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CHANGING SCENE OF CHEST DISEASES

The intimate connection between the heart and lung is well known and has been well documented. Not so well known, however, are other late complications of relatively chronic lung diseases which may not kill the patient who undergoes proper treatment. The two commonest chronic respiratory ailments in this country are Bronchitis and Tuberculosis. The specialists in chest diseases and the generalists are fully aware of the frightening complications of Chronic Bronchitis, in the form of emphysema, chronic respiratory failure (CRF) and cor pulmonale, apart of course, from the fact that this condition is characterised by an inexorable downhill slide of the unfortunate victim.

In the case of Respiratory Tuberculosis, however, the scenario is different. Not only is it easily curable but modern chemotherapy has also made it possible now to sterilise the lesions. This has led to a situation where the treating physician and even the specialist has gone into a state of complacency- There is a tacit assumption that once you have given your patient an adequate course of chemotherapy, there is nothing more to be done.

This would certainly be the case if the patient is diagnosed and put on treatment early enough. Unfortunately, the only definitive method of diagnosis of Pulmonary Tuberculosis, available to most of us, is the sputum smear—a notorious late comer. In a situation where the overwhelming majority of patients first report to a Chest Clinic/Physician when the disease is well established, less than half of such cases are found smear positive (after the most careful search for the bacillus) and only about a tenth where the search is less stringent. The lung tissue has already suffered destructive change when chemotherapy is instituted. It has also to be remembered that chemotherapy can only eliminate the infecting agent. Repair of the destruction suffered by the tissues of the host is dependent on the body's own mechanisms, and cannot restore the original architecture. The repair process ends in fibrosis, bronchial distortion and bronchiectasis, or in epithelialisation of cavities which do not close, depending upon the original extent of, and destruction caused by, the disease. Sometimes vast areas of the lung are rendered incapable of participating in oxygen exchange and shunts develop through the bronchial vasculature, shunting unoxygenated blood into the systemic circuit. Secondary infections are frequent in the damaged bronchial tree, with resultant hypoxia, pulmonary hypertension and cor pulmonale. The hypoxia may be severe enough to be crippling, resulting in a state of C.R.F. Even the left side of the heart may suffer severe damage due to poor oxygen delivery to the myocardium and anaerobic metabolism and acidosis. If fibrosis has involved the

mediastinum, strangulation of the main veins can, and does, occur. The arteries supplying the imperfectly healed areas may undergo dilatation and develop aneurysms, resulting in massive haemoptysis. The fibrosis and epithelial metaplasia, part of the healing process, may not get arrested, and actually undergo malignant change.

A 5-13 year follow up of over 900 patients who had received adequate (even excessive) conventional anti-tubercular drugs and had their sputum converted over long periods, revealed a sorry state as far as patient well being is concerned*. Only 11% of these patients remained in good health. Radiologically significant residual lesions were seen in 40 %, of these cases, and almost all of them had one or more complications, such as repeated respiratory infections, respiratory insufficiency, C.R.F., recurrent and sometimes massive, haemoptysis, cor pulmonale etc. A recent report from the same Centre, on the results of short course chemotherapy, revealed that residual lesions were still as frequent. Another study, as yet unpublished, reports the diagnosis of 9 cases of bronchopulmonary malignancies among treated cases of proved pulmonary tuberculosis.

The conditions enumerated above, and elsewhere in this issue, were almost unknown in pre-chemotherapy era. The patient then, simply did not live long enough. The incidence of these complications, at present, is high enough to make all respiratory physicians sit up and take notice. We have seen that these untoward sequelae occur principally among patients who came with advanced disease, and those left with significant residual lesions. Early diagnosis, early institution of effective chemotherapy, and elimination of resectable residual lesions by surgery, would certainly help to mitigate the problem. We have to make up our minds whether we want to treat the patient, or only the tubercle bacillus.

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ADULT RESPIRATORY DISTRESS SYNDROME (ARDS)

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ARDS represents a final common pathway of injury due to a variety of massive, often unrelated insults to the lungs, resulting in respiratory distress, decreased pulmonary compliance and severe arterial hypoxaemia along with acute diffuse infiltrative lung lesions. It is a form of acute respiratory failure with noncardiogenic pulmonary oedema (Fein et al, 1982; Petty and Fowler, 1982; Rinaldo and Rogers., 1982; Tranbaugh and Lewis, 1982; Bernard and Brigham, 1985).

