Aspects of mycobacterial disease in Ghana. Studies on tuberculosis and Buruli ulcer in Agogo Hospital, Ashanti
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Tuberculosis remains one of the major scourges affecting mankind, and there is probably no other pathogen causing as many deaths as \textit{M tuberculosis}. It has been estimated by WHO experts that today, 3 million people, most of whom live in the developing countries die every year due to tuberculosis. Eighty percent of these premature and preventable deaths occur in the economically most productive age groups (15–60 years). In this age group tuberculosis accounts for more than one-quarter of the total number of avoidable deaths. The annual risk of tuberculosis infection in the world is highest in sub-Saharan Africa, with an estimated number of diseased persons of 126 per 100,000. In Africa alone, 660,000 are believed to die annually from tuberculosis. Tuberculosis control programmes are now considered the most cost-effective health interventions. It is generally accepted that for a tuberculosis control programme to be effective in any given area, operational studies into drug resistance and patient compliance are necessary.

In contrast to these considerations however, tuberculosis control has enjoyed relatively low priority in health management planning in Ghana, and there were no data available on primary drug sensitivity of \textit{M tuberculosis}, except data of more than 20 years ago, from the Chest Clinic of the Korle Bu Teaching Hospital in the capital Accra.

Drug resistance was therefore studied as described in chapter II, in patients, presenting with tuberculosis, who claimed not to have received previous anti-tuberculous chemotherapy. The drug resistance found in this study was referred to as “initial,” i.e., drug resistance found among patients believed to be naive for anti-tuberculous drugs. The possibility that some of these patients had acquired drug-resistant bacilli through inadequate earlier treatment cannot be ruled out. The level of initial drug resistance is however more relevant than the level of “true primary” drug resistance, as those managing a tuberculosis control programme are faced with the problem of initial drug resistance. The incidence of initial drug resistance to isoniazid (27%), streptomycin (23%) and thiacetazone (29%) was such that, from the \textit{in vitro} data, it was concluded that standard chemotherapy as proposed by the health authorities in Ghana and as taught in the medical schools of Kumasi and Accra is no longer effective. In addition, \textit{in vivo} data supported this finding in that there was a small sub-group out of these patients, who could not receive other than these three standard drugs; six of these 13 patients appeared to have resistant bacilli and four of these six patients failed to respond to therapy.
and three of these four patients died before rifampicin and pyrazinamide became available. It was therefore concluded that it was possible to perform reliable in vitro testing by cryo-preservation of sputum specimens, and that the in vitro results were clinically relevant.

Default is generally believed to be the most important determinant of success in tuberculosis control. Every country, every ethnic group and every society have their own culture and peculiarities which one should know before an effective control programme can be designed, as a Ghanaian proverb says: ahohoa te se abofra (the stranger is like a child). Chapter III describes two different studies into factors that may influence patient compliance with therapy. First, the data-base of patient records was analysed. Home-to-clinic distance, one of the main determinants in compliance, was also found to influence the outcome in the tuberculosis patients attending the Agogo Chest Clinic in general. In tuberculosis patients from the Ashanti-Akim district however, no such relation could be found. In the district, an intervention programme with home visits made regularly by extension workers appeared to disrupt the home-to-clinic distance effect on patient compliance, and indeed, the differences found could equally well be explained by the presence of this programme in general. Men were generally less compliant than women; the effect of age on compliance was less important, young male patients appeared to do slightly better but these patients came more often from the district. In a second study, two questionnaires were held among patients attending the Chest Clinic in Agogo, the first one in 1985 when also a limited number of defaulting patients were interviewed in their homes, while the second questionnaire was held in 1987, without home visit interviews. There appeared to be a significant improvement in the knowledge of patients about how and when to take their drugs in the two years lapsed between the two questionnaires. Social disruption and social stigmatisation was less important than economic problems inflicted by the disease. Expenses paid for transport to the hospital were often higher than the hospital charges for treatment. A low educational level was not associated with poorer compliance, the trend was rather the opposite. In conclusion, the liaison work improved patient compliance significantly, despite the fact that this system of home-visits paid by liaison workers, who had very limited medical knowledge and education, was still rather poorly functioning. It is therefore strongly recommended to train and employ liaison workers for rural African tuberculosis programmes as it is cheap and cost-effective, as well as practicable.

In the past, the role of surgery in pulmonary tuberculosis, even in Agogo Hospital, was important, as until the 1970s, thoracoplasty was performed in those patients who failed to improve on chemotherapy alone. Recently, resection therapy for multi-drug resistant pulmonary tuberculosis has been recommended and reported to yield bacillary remissions with satisfactory clinical results in the United States of America.
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results in the United States of America, but this approach is not recommended for rural hospitals with limited facilities in Africa In Chapter IV, eight patients, retrieved from the Operating Theatre records, are reported with pulmonary tuberculous complicated by broncho-pleural fistula, as evidenced by an air-fluid level in one hemithorax at fluoroscopy. The outcome of treatment by simple closed chest drainage with an underwater-seal suction system was evaluated, and found not to differ significantly from non-complicated pulmonary tuberculosis. As much more sophisticated, and equally more hazardous interventions have been proposed to treat this complication this simple and effective method is recommended for rural African hospitals.

