tubercle bacilli associated with these HIV seroprevalence rates are 1% and 2%.

The results show that at the low level of risk, i.e. a 1% risk of tuberculosis infection in 1980, 45% tuberculosis infection prevalence, and 2% HIV prevalence in 1989, there will be an increase of 68% in the number of cases of tuberculosis by the year 2000 when the predicted incidence rate of all cases will be 300/100,000. The upper boundary using risks outlined for scenario 4, i.e. 2% risk of tuberculosis infection, 60% of prevalence of tuberculosis and 20% HIV prevalence rates, shows that the incidence rate of tuberculosis will rise to 4,218 per 100,000 which would represent a 12-fold increase from the 1980 figures.

These estimates apply to a 15-49 age group of the population. When these restricted estimates are adjusted and extended to the total population, as shown in Table 5, the worst scenario indicates that the incidence rate for the total population of Kampala, Uganda in the year 2000 would be 1,875/100,000. The prediction that by the year 2000 almost 2% of the population of the city will develop tuberculosis every year seems at first sight unbelievable, yet this figure is not very different from that reported by Cummins for the black troops from South Africa who came to France in the First World War, or from that reported by Ferguson for Saskatchewan Indians in 1886.

It appears that HIV infection is, as it were, pushing the epidemiological clock back towards the time of the first encounter of human populations with tubercle bacilli.

In this model we have not taken into account the possible epidemiological role of exogenous reinfection which would further exacerbate the situation; while there is still no agreement on its role in the epidemiology of tuberculosis, it is possible that it may be important in the HIV-positive group, even if it was relatively unimportant in the HIV-negative one.

We realize that the data on which our assumptions are based are often rather scant. The risks of dually infected individuals in whom tuberculosis infection anteceded HIV infection are reasonably well delineated, yet little is known about the reverse situation. It is indeed surprising that there are so few studies on the natural history of tuberculosis in individuals infected by HIV.

In this analysis we have not considered tuberculosis in children; the rising risks of infection by tubercle bacilli will inevitably cause high morbidity in that group. In our worst scenario, for instance, the risk of infection will exceed 15% in the year 2000; this will be responsible for some 2,500 cases/100,000 of tuberculosis in children under 15 years of age.

These dramatic predictions of a very rapid increase in the incidence of tuberculosis will have a considerable negative impact on the economic development in these countries and constitute a considerable challenge to the national and international health services which are already under stress. We seem to be singularly ill-prepared to meet this challenge. At the present time, apart from a handful of countries in which tuberculosis programmes are conducted through mutual aid coordinated by the International Union Against Tuberculosis, the national tuberculosis programmes are either non-existent or just being organized. In countries with the IUAT-assisted programmes the patients with positive smears receive all optimal regimens during the first 2 months of treatment (usually in hospital) followed by isoniazid (INH) and thiacetazone during the subsequent 6 months. Other countries cannot afford the cost of rifampicin and pyrazinamide and treat all cases with INH and thiacetazone, usually with streptomycin in the initial month or two; default rates are very high and results poor.

In this article we have limited our predictions up to the year 2000 — there is, however, every reason to expect that the disastrous increase in the number of tuberculosis cases will continue well into the 21st century. This model is confined to the countries of sub-Saharan Africa. There is evidence that the HIV epidemic is beginning to spread through Asiatic countries in which the current tuberculosis situation is similar to that seen in Africa in 1980; these Asiatic countries have an advantage in knowing what to expect and in being able to take appropriate preventive action by intensifying the efficiency and scope of their national tuberculosis programmes now.

A great deal of improvement may come from further progress in the fight against HIV infection but, even if this were very successful, it is unlikely to have an immediate effect; the decrease in the rate of new HIV infections would obviously affect the problem in the long run. The development of new antiviral drugs may also reduce the risk of tuberculosis among individuals infected with both the virus and with tubercle bacilli but their use in Africa may be limited by cost factors. With respect to tuberculosis, an efficient control programme with strong treatment, case finding and preventive components must be organized. The international community must ensure that the most effective drugs are available and used widely both in treatment and in prophylaxis.

References


Should pulmonary tuberculosis be an AIDS-defining diagnosis in patients infected with HIV?

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SUMMARY. Between 1983 and 1989, we cared for 56 patients with tuberculosis and human immunodeficiency virus (HIV) infection. In 37 patients (66%), tuberculosis occurred before any other AIDS-defining disease (group 1); in 10 (18%) it occurred during the same month as another AIDS-defining disease (group 2); and in 9 (16%), after the diagnosis of AIDS (group 3). Tuberculosis was entirely pulmonary in 14 patients (25%), entirely extrapulmonary in 9 (16%), and both pulmonary and extrapulmonary in 33 (59%). The frequency of extrapulmonary involvement was similar in patients from group 1 and from groups 2 and 3 (combined): 76% versus 74%. Needle biopsy of the liver revealed hepatic involvement in 18 patients (32%). The mean CD4 lymphocyte count was 232/mm³ when tuberculosis was entirely pulmonary, and 243/mm³ when extrapulmonary disease was present (difference not significant). In group 1, the onset of both pulmonary and extrapulmonary tuberculosis occurred at the same stage of HIV infection, 12 and 10 months, respectively, before any other AIDS-defining disease. Treatment, planned to last 1 year, was highly effective, despite frequent side-effects. Among the 32 patients who completed treatment, relapse of tuberculosis occurred in 2 (6%) with a mean follow-up of 16 months (0-53 months) after completion. Our results suggest that pulmonary tuberculosis should be included in the criteria for diagnosis of AIDS.