The awareness of Adult Respiratory Distress Syndrome can be traced to World War II but the magnitude and nature was appreciated in Vietnam War. Soldiers with nonthoracic injuries were treated and sent to regional hospital where during convalescence unexpectedly life threatening respiratory distress occurred. Lungs seemed to be full of water. It was called 'wet lung', 'shock lung' or 'Da-Nang lung' - the site of hospital in Vietnam. Various synonyms (Wilson and Bone, 1979) for ARDS are given in Table I.

The term was coined (Ashbaugh et al, 1967) due to clinico-pathologic similarities with infantile respiratory distress syndrome (IRDS). However, in infants, the alveoli are small, the chest wall is highly compliant, distending pressure at the end of expiration is small and these combined with lack of decrease in surface tension at the alveolo-capillary membrane leads to atelectasis which is characteristic of IRDS, while, in ARDS, diffuse injury to pulmonary capillary membrane leads to increased permeability and pulmonary edema. The surfactant deficiencies are secondary to diffuse lung injury in ARDS in contrast to a deficiency of surfactant as primary etiology in IRDS. Similar clinical profile of ARDS may result from different specific conditions which may require specific diagnostic and therapeutic measures. Thus, this term may obscure clinically important differential diagnosis with serious, therapeutic implications. Therefore, specific etiologic conditions should always be retained with this diagnosis. The term ARDS emphasises the respiratory element of the syndrome but conceals the fact that there is extensive damage throughout the body (Wallace and Spence, 1983).

Etiology : ARDS occurs following a variety of catastrophic events which represent risk factors (Table II). These include shock, overwhelming infections, trauma, aspiration and damage due to various drugs and physiochemical agents. More and more specific entities are being recognized to be associated with ARDS. Some risk factor for the development of ARDS are more likely to produce the syndrome than other. A recent study suggested that sepsis syndrome results in development of ARDS in 36 % whereas less than 1%, of patients undergoing cardiopulmonary bypass, develop ARDS (Demling, 1980; Modig, 1980; Pope et al, 1983).

Pathogenesis : Different noxious stimuli produce uniformly diffuse damage to alveolo-capillary membrane. Damage to either alveolar or capillary surface of this membrane can produce ARDS (Fig. I). Diffuse alveolar injury i.e. to alveolar lining cell, type I alveolar cell results from contact with toxins like gasses hydrocarbons or gastric acid. Diffuse capillary endothelial injury is probably the commonest mechanism of ARDS. Implicated humoral and cellular mechanisms of capillary endothelial injury are :

1. *Neutrophil injury* : Oxygen free radicals, proteases, arachidonic acid metabolites, platelet activating factor.
3. *Arachidonic acid metabolite injury* : Leukotrienes, thromboxanes, prostaglandins.
4. *Others* : Serotonin, bradykinin, histamine, B-endorphin, complement, platelets, free fatty acids.
5. *Direct injury* : Gastric acid, hyperoxia toxins

Neutrophil injury

Th polymorphonuclear neutrophil, by producing potentially toxic mediators of injury, plays a central role in the genesis of certain forms of ARDS. Fowler et al (1983) and Fowler et al (1983) demonstrated large numbers of

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TABLE I
Synonyms for ARDS

Acute respiratory distress in adults
Adult hyaline membrane disease
Bronchopulmonary dysplasia
Congestive atelectasis
Da Nang lung
Hemorrhagic atelectasis
Hemorrhagic lung syndrome
Hypoxic hyperventilation
Noncardiogenic pulmonary edema
Oxygen toxicity
Post-perfusion lung
Post-transfusion lung
Post-traumatic atelectasis
Post-traumatic pulmonary insufficiency
Progressive respiratory distress
Pulmonary contusion
Pulmonary microembolism
Pump lung
Respiratory insufficiency syndrome
Respirator lung
Shock lung
Stiff lung syndrome
Transplant lung
Traumatic wet lung
Wet lung
White lung syndrome

neutrophils in bronchoalveolar lavage taken from ARDS patients. Neutropenic animals fail to develop capillary leak when confronted

only increased in number but also are in metabolically active state and produce proteases and oxygen metabolites that are toxic to the lung (Fantone and Ward, 1982). The complement system involvement in human ARDS was first recognized by Hammerschmidt et al (1980). Patients with the active syndrome had elevated levels of the cleavage product of the fifth component (C5-a) in plasma (Haynes et al, 1980). It summoned neutrophils to the pulmonary vascular bed and stimulated them to release many factors including oxygen free radicals, proteases, arachidonic acid metabolites and platelet activating factor (AGEPC). It appears that during sepsis, granulocytes become activated by bacteria and in their attempt to destroy bacteria release oxygen radicals and proteolytic enzymes that can severely damage the pulmonary endothelium and the pulmonary interstitium (Bernard, 1983). The proteases so released activated Hageman factor and its associated coagulation pathway. Platelet activating factor released from neutrophils causes platelet and neutrophil activation, smooth muscle constriction and increased vascular permeability.