In Chapter V, serologic studies are reported. Sera were sampled and kept frozen for analysis in Dutch research laboratories. In the first serologic study, sera of tuberculosis patients, healthy controls and a limited number of patients suspected to have AIDS, were analysed for the presence of antibodies to HIV-1 and HIV-2, by immunoblot analysis. Of 53 tuberculosis patients, seven appeared to be co-infected with HIV-1. One of the apparently healthy control subjects had HIV-2 antibodies. All of the AIDS suspects had antibodies against HIV-1, HIV-2 or both. Dual infections with both retroviruses have been documented by viral genome isolation, but are considered rare, and the relatively frequent serologic evidence of dual retroviral infections is believed to be an immunologic cross-reaction. The second serologic study was performed to assess the usefulness of an Enzyme-Linked Immuno-Sorbent Assay (ELISA) for the detection of IgG antibodies directed against the A60 antigen of *M. bovis BCG* for the detection of tuberculosis in rural Africa. In the non-AIDS infected groups, a specificity of 86% and a sensitivity of 78% was found, comparable to reports by other groups. In the HIV-infected groups however, the test failed to discriminate between tuberculosis and non-tuberculosis. Further studies are required to test the hypothesis that co-infection with HIV results in a defective antigen presentation and CD4+ helper cell function for an effective and measurable *de novo* humoral immune response to the A60 antigen, possibly along with other antigenic epitopes of *M. tuberculosis*.

Chapter Va contains an argument against a paper by Dr Wilkins and Professor Ivanyi in the Lancet. These authors claimed to have found a highly reliable serologic test for the detection of active tuberculosis, with a specificity of 97.6% and a sensitivity of not less than 78%. Such results for a serodiagnostic test would be a major break-through in the field of serodiagnosis. Unlike their claim in the paper however, inactive tuberculosis was ignored in the control group, and, had these patients been included, their results would have been far less conclusive. The authors admitted in their reply that the inactive tuberculosis patients had been left out, but claimed that only patients who had been treated for tuberculosis in the past would have affected the specificity of their test.
In conclusion, no serodiagnostic test has been published that can detect tuberculosis reliably in patients with an uncertain history of previous tuberculosis treatment, and co-infection with HIV still adds to the confusion about the usefulness of sero-diagnosis in tuberculosis. Whether the use of mycobacterial antigens secreted by life bacilli might overcome the problem of discriminating active from extinct tuberculosis,\textsuperscript{24} as has been tried recently,\textsuperscript{25} deserves further evaluation.\textsuperscript{26} Like leprosy, tuberculosis is a disease with an immune spectrum.\textsuperscript{27} Possibly, serodiagnosis may eventually be useful as a complementary test to Tuberculin skin testing.\textsuperscript{24} There is however increasing evidence\textsuperscript{28} that antigen detection will prove superior to antibody detection in the diagnosis of tuberculosis.

Around 1980, Professor E.H.O. Parry, then Dean and professor of Medicine at the Medical School, University of Science and Technology in Kumasi, visited Agogo Hospital and saw patients with large ulcerative lesions with extensive necrosis of subcutaneous tissues, and postulated that these lesions might be due to \textit{M. ulcerans} infections. In 1986, a retrospective study was begun, using Operating Theatre data to retrieve all patients from 1980 onwards with clinically diagnosed \textit{M. ulcerans} infections, and 45 such patients were studied. Most cases came from the area north of Agogo, towards the Afram plains, a hardly accessible area with mud roads with vegetation not unlike the riverine areas from where \textit{M. ulcerans} infections have been reported.\textsuperscript{29} In the next one and a half year, another 51 patients were seen and studied prospectively, and biopsies were taken to obtain histopathology, while from five of 26 attempts, culture of \textit{M. ulcerans in vitro} was achieved, using the same cryo-preservation technique as used in the \textit{M tuberculosis} cultures.

In children, who wear clothes less often than adults, the trunk was significantly more affected compared to adults, and there was a significant preponderance of ulcers at the right arm; in adults, who use more often a cutlass, the left leg was significantly more often affected. These localisations support the theory that infection takes place near the ground, at those sites that are most exposed to environmental vegetation: the common stance in farming for adults is with the left leg forward, while children use the right hand predominantly when they help their parents in farming. Among the Ashanti, the use of the right hand is a cultural imperative. If a Ghanaian would offer something using his left hand, he would use the standard phrase of politeness: kafra me binkom (excuse my left). There are no new facts reported to support the possibility of other modes of transmission, eg, by skin-to-skin contact from one person to another,\textsuperscript{30} although such transmission has been reported in the literature.\textsuperscript{31}

Chapter VIa contains an argument against the view that skin-to-skin contact would be an important mode of transmission of \textit{M. ulcerans} infection. Our view was supported by a similar Letter to the Editor from Australia.\textsuperscript{32}

Buruli ulcer is a devastating condition causing extensive lesions and complications with 17 contractures and loss of an eye in two patients in this series.
Chemotherapy using anti-leprosy and anti-tuberculosis drugs have been tried without beneficial results. In Agogo, no clear beneficial effects have been observed either, so that only extensive and mutilating surgery with split-skin grafting could eventually heal the patients, at the cost of long hospital admissions, of almost three months on average. Research and development of a chemotherapeutic treatment for this subcutaneous infection is urgently needed.