RÉSUMÉ. Entre 1983 et 1989 ont été soignés 56 malades porteurs de tuberculose et du virus de l'immunodéficience humaine (VIH). Dans 37 des cas (66%), la tuberculose s'est déclarée avant toute autre maladie entrant dans la définition du SIDA (groupe 1); dans 10 des cas (18%), elle est survenue pendant le même mois qu'une autre maladie entrant dans la définition du SIDA (groupe 2); et dans 9 des cas (16%), elle est postérieure au diagnostic du SIDA (groupe 3). La tuberculose était exclusivement pulmonaire chez 14 malades (25%), exclusivement extrapulmonaire chez 9 malades (16%), et à la fois pulmonaire et extrapulmonaire chez 33 malades (59%). La fréquence de l'atteinte extrapulmonaire était similaire dans les malades du groupe 1 et des groupes 2 et 3 (combinés): 76% contre 74%. Une ponction-biopsie à l'aiguille du foie a révélé une atteinte hépatique chez 18 des malades (32%). Le nombre moyen de lymphocytes CD4 était de 232/mm³ quand la tuberculose était exclusivement pulmonaire, et de 243/mm³ quand une atteinte extrapulmonaire était présente (différence non significative). Dans le groupe 1, le début de la tuberculose, qu'elle soit pulmonaire ou extrapulmonaire, est survenu au même stade de l'infection VIH, soit respectivement à 12 et 10 mois, avant toute autre maladie entrant dans la définition du SIDA. Le traitement, prévu pour une année, a été très efficace, en dépit de fréquents effets secondaires. Parmi les 32 malades qui ont accompli leur traitement, une récidive de la tuberculose a été observée dans 2 des cas (6%) à un suivi moyen de 16 mois (0-53 mois) après la terminaison. Ces résultats suggèrent que la tuberculose pulmonaire devrait être incluse parmi les critères exigés pour le diagnostic du SIDA.

RESUMEN. Entre 1983 y 1989, atendimos a 56 pacientes con tuberculosis e infección por virus de la inmunodeficiencia humana (VIH). En 37 pacientes (66%), la tuberculosis se presentó antes que cualquiera otra enfermedad diagnóstica de SIDA (grupo 1): en 10 (18%), se presentó durante el mismo mes que cualquier otra enfermedad diagnóstica de SIDA (grupo 2); y en 9 (16%) después del diagnóstico de SIDA (grupo 3). La tuberculosis fue solamente pulmonar en 14 pacientes (25%), solamente extrapulmonar en 9 (16%) y tanto pulmonar como extrapulmonar en 33 (59%). La frecuencia de compromiso extrapulmonar fue similar en los pacientes del grupo 1 y de los grupos 2 y 3 combinados: 76% versus 74%. La biopsia hepática...
Tuberculosis is a frequent and important opportunistic infection in patients infected with the human immunodeficiency virus (HIV). Since 1987, extrapulmonary tuberculosis has been included among the criteria of the Centers for Disease Control (CDC) for the acquired immunodeficiency syndrome (AIDS). However, this created a distinction between pulmonary and extrapulmonary tuberculosis, which appeared arbitrary and was not clear cut in our experience. Therefore, the first aim of this retrospective study of 56 patients coinfected with HIV and Mycobacterium tuberculosis was to determine the proportion of patients with and without another AIDS-defining disease who developed extrapulmonary tuberculosis. The second aim of the study was to compare the time of onset of another AIDS-defining disease in patients with and without extrapulmonary tuberculosis. The third aim of the study was to evaluate the efficacy of a 1-year course of treatment for HIV-related tuberculosis.

PATIENTS AND METHODS

Study pattern

All patients seen in our Department of Infectious Diseases in whom the diagnoses of both HIV infection and tuberculosis were made between May 1983 and January 1989 were included in this study. Data were obtained from their hospital records.

HIV serological assays and HIV disease staging

All patients had serum antibodies to HIV type 1 by the enzyme-linked immunosorbent assay (Elavia) and by Western blot. The HIV disease was staged according to the criteria published by the Centers for Disease Control in 1987.

To compare the occurrence of tuberculosis with other HIV-related events, patients were divided into three groups: in group 1 tuberculosis occurred before any other AIDS-defining disease; in group 2 it occurred the same month as another AIDS-defining disease; and in group 3 it occurred after the diagnosis of AIDS. CD4 lymphocytes were counted at the onset of tuberculosis by immunofluorescence from 1983 to 1985, by immunogold method from 1985 to 1987, and by flow cytometry (FACScan, Becton-Dickinson) since 1987. These techniques yielded similar results (M. Levacher, S. Chollet-Martin. Laboratory of immunohaematology, Hôpital Bichat-Claude Bernard, Paris. Personal communication).

Diagnosis of tuberculosis

Diagnosis was established in all patients either by the identification of M. tuberculosis in one or more specimens, or by the presence of characteristic histological abnormalities. M. tuberculosis was sought in sputum and/or gastric fluid from all patients. For some patients, M. tuberculosis was sought in broncho-alveolar lavage, in urine, in cerebrospinal fluid or in biopsy samples from extrathoracic sites of suspected tuberculosis. Direct examination for acid-fast bacilli was made after Ziehl-Neelsen or auramine staining, and cultures were inoculated on Löwenstein-Jensen medium. Histological examination was performed on biopsy samples, with special attention being paid to tuberculoid granulomas and caseous necrosis. Needle biopsy of the liver was performed in cases of prolonged fever with weight loss, when the diagnosis had not yet been made by other means.

Serum transaminase (SGPT) and alkaline phosphatase levels were determined at the time that tuberculosis was diagnosed, and before antituberculosis treatment was begun.

Treatment and follow-up

In 1983, it was decided in our department to treat all cases of tuberculosis in HIV-infected patients for 1 year. Initial treatment was a combination of either 3 drugs, rifampicin, isoniazid and ethambutol, or 4 drugs with the addition of pyrazinamide. After 3 months, patients received only 2 drugs, usually rifampicin and isoniazid, for a further 9 months. After discharge, patients were followed as outpatients. The outcome of patients was determined up to January 1991.

Statistical analysis

CD4 lymphocyte counts were compared by means of
student's t-test. Comparisons of patients for levels of hepatic enzymes or sites of tuberculosis, were made by the chi-square test. Probabilities of occurrence of another AIDS-defining disease, according to the localization of tuberculosis, were compared by use of a log-rank test.