Coagulation product injury

Saldeen (1976) demonstrated the presence of platelet-fibrin microemboli in the post-mortem sections of the lungs of patients of ARDS. The extrinsic and intrinsic coagulation cascades are activated by endotoxemia, Hageman factor, collagen exposed due to damaged endothelium and released thromboplastin and proteases from degenerated leucocytes. The fibrin-degradation product, 'D' antigen is increased in ARDS. Since activation of intravascular coagulation causes complement activation, both fibrin entrapment and complement mediated leuco-aggregation may contribute to development of ARDS following pulmonary intravascular coagulation (Malik et al, 1982).

Arachidonic acid metabolite injury

Neutrophils, platelets and pulmonary endothelial cells are all potential manufacturers of arachidonic acid metabolites. They cause vasoconstriction (prostaglandins E₂, I₂ and H₂ and thromboxane A₂), increase pulmonary vascular permeability (leukotrienes, C₄, D₄, and E₄) and bronchoconstriction. Certain metabolites of arachidonic acid have protective effects also. The prostaglandin I₂ has a vasodilator, antiplatelet aggregating, membrane stabilizing and antineutrophil aggregating properties.

Thus, a catastrophic clinical setting activated complement cascade or the coagulation pathway. This leads to leucostasis and leucocyte

TABLE II

Disorders Associated with ARDS

<i>Shock</i>	<i>Physiochemical</i>	<i>Miscellaneous</i>
Septic	Inhaled toxin (NO ₂ , MB, Cl ₂ , MIC, Cadmium, phosgene, smoke, O ₂)	Amniotic fluid embolism
Haemorrhagic	Pancreatitis	Bowel infarction
Cardiogenic	Smoke-inhalation	Carcinomatous lymphangitic
Anaphylactic	<i>Drugs</i>	Dead fetus, eclampsia
<i>Infections</i>	Chlordiazepoxide	Post-perfusion lung
Bacterial pneumonia	Colchicine	Radiation pneumonitis
Gram negative sepsis	Dextran 40	Thrombotic-thrombocytopenic purpura
Tuberculosis-miliary	Ethchlorvynol	Acute leukemia
Viral pneumonia	Fluorescein	Disseminated intravascular coagulation
Fungal and pneumocystis carinii pneumonia	Heroin	Postcardio-version
<i>Trauma</i>	1 leukoagglutinin reaction	
Burns	Methadone	
Fat embolism	Nitrofurantoin	
Fractures	Paraquat toxicity	
Head trauma	Propoxyphene	
Lung contusion	Salicylates, Thiazides	
Nonthoracic-trauma	<i>Metabolic disorders</i>	
<i>Aspiration</i>	Diabetic ketoacidosis	
Gastric acid	Uraemia	
Near drowning		

entrapment in fibrin matrix. The aggregated neutrophils release proteases, oxygen free radicals and other substances which caused further lung injury and attracted more neutrophils. This in turn perpetuated complement activation and coagulation pathway and synthesis of more arachidonic acid metabolites—a vicious cycle (Diagram I).

Pathophysiology

Diffuse pulmonary injury, whether the primary lesion is alveolar or vascular, results in increase in capillary permeability and extravasation of fluid ensues with initial accumulation in lung interstitium then into alveoli. Alveolar filling causes increased surface forces and

alveoli collapse diffusely over entire lung. Surfactant is necessary for normal pulmonary function. In ARDS, surfactant is aggregated, oxidized and non-functional and results in stiff (low compliance) lungs with areas of atelectasis and alveoli filled with fluid. The terminal bronchiole may also be the site of increased permeability (Bone, 1979).