RESULTS

Patients

Among 421 patients infected with HIV who were hospitalized in our department during the study period, 56 (13%) had tuberculosis. They were 47 males and 9 females, with a mean age of 37 years (21–70 years). Risk factors for HIV infection were homosexuality in 20 patients, ethnic origin only in 15 patients (coming from pattern II endemic areas of HIV infection, according to World Health Organization definition), intravenous drug abuse in 11, blood transfusion in 6, and others in 4. There were 26 French patients and 30 (53.5%) foreigners to France: 10 were from Sub-Saharan Africa, 8 from Haiti, 8 from North Africa, 2 from Spain, 1 from Brazil, and 1 from Turkey. Two patients had a previous history of tuberculosis.

As shown on Table 1, most cases of tuberculosis (66%) occurred before any other AIDS-defining disease (group I). CD4 lymphocyte counts (Table 1) were not significantly different between patients with pulmonary or extrapulmonary tuberculosis.

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of patients (%)</th>
<th>No. of CD4 lymphocytes/mm³ Mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>37 (66)</td>
<td>251 (11-1363)</td>
</tr>
<tr>
<td>Group 2</td>
<td>10 (18)</td>
<td>189 (33-619)</td>
</tr>
<tr>
<td>Group 3</td>
<td>9 (16)</td>
<td>159 (8-561)</td>
</tr>
<tr>
<td>CDC group IV-C2</td>
<td>9 (16)</td>
<td>262 (38-743)</td>
</tr>
<tr>
<td>CDC group IV-C1</td>
<td>47 (84)</td>
<td>235 (8-1363)</td>
</tr>
<tr>
<td>Pulmonary tuberculosis</td>
<td>14 (25)</td>
<td>222 (10-743)</td>
</tr>
<tr>
<td>Extrapulmonary tuberculosis</td>
<td>42 (75)</td>
<td>243 (8-1363)</td>
</tr>
</tbody>
</table>

* Group 1: occurrence of tuberculosis before any other AIDS-defining disease.
Group 2: occurrence of tuberculosis simultaneously with another AIDS-defining disease.
Group 3: occurrence of tuberculosis after the diagnosis of AIDS.

CDC classification before and after the diagnosis of tuberculosis

In group 1, tuberculosis was the first symptomatic disease in 22 patients, and occurred in 15 patients already in CDC group IV-C2. In group 2, the other AIDS-defining disease was an opportunistic infection (CDC group IV-C1) in 9 patients, and was a Kaposi's sarcoma (CDC group IV-D) in 1 patient. In group 3, 8 patients were already in CDC group IV-C1 and 1 patient in CDC group IV-D for a mean period of 8 months (2-21 months).

After the onset of tuberculosis, only 9 patients of group 1 with pulmonary tuberculosis belonged to CDC group IV-C2. The 28 patients of group 1 with extrapulmonary tuberculosis moved to CDC group IV-C1. The 19 remaining patients of groups 2 and 3 belonged to CDC group IV-C1 (including the 2 patients already in CDC group IV-D).

Diagnosis of tuberculosis

This was confirmed by culture of M. tuberculosis in 46 patients, and by histological results only in 10 patients with extrapulmonary tuberculosis. Among the 46 patients with positive cultures, a positive histological result was also available in 16 of them.

The 10 patients with histological results only had prolonged fever and weight loss; 7 had a hepatic granuloma (including 1 with caseous necrosis), 1 had ascitis with granuloma and caseous necrosis on the peritoneal biopsy, and 2 had enlarged superficial lymph nodes containing granulomas and caseous necrosis. In these 10 patients, antituberculosis treatment led to resolution of fever in 2-5 days and to a rapid gain of weight. All 10 were cured without relapse.

Pulmonary tuberculosis

The X-ray films of the chest at the time of diagnosis showed a pulmonary involvement, compatible with tuberculosis, in 47 patients (84%). The pulmonary localization was proven in 39 patients by positive culture of sputum or gastric fluid (n = 34), or of bronchoalveolar lavage only (n = 5). Acid-fast smears were positive in 26 of these 39 patients (67%). In the 8 remaining patients with negative cultures of sputum, tuberculosis was proven in an extrathoracic site.

Extrapulmonary tuberculosis

The involved sites of the 42 patients with extrapulmonary tuberculosis are detailed in Table 2. Tuberculous hepatitis was proven in 18 patients (32%). The mean level of transaminases (SGPT) was 46 iu/l (10-114 iu/l) in patients with tuberculous hepatitis, and was 40 iu/l (7-250 iu/l) in the others (difference not significant). The mean level of alkaline phosphatases was 95 iu/l (34-282) in patients with tuberculous hepatitis and 102 iu/l (10-687) in the others (difference not significant). Among patients with tuberculous hepatitis, 8 had a normal level of SGPT, and 13 a normal level of alkaline phosphatases. Four of them had normal sized livers on ultrasonography, and normal liver function tests (Table 3).
Table 2. Extrapulmonary sites involved by tuberculosis in 56 patients (75%)

<table>
<thead>
<tr>
<th>First extrapulmonary site</th>
<th>No. of patients</th>
<th>Group 1*</th>
<th>Group 2</th>
<th>Group 3</th>
<th>With combined pulmonary involvement</th>
<th>With other extrapulmonary site(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>18</td>
<td>11</td>
<td>5</td>
<td>2</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Superficial lymph nodes</td>
<td>10</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Urine</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Mediastinal lymph nodes</td>
<td>5</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Meninges</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>42</td>
<td>28</td>
<td>10</td>
<td>4</td>
<td>33</td>
<td>19</td>
</tr>
</tbody>
</table>

* Groups 1, 2 and 3: see Table 1.

† Other extrapulmonary sites were superficial, mediastinal or abdominal lymph nodes; pleural or pericardial effusion; myocardopathy; bone marrow; urine; peritoneum; duodenum; jejunum; meninges; blood.