Ventilation perfusion mismatch interferes with CO₂ elimination and causes an increased A-aO₂ difference. Areas of lung with high V/Q result in an increased physiological dead-space. The functional residual capacity is decreased in ARDS secondary to microatelectasis and edema. Failure of minute ventilation

to increase will result in increase in PaCO₂. The lung volumes are reduced due to fluid-filled alveoli, atelectasis, compression of alveoli by interstitial edema and increased surface tension due to decreased surfactant production and its inactivation. The decreased compliance is due to active bronchoconstriction and interstitial and alveolar edema. There may be airway obstruction by edema and debris also. In addition, loss of hypoxic pulmonary vasoconstriction may contribute to severe hypoxemia (Lamy et al, 1976; Snapper et al, 1983).

Profound arterial hypoxaemia is a diagnostic criterion of ARDS. Ventilation perfusion

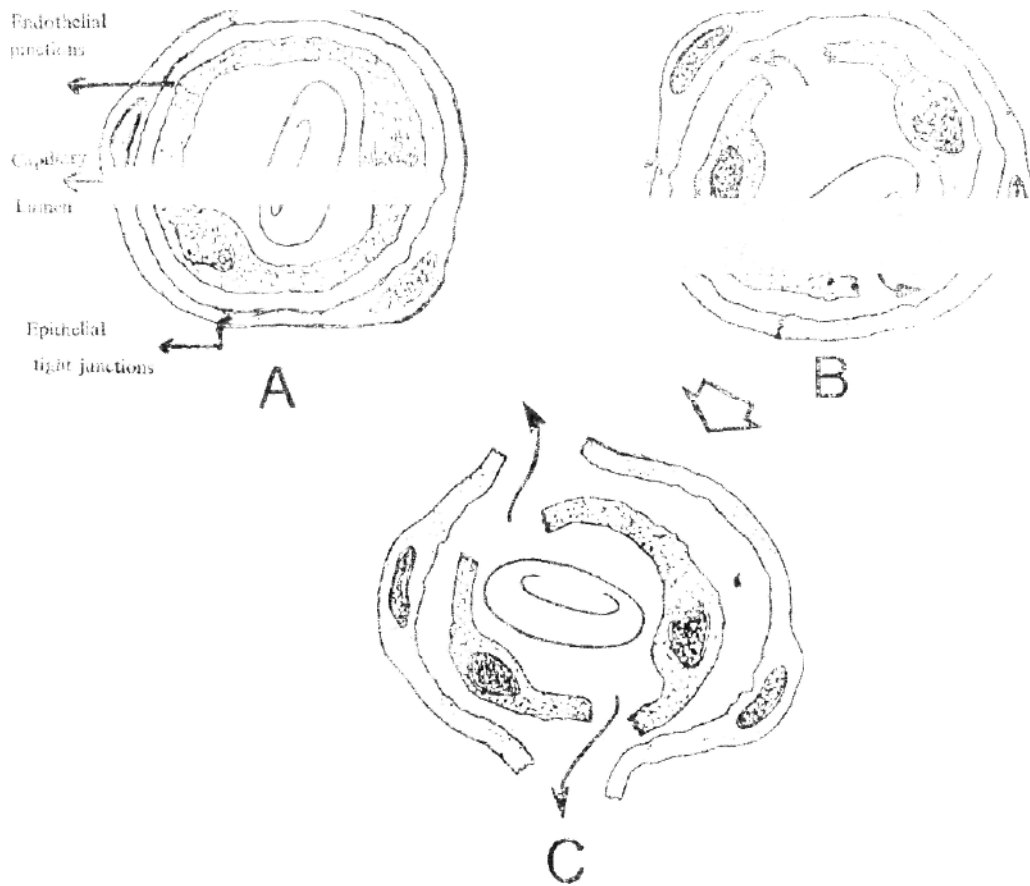


Fig 1.

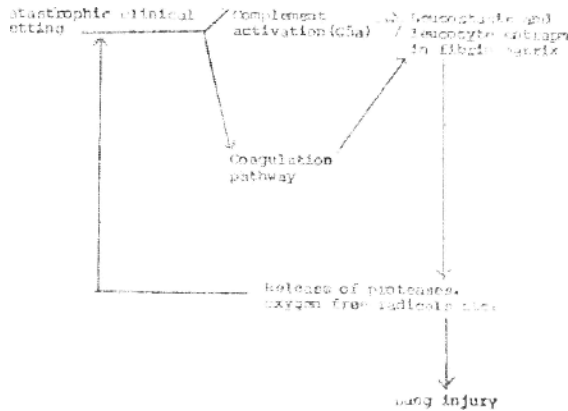
Showing the Site of injury in acinus in ARDS.