Table 3. Impact of the needle biopsy of the liver on the classification of cases in the 24 patients with clinical pulmonary tuberculosis and without evidence of extrapulmonary localization

<table>
<thead>
<tr>
<th>Patients with normal size of the liver and normal liver function tests</th>
<th>Patients with hepatomegaly and/or increase of transaminases</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>No. of biopsies positive for tuberculosis/no. of patients biopsied</td>
<td></td>
<td>4/12</td>
</tr>
<tr>
<td>No. of cases of entirely pulmonary tuberculosis after biopsies</td>
<td></td>
<td>14</td>
</tr>
</tbody>
</table>

Proportion of patients with pulmonary and/or extrapulmonary tuberculosis (Table 4)

At least one extrapulmonary lesion of tuberculosis was present in 28 of 37 patients (76%) in group 1, and in 14 of 19 patients (74%) in groups 2 and 3 (difference not significant). Extrapulmonary tuberculosis was diagnosed in 17 of the 26 French patients (65%), in 7 of the 10 patients from Sub-Saharan Africa (70%), in 7 of the 8 patients from Haiti (87%), and in 7 of the 8 patients from North Africa (87%), and in the 4 patients from other countries.

Probability of occurrence of another AIDS-defining disease in patients of group 1, according to the localization of tuberculosis

As shown in the Figure, the probability of developing an AIDS-defining disease other than tuberculosis after the onset of tuberculosis was not higher after extrapulmonary tuberculosis than after pulmonary tuberculosis. The mean delay to the occurrence of an AIDS-defining disease other than tuberculosis was 12 months (2-3-26 months) when tuberculosis was entirely pulmonary, and 10 months (2-26 months) when an extrapulmonary site was involved (difference not significant).

Treatment of tuberculosis

One patient died of *Pneumocystis carinii* pneumonia before antituberculosis treatment was started. The 5 other patients were treated. Two patients with severe tuberculosis died shortly after the beginning of antituberculosis treatment. Treatment was effective in the 53 other patients, with a marked improvement of signs and symptoms of tuberculosis in less than 2 months. During treatment, 8 patients were lost to follow up, and 10 died of causes other than tuberculosis.

Relapse of tuberculosis (Table 5)

Among the 32 patients who completed the 1-year treatment, 2 suffered a relapse during the follow-up period of 1 year to 18 months. The first relapse occurred in a patient from group 1, with 167 CD4 lymphocytes per mm², and with pulmonary and mediastinal tuberculosis; and the second occurred in a patient also from group 1, with 250 CD4 lymphocytes per mm² and...
with pulmonary tuberculosis. Both patients received 4
drugs for 3 months and rifampicin plus isoniazid for
the next 9 months. These 2 patients were seen every
month during the treatment period and seemed to be
compliant with treatment. All relapses were proven by
culture of M. tuberculosis that remained drug
susceptible.

Side-effects of antituberculosis treatment

Side-effects occurred in 21 of 55 treated patients (38%):
mainly isolated fever, febrile rash or increase of
transaminase levels. In 15 treated patients (27%), at
least 1 antituberculosis drug had to be permanently
discontinued, with a definite incrimination of the drug.
No side-effect was observed with ethambutol.

DISCUSSION

In this study, tuberculosis occurred before any other
AIDS-defining disease in 66% of patients, confirming
the early occurrence of tuberculosis during the evolution
of the HIV disease.13 15 We observed a pulmonary
localization of tuberculosis in 84% of patients and at
least one extrapulmonary site in 75% of patients. Thus,
the proportion of extrapulmonary tuberculosis was higher
in our series than in the literature where this proportion
varies from 14–70% of cases.13 16 17 with a recent report
of 62% of cases.13 This discrepancy could be due to the
frequent use of needle biopsy of the liver in our study.
This procedure led to the diagnosis of tuberculous
hepatitis in 32% of patients. This proportion is far higher
than in other reports 13 18 where liver biopsy was rarely
done. In contrast to previous reports, the frequency of
tuberculosis with an extrapulmonary site was similar in
patients who did or did not experience another AIDS-
defining disease: 76% versus 74%. Mean CD4
lymphocyte counts were similar when tuberculosis was
entirely pulmonary or when an extrapulmonary site was
involved: 232/mm³ versus 243/mm³.18 In our experience,
pulmonary and extrapulmonary tuberculosis occurred at
the same stage of the HIV disease. In a preliminary
report from 9 towns located in the south of France, no
difference was observed between pulmonary and
extrapulmonary tuberculosis in HIV-infected patients
(Dupon et al. Seventh International Conference on
in a recent American publication, where only patients
that reached the stage of AIDS were included, 71% of
the patients with a diagnosis of tuberculosis made prior
to any other AIDS-defining disease (group 1) had extra-
pulmonary tuberculosis (38% with entirely extrapulmonary
tuberculosis and 33% with both pulmonary and
extrapulmonary tuberculosis).13 In addition, the
modification of the CDC case definition for AIDS in
1987, including extrapulmonary tuberculosis in the
criteria of AIDS, led to an immediate increase of 24%

Table 5: Relapses of tuberculosis

<table>
<thead>
<tr>
<th>No. of relapses/ no. of patients</th>
<th>Duration of treatment, mean (range)</th>
<th>Delay between end of treatment and relapse, mean (range)</th>
<th>Follow-up after completion of treatment, mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>After premature discontinuation of treatment</td>
<td>4/4</td>
<td>3 months (1–6 months)</td>
<td>2 months (1–3 months)</td>
</tr>
<tr>
<td>After completion of a 12-month treatment</td>
<td>2/2</td>
<td>12 months</td>
<td>5 months, 36 months</td>
</tr>
</tbody>
</table>
of AIDS cases in Barcelona, Spain.12,16 This massive impact of the modification of the CDC case definition in a town where tuberculosis is a frequent opportunistic infection in HIV-infected patients demonstrates that extrapulmonary tuberculosis often occurs before any other AIDS-defining disease. Since, in recent epidemiological studies of HIV-infected patients, cases of extrapulmonary tuberculosis are systematically registered as cases of AIDS, the link between these two entities will be artificially strengthened. We suggest that the difference made between pulmonary and extrapulmonary tuberculosis is artificial, and that pulmonary tuberculosis should be included in the criteria for AIDS.

Antituberculosis treatment was highly effective in most patients. Side-effects of treatment were frequent, as already reported, leading to a permanent discontinuation of the responsible drug in 27% of patients.31 19, 20, 21, 22 Very little information was available concerning the frequency of relapse of tuberculosis after completion of treatment. Sunderam et al reported a relapse after a 6-month treatment.23 In a recent study, 3 of 58 patients (5%) suffered a relapse.13 In our study, with a longer follow-up of patients, only 2 of the 32 patients (6%) who completed the 1-year treatment suffered a relapse. Relapse was frequent in cases of poor compliance with premature discontinuation of treatment. The ideal duration of treatment remains to be determined.

Diagnosis of tuberculosis is often delayed in HIV-infected patients.24 In our experience, needle biopsy of the liver is of value for a rapid diagnosis of tuberculosis.

Acknowledgements

We thank Professors John F. Murray and Jacques Grosset for their constructive review of the manuscript, and Dr Franck Rousseau for statistical calculations.

References

AN OUTBREAK OF TUBERCULOSIS WITH ACCELERATED PROGRESSION AMONG PERSONS INFECTED WITH THE HUMAN IMMUNODEFICIENCY VIRUS

An Analysis Using Restriction-Fragment-Length Polymorphisms

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Abstract Background. Tuberculosis typically develops from a reactivation of latent infection. Clinical tuberculosis may also arise from a primary infection, and this is thought to be more likely in persons infected with the human immunodeficiency virus (HIV). However, the relative importance of these two pathogenetic mechanisms in this population is unclear.

Methods. Between December 1990 and April 1991, tuberculosis was diagnosed in 12 residents of a housing facility for HIV-infected persons. In the preceding six months, two patients being treated for tuberculosis had been admitted to the facility. We investigated this outbreak using standard procedures plus analysis of the cultured organisms with restriction-fragment-length polymorphisms (RFLPs).

Results. Organisms isolated from all 11 of the culture-positive residents had similar RFLP patterns, whereas the isolates from the 2 patients treated for tuberculosis in the previous six months were different strains. This implicated the first of the 12 patients with tuberculosis as the source of this outbreak. Among the 30 residents exposed to possible infection, active tuberculosis developed in 11 (37 percent), and 4 others (13 percent) had newly positive tuberculin skin tests. Of 28 staff members with possible exposure, at least 6 had positive tuberculin-react test reactions, but none had tuberculosis.

Conclusions. Newly acquired tuberculous infection in HIV-infected patients can spread readily and progress rapidly to active disease. There should be heightened surveillance for tuberculosis in facilities where HIV-infected persons live, and investigation of contacts must be undertaken promptly and be focused more broadly than is usual. (N Engl J Med 1992;326:231-5.)

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Results. Organisms isolated from all 11 of the culture-positive residents had similar RFLP patterns, whereas the isolates from the 2 patients treated for tuberculosis in the previous six months were different strains. This implicated the first of the 12 patients with tuberculosis as the source of this outbreak. Among the 30 residents exposed to possible infection, active tuberculosis developed in 11 (37 percent), and 4 others (13 percent) had newly positive tuberculin skin tests. Of 28 staff members with possible exposure, at least 6 had positive tuberculin-react test reactions, but none had tuberculosis.

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tions among the residents, but five of the staff members tested positive, whereas 10 weeks earlier they had been negative. No new cases of tuberculosis were identified.

RFLP Analysis

The RFLP patterns of the genomic DNA of *M. bovis* BCG, *M. avium*, *M. intracellulare*, and clinical mycobacterial isolates are shown in Figure 2 (for Patients 1 through 7 and 9 through 14; Patient 8 had negative cultures) and Figure 3 (random clinical isolates). The *M. bovis* BCG strain tested yielded an RFLP pattern containing two bands. However, other BCG strains have yielded from one to three bands under the same conditions. No *M. avium* or *M. intracellulare* restriction fragments hybridized with the *M. tuberculosis* probe. The mycobacteria isolated from the treated patients (Patients 1 and 2) had unique RFLP patterns, whereas those from the residents in whom tuberculosis was diagnosed between December and April had very similar patterns (Patients 3 to 14). The RFLP patterns of nine of the strains are identical. The slight difference in the patterns in Patients 9 and 11, as compared to the other nine patients starting with Patient 3, appears to be due to the movement of the insertion element. In contrast, all 13 randomly selected isolates of *M. tuberculosis* from San Francisco were found to have unique patterns (Fig. 3).

Demographic and Clinical Data

The mean age of Patients 3 through 14 was 37.2 years (range, 26 to 49). Eleven patients were men; 8 were white, and 4 were black; and 11 were homosex-

In summary, tuberculosis developed in 10 of 29 residents (34 percent) who were exposed to Patient 3 or Patient 4. Beginning with Patient 3, the rate of new infections was 37 percent (11 of 30 residents). Tuberculosis did not develop in any of 28 staff members with exposures, although there were 6 with documented tuberculosis conversions and 8 others had positive tuberculin reactions of unknown duration. Eight of the 12 cases occurred among the residents of the 13 rooms on the second floor. However, no specific features of the building's heating and ventilation system or of the residents' patterns of socialization were found to correlate with the risk of acquiring *M. tuberculosis*.