- A. Intact cell junctions of capillary endothelial and alveolar Type I epithelial cells.
- B. Loose junctions of capillary endothelial cells have separated, with escape of plasma into the interstitial space.

Tight junctions of alveolar Type I epithelial cells have separated, with escape of plasma into the alveolar space.

Diagram 1

HYPOTHESIZED VICIOUS CYCLE

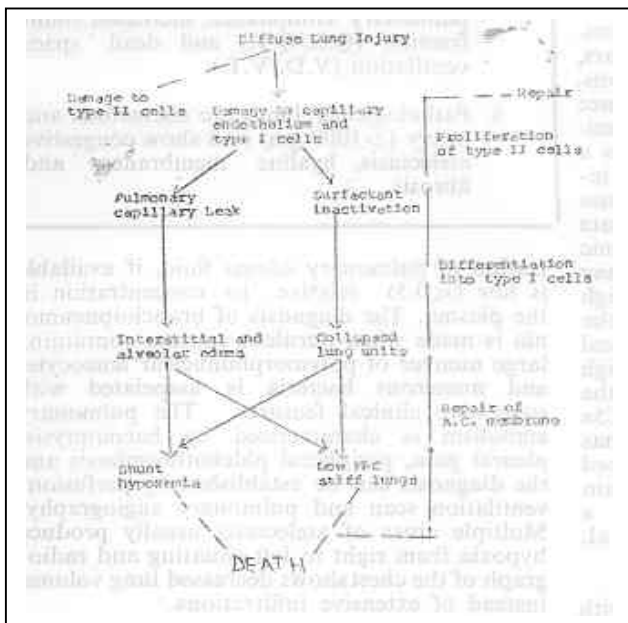


mismatch and right to left shunt mechanisms, of arterial hypoxaemia

atelectasis (Diagram 2).

Diagram 2.

PATHOPHYSIOLOGY OF ARDS



Pathology: Lungs are heavy, airless, congested and do not collapse when thorax is opened.

Pathological features include damage to type I alveolar epithelial cell, protein rich interstitial and alveolar edema and small thrombi in pulmonary vasculature (Phase I of injury) (Bachofen and Weibel, 1982). The alveolar

spaces are non-homogenously filled with a proteinaceous, often haemorrhagic, fluid. White blood cells, macrophages, cell fragments, amorphous material, protein, fibrin strands and remnants of surfactant are also present along with an occasional hyaline membrane. Later in course, hyaline membranes, marked, capillary congestion and pulmonary edema are seen (Phase I; early progressive phase, 4-5 days of insult). Subsequently, edema and hyaline membranes decrease and interstitial fibrosis, localized primarily in alveolar ducts occurs with an increase in number of cuboidal epithelial cells (type II pneumocytes). Thus, interstitial thickening occurs (Phase III; Late Progressive phase-- beyond ten days). Finally, lysis of interstitial fibrosis by alveolar macrophages with improvement in pulmonary function (Phase IV of recovery).

Clinical features: ARDS can affect all ages but usually healthy young people are afflicted. Once a patient has been exposed to the pulmonary insult, there is a latent period that can range from minutes to days (usually 18 to 24 hours) before frank respiratory symptoms develop. It is important for the physician to be aware of ARDS risk factors so that patients can be closely observed during this latent period.

No matter what the cause, clinical course is characterised by 4 stages: (1) Injury (2) Apparent stability (3) Respiratory insufficiency (4) Terminal stage. During initial injury there are usually no evident clinical signs and chest-x-ray may be clear. This stage usually lasts for as long as 6 hours.

Hyperventilation and abnormalities on x-ray and on clinical examination are seen in second stage of apparent stability. Tachypnoea is often the first sign. Approximately 12-24 hours after injury, x-ray shows fine reticular infiltrates representing perivascular fluid accumulation and interstitial edema.

During the next 12-24 hours - phase of respiratory insufficiency—patient is in obvious respiratory distress with laboured breathing, tachypnoea, possibly central cyanosis, crackles and rhonchi and severe hypoxaemia despite high inspired oxygen concentrations. Patient has tachycardia, gallop-rhythm, engorged veins, cardiomegaly and clinical differentiation from cardiogenic pulmonary edema is extremely difficult. X-ray chest reveals a diffuse, 5-lobed alveolar and interstitial infiltrate. Terminal phase is characterized by persistent hypoxaemia (despite 100% O₂) and CO₂ retention. Similar features, with some variation, are observed

During the 'shock-lung' which are as follows

Phase I: Traumatic shock necessitating resuscitation, blood and plasma infusion: spontaneous hyperventilation and hypocapnia (no hypoxaemia). This is followed by stabilization of circulation and respiration.