DISCUSSION

The outbreak of tuberculosis described in this report shows that in HIV-infected patients, recently acquired tuberculosis infections can progress rapidly to cause tuberculosis. This pathogenetic sequence can be inferred from the report by DiPerri and coworkers, who examined a nosocomial outbreak of tuberculosis among 13 HIV-infected inpatients, 7 of whom had active disease within 60 days of exposure to the index
patient. In the outbreak reported here, however, RFLP analysis was used to provide positive identification of strains and thus confirm that 11 patients had disease caused by a single strain. The contention that this outbreak represented a spread of infection from Patient 3 is strengthened by the failure to identify the same strain or similar strains among isolates from patients with tuberculosis selected at random from San Francisco at approximately the time of the outbreak. It is reassuring to note that isolates from the first two patients (Patients 1 and 2), who were being treated for tuberculosis when they entered the facility, bore no similarity to the strain associated with the outbreak. The finding that these two patients had unique RFLP patterns served to exclude them from consideration as sources and focused the investigation on Patient 3.

The usefulness of RFLP analysis as an epidemiologic tool has been suggested by work with other pathogens as well as with M. tuberculosis. Because this method yields a kind of “fingerprint,” strains can be tracked accurately. In the patients described in this report, nearly identical RFLP patterns were obtained with DNA probes derived from the insertion element IS986 (essentially the same as IS6110). The similarity of the RFLP patterns, the temporal association of the onset of disease, or both clearly indicate that Patients 3 through 14 were epidemiologically connected. The slightly different patterns in Patients 9 and 11, thought to be due to movement of the insertion element, could have been caused by the transposition of the insertion element in a proportion of the organisms, resulting in a more weakly hybridizing 6-kb band.

Two features of this outbreak were striking. The first was the extraordinarily large number of tuberculous infections resulting from the exposure. In the United States, approximately 30 percent of the close contacts of newly identified patients with tuberculosis have positive tuberculin skin tests, indicative of infection with M. tuberculosis, presumably acquired from the index patient. In this outbreak in which all residents and staff members could be considered to be close contacts, the incidence of new, active tuberculosis, and not just quiescent infection, was 37 percent among the HIV-infected residents, whereas no cases were identified among the staff members. The number of new infections among residents in whom the disease did not develop cannot be determined, because previous tuberculin-test results were generally not known. Given the high rate of anergy among the residents who did not have the disease (52 percent), it is likely that not all tuberculous infections were detected. However, of the 18 people in whom tuberculosis did not develop had positive reactions to purified protein derivative detected during the course of the outbreak investigation, for a minimal overall rate of tuberculous infection among exposed HIV-infected patients of 50 percent (15 of 30). Among the 28 staff members, 6 had tuberculin-test conversions, 3 were tuberculin-positive without previous testing, and 5 were known to have had previous positive reactions, for an overall prevalence of positive reactions of 50 percent by the end of the outbreak. On the basis of these data, and assuming an artificially low rate of positive skin-test results.

Table 1. Immunologic and Microbiologic Data on the Patients with Tuberculosis.*

<table>
<thead>
<tr>
<th>PATIENT NO.</th>
<th>TUBERCULIN TEST RESULTS</th>
<th>RESPONSE TO CONTROL ANTIGENS</th>
<th>COGAL- SG (+ PER MILL)</th>
<th>SPUTUM TEST RESULTS</th>
<th>CULTURE FOR M. TUBERCULOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>NA</td>
<td>12</td>
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*Plus signs denote positive tests, minus signs negative tests, and NA not available. Numbers in parentheses are the dates when the results were obtained.

* A positive test was defined as an induration of 10 mm or more in response to 5 tuberculin units of purified protein derivative.

A positive test was defined as an induration of 10 mm or more in response to either mycobacterial or candidal antigens.

Within 12 months of the beginning of the outbreak.
tests by the Mannox method, with 5 tuberculin units of commercial purified protein derivative of tuberculin (Aplud, Park-Davis, Morris Plains, N.J.). Intradermal tests for both mumps (40 colony-forming units per milliliter; Connaught, Swiftwater, Pa.) and candida (100 micrograms per milliliter; "O" 1.100; Miles, West Haven, Conn.) were administered to residents of the facility (all of whom were known to be infected with HIV). For persons whose initial tuberculin skin tests were negative, the tests were repeated approximately 10 weeks after the discovery of the 11th secondary case of tuberculosis in the facility. For each of the antigens, a reaction ≥ 3 mm of induration was considered positive.

The residents of the facility were also evaluated with standard frontal and lateral-view chest radiographs. The staff members of the facility underwent chest radiography only if they had positive tuberculin reactions. Persons with abnormal findings on chest radiographs were evaluated in a standard fashion, with specimens from the respiratory tract being submitted for acid-fast staining and mycobacterial culture, as well as for the identification of other respiratory pathogens. Standard laboratory procedures were used for the mycobacterial cultures, the determination of species, and testing of any organisms isolated for drug susceptibility.

A patient was considered to have tuberculosis if M. tuberculosis was isolated from any specimen or if there were symptoms and radiographic abnormalities of undetermined cause that responded to antituberculosis chemotherapy.

RESULTS

Investigation of Contacts

Thirty-one other residents were living in the facility when Patients 3 and 4 were living there. Of these 31, 18 were still living in the facility and had not yet been identified as having tuberculosis when the investigation of contacts took place. These 18 residents had tuberculin tests performed, of which 7 were positive and 1 was negative with positive control antigens. The remaining 10 residents were anergic. In addition, all the residents had chest radiography. Three of those with positive tuberculin reactions and two who were anergic were found to have tuberculosis (Patients 8, 9, 10, 11, and 12). None of the remaining 13 residents who were evaluated had evidence of active tuberculosis. All 13 were offered isoniazid, and 11 accepted this therapy.

The final patient with tuberculosis was identified on April 4. In the course of the investigation he was found to be anergic and to have a normal chest radiograph. Although preventive therapy with isoniazid was recommended, in consultation with his physician he decided not to take the drug, because of markedly abnormal liver-function tests.

Each of the M. tuberculosis isolates was sensitive to all the primary antituberculosis agents.

Fourteen of the 28 staff members who had potentially been exposed to 1 or more of the 14 patients were evaluated in the outbreak investigation, and 4 had positive tuberculin reactions, one of which was a documented conversion. Five staff members had previously documented positive tuberculin tests and were not tested. The remaining 19 staff members had negative tuberculin reactions (9 were tested by private physicians). No cases of tuberculosis were found among them.

Repeat tuberculin testing was performed in early June 1991 for the residents and staff who had negative reactions on initial testing. There were no new reac-
The second striking feature of this outbreak was the high percentage of exposed people in whom tuberculosis developed and the rapidity with which it did so. Usually, new tuberculous infections are quiescent, with clinically evident tuberculosis developing within the first year after infection in only 3 to 5 percent of persons who acquire new infections. It is estimated that another 3 to 5 percent of the infected persons in whom disease does not develop in the first year will become ill with tuberculosis at some point in their lives. The total duration of this outbreak (from Patient 3 to Patient 14) was 106 days, and in one patient (Patient 7) disease developed within 4 weeks of exposure. This rapid progression suggests that the organisms proliferated very rapidly without the usual inhibition from specific cell-mediated immunity. Although the data are not presented, the clinical manifestations of tuberculosis in this outbreak were essentially those of primary tuberculosis. These features have commonly been described among HIV-infected patients with tuberculosis and have generally been ascribed to the lack of an immune response in the host rather than to the actual presence of progressive primary infection.

This outbreak presents a number of implications for the control of tuberculosis in HIV-infected populations. Clearly, prompt and thorough investigation of contacts is exceedingly important when tuberculosis is diagnosed in a person who is in contact with HIV-infected persons, whether or not the source patient is HIV-infected. The usual criteria for judging an exposed person’s risk for acquiring tuberculous infection should be modified when that person is known or thought to be infected with HIV. In general, this will enlarge the scope of contact investigations.

In evaluating persons who are known or suspected to be infected with HIV and who are exposed to infectious tuberculosis, the value of skin testing with either tuberculin or control antigens is questionable. In this outbreak, little information was gained by skin testing. Among the patients, all the possible combinations of reaction patterns were found. Given a substantial exposure history, all the persons who have been in contact with the source patient, regardless of their skin-test reactions, should be offered preventive therapy with isoniazid if they have no clinical or chest radiographic evidence of tuberculosis. In view of the rapid progression from infection to disease, however, HIV-infected contacts must be carefully evaluated before preventive therapy with isoniazid is begun. If active tuberculosis has developed, treatment with isoniazid alone would be a major error. Besides the usual first step of tuberculin testing, persons with possible exposure should be asked about their symptoms and a chest radiograph should be obtained in those with HIV infection or at risk for it. If there is even suggestive evidence of active tuberculosis, therapy with multiple drugs should be instituted until the situation is clarified. It is noteworthy that Patients 1 and 2 came to the facility after receiving antituberculous therapy for a relatively short time, but they caused no secondary cases.

There should be heightened concern about the screening for tuberculosis of persons who are admitted to HIV care facilities, as well as the screening of employees. Moreover, surveillance for tuberculosis in such facilities should be maintained, and persons with suspicious symptoms should be evaluated promptly. The risks of acquisition of tuberculous infection should be made known to HIV-infected health care workers, and surveillance should be extended to them as well.

In patients with both tuberculous infection and HIV infection, limited data suggest that preventive therapy with isoniazid is effective. During this outbreak, tuberculosis did not develop in any of the residents taking isoniazid chemoprophylaxis. However, pulmonary tuberculosis did subsequently develop in one of the two patients who did not take isoniazid. At least in this outbreak, isoniazid seemed to be effective in preventing the rapid progression to tuberculosis.

We are indebted to Antonio Paz, Hourmephe Banouvung, Carlos Balladares, and Octavio Lumba for conducting the investigation of contacts; to Marilyn Girodo and Arthur Back for providing clinical isolates; to William Charney and Leonard Fisher for assessing the ventilation system; to Jack Crawford and Barry Bloom for their thoughtful comments; and to Peter M. Herman and Jan van Embden for providing pAL5000 DNA, as well as technical assistance and guidance with the RFLP analysis.

Not added in proof: One staff member whose tuberculin reaction had been negative on initial testing but was positive on retesting in June has been found to have pulmonary tuberculosis with positive spum cultures. The RFLP pattern of the organisms has not been determined as of this writing.

References

Hospital Infection

NOSOCOMIAL EPIDEMIC OF ACTIVE TUBERCULOSIS AMONG HIV-INFECTED PATIENTS

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Summary  In an investigation of a nosocomial outbreak of tuberculosis, 18 HIV-infected inpatients were found to have been exposed to Mycobacterium tuberculosis; active tuberculosis developed in 8, 7 within 60 days of diagnosis of the index case. The patients with lower total lymphocyte and CD4 lymphocyte counts were more likely to get the disease than were those with higher counts. A low score on multiple antigen skin testing was also associated with the development of active tuberculosis. 4 of the 18 patients had a positive tuberculin skin test before exposure to M tuberculosis; none of them subsequently got the disease.

INTRODUCTION

In the USA, an increase in cases of tuberculosis has coincided with the AIDS epidemic. Development of active...
tuberculosis in patients with human immunodeficiency virus (HIV) infection seems to be related to reactivation of a latent mycobacterial infection. That HIV-infected patients who have not had a previous tuberculous infection are less likely to get the disease was confirmed by Selwyn, who found that in HIV-infected drug abusers, the development of active tuberculosis was strongly associated with a previous positive tuberculin skin test.

We have recorded an outbreak of tuberculosis among HIV-infected patients in our hospital. We here evaluate some factors that predisposed to the development of the disease.

The Epidemic

We identified 18 HIV-infected patients who had been exposed to other patients with active tuberculosis. Complete medical records for the period preceding the epidemic were available for all patients since they had been previously seen on a monthly or bimonthly day-hospital basis. The index case, a 23-year-old male drug abuser, was admitted to our department with non-specific clinical features. He had fever and cough; blood gas estimation and chest radiograph were normal. Biopsy samples were taken by bronchoscopy, stained (Ziehl-Neelsen, gram, Giemsa, and Grocott-Gomori), and cultured for mycobacteria and for other organisms (bacteria, fungi, cytomegalovirus). Acid-fast organisms and other pathogens were not detected. Blood cultures, and analysis and culture of cerebrospinal fluid were negative. 28 days later Mycobacterium tuberculosis was grown on specific culture medium and antituberculous therapy was then started. Because of the low frequency of tuberculosis in AIDS in Italy and elsewhere in the world and because there could have been more plausible explanations for such a clinical picture, empirical therapy was not given before confirmation of diagnosis. Moreover, in the past 4 years, we have seen only 3 cases in a local population of more than 600 HIV-infected subjects.

Several other patients had at some time shared a room with the index patient. In our department most of the beds are grouped in rooms of four, a bathroom is shared by two rooms, and the recirculated air is not filtered. 20 days after the first diagnosis, another patient with tuberculosis was identified, followed shortly by 2 more. Within 60 days of diagnosis of the index case a total of 7 additional patients with active tuberculosis were seen; M tuberculosis was grown from 5, and in 2 the organisms were seen only in acid-fast smears. 1 patient had extrapulmonary tuberculosis (with hepatic, pericardial, and peritoneal involvement); in the others the clinical, microbiological, and radiographic findings were consistent with pulmonary involvement only. In these 6 patients there were none of the classic signs such as cavitation, and diffuse pulmonary infiltrates (with evidence of consolidation in 1 patient only) were the most common presentation. In all patients the response to treatment with rifampicin, isoniazid, and ethambutol was excellent, 6th defervescence usually within a week and chest radiographic improvement within a month.

The mean lymphocyte count of those who did not get active tuberculosis was 1221 (SD 729) compared with 708 (247) in those who had the disease (p < 0.04). Likewise, there was a pronounced difference in mean CD4 lymphocyte count (562, SD 339 vs 232, 143; p < 0.01). 4 patients had a previous positive tuberculin test; active tuberculosis did not develop in any of them whereas 7 of 14 who were tuberculin-negative had the disease (p < 0.1). Similarly, 4 of 5 patients who had no reaction to multiple antigens had active tuberculosis compared with only 3 of 13 patients with some response (p < 0.05). 25 members of the hospital staff came into contact with either the index case or the other 7 patients with tuberculosis. However, data about tuberculin test conversion among the staff are misleading because most of them had been given the Bacille Calmette-Guerin vaccine. 4 months after the diagnosis of the final case, pulmonary tuberculosis developed in a nurse, and the antibiotic susceptibility pattern of the isolate grown from her sputum was similar to the epidemic strain. Since there had been no cases of tuberculosis among members of the hospital personnel in the previous 10 years, an association with the above cases seems to be likely. Additionally, 9 volunteers also took care of the HIV-infected patients with tuberculosis; baseline medical records were available for 7, including the results of previous tuberculin skin tests, which showed that only 1 was positive. Of the 6 volunteers with a previously negative tuberculin test, 4 had a documented conversion (induration > 10 mm diameter), which further supports the occurrence of nosocomial spread of M tuberculosis.

Discussion

We believe that this was an epidemic of active tuberculosis rather than the reactivation of latent infection. First, the spatial and temporal clustering of so many cases suggests that there is an association since there were no cases of tuberculosis among HIV-infected individuals who were admitted to our department at the same time but to a different ward (upstairs). Second, during the time in which all cases were identified, the frequency of tuberculosis of 35% among all patients in our department with full-blown AIDS seems to be much higher than expected. The similarity of the antibiotic susceptibility patterns also suggests that this cluster of cases was transmitted from a common-source exposure. Finally, as soon as we had realized what was going on, and had separated patients from suspected contacts, no new cases were diagnosed over the following 4 months.

Even though a positive tuberculin test was non-significant, this response, together with high total lymphocyte and CD4 lymphocyte counts, probably indicates that the patient will be protected against the development of active tuberculosis during close exposure to M tuberculosis. Selwyn and colleagues assessed the chance of getting tuberculosis as the result of a progressive deterioration of the immune system in previously infected patients. In their study, a positive tuberculin test pointed to previous exposure to M tuberculosis; thus, reactivation of the disease would be more likely in patients with a positive tuberculin test than in those with no evidence of previous exposure. By contrast, in our patients a tuberculin response probably points to the expression of an immune surveillance system that it still functioning. This hypothesis is supported by the immunological features of the tuberculin-positive patients. Moreover, 1 of the patients was tuberculin-negative before the epidemic and later had a positive reaction without any evidence of disease.

After the onset of the AIDS epidemic, great attention was paid to the risk of acquiring HIV infection in the care of infected patients. Little importance was attached to the chance of contracting associated infections because most of the AIDS-related opportunistic infections very seldom cause symptomatic disease in immunocompetent healthy people. However, tuberculosis should be highlighted since it is probably the most hazardous for hospital personnel.

This epidemic raises some concern about the organisation and management of hospital wards for patients with HIV infection. Lately, a possible association between cough-inducing procedures and transmission of M tuberculosis in health clinic settings and development of active tuberculosis after close exposure to the organism among HIV-infected inmates of the New York State prison have also been described. These reports add to the evidence that transmission of the disease was nosocomial and also stress the difficulties in management of this problem, because of delay in diagnosis. Our experience may be useful for the
Timing of antituberculous chemoprophylaxis for HIV-infected patients; current Centers for Disease Control guidelines recommend isoniazid for those who are tuberculin-positive, irrespective of their immune status. Our findings suggest that indices such as total lymphocyte count, CD4 lymphocyte count, multiple antigen skin testing score, and tuberculin test together are better than tuberculin test alone to estimate the right time to start antituberculous therapy. Reliance on tuberculin status alone, may lead to long-term administration of a drug which is ineffective. Moreover, individuals who are taking other drugs (eg, antiretroviral agents) are more likely to get a toxic reaction and also often have a liver dysfunction.

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REFERENCES