Phase II: Early respiratory distress and V/Q imbalance. Hypoxaemia accompanied by 10-20% pulmonary AV shunting, hyperventilation and hypocapnia.

Phase III: Hypoxia necessitating mechanical ventilation. Alveolar infiltrates on radiograph.

Phase IV: Terminal hypoxia and hypercarbia (greater than 30% AV shunting).

Diagnosis

The diagnosis of ARDS is easier when all the characteristic clinical, radiographic, laboratory and physiological abnormalities are present (Table III) but it may remain extremely obscure when various features are evolving in seriously ill patients, ARDS occurs following a catastrophic injury or risk factors. Usually after a latent period of 12 to 48 hours, laboured breathing, intercostal retractions, tachypnoea due to decreased lung compliance and gas transfer abnormalities become manifest. The radiograph of the chest shows a characteristic diffuse and rapidly progressive infiltrate which is interstitial at first and becomes bilateral, often symmetrical alveolar infiltrate

Cardiogenic edema is usually associated with cardiac enlargement, heart murmur, gallop-rhythm and raised jugular venous pressure. The radiograph of the chest shows parahilar butterfly pattern of pulmonary edema including pleural effusions and prominence of pulmonary lymphatic channels often called 'Kerley lines'. However, the most sensitive method is to demonstrate raised pulmonary capillary wedge pressure (>16 mm Hg.) The protein concen-

TABLE III

Diagnostic Criteria of ARDS

First four criteria are mandatory to make diagnosis of ARDS:

1. Clinical setting of a pulmonary or nonpulmonary catastrophic event (e.g. sepsis, aspiration) with respiratory failure.
2. Exclusion of cardiogenic pulmonary edema or chronic pulmonary disease as the main cause of respiratory failure.
3. Clinical respiratory distress with tachypnoea (>20/min, usually greater), laboured breathing with hypoxaemia and possibly central cyanosis when breathing air.
4. Diffuse pulmonary infiltrates on chest X-ray: Interstitial (initially), alveolar (later).
5. Physiologic measurements: PaO₂ <50 mmHg with FiO₂ > 0.6, reduced pulmonary compliance, increased shunt fraction (Q.S./Q.T.) and dead space ventilation (V.D./V.T.).
6. Pathologically, lungs are edematous and heavy (>1000 gm) and show congestive atelectasis, hyaline membranes and fibrosis.

tration of pulmonary edema fluid, if available is low (<0.5) relative to concentration in the plasma. The diagnosis of bronchopneumonia is made when purulent sputum containing large number of polymorpho nuclear leucocytes and numerous bacteria is associated with suggestive clinical features. The pulmonary embolism is characterized by haemoptysis, pleural pain, peripheral phlebothromboses and the diagnosis can be established by perfusion-ventilation scan and pulmonary angiography. Multiple areas of atelectasis usually produce hypoxia from right to left shunting and radiograph of the chest shows decreased lung volumes instead of extensive infiltrations.

Management: Since the mortality of ARDS patients is in excess of 50% in most studies, regardless of treatment, prevention becomes of a paramount importance. Prophylaxis especially during the period between the insult and the onset on ARDS is important because treatment at this stage is more likely to succeed than after ARDS becomes manifest.

Coping with initiating mechanisms

Prompt pain relief and restoration of blood-pressure and urine flow are important prophylactic measures in preventing ARDS. Antibiotics should be given for specific identified infection and not prophylactically as this does not prevent bacterial colonization or invasion. Sepsis remains a problem even if antibiotics are used liberally in clinical setting (Clowers, 1974). These patients are so fragile that turning or even auctioning them can cause hypotension and arrhythmias. In case of low cardiac output, inotropic agents like Dopamine are helpful. However, a combination with drugs like sodium nitroprusside which promote peripheral dilatation, may aid in tissue perfusion and oxygen delivery even with a low left ventricular pressure (Wood and Prewitt, 1981). This lowers the pulmonary microvascular pressure and despite the increased capillary permeability of ARDS, might minimize the extravascular water and protein accumulation in alveolar spaces.

Fluid management

In severely hypotensive and hypovolumic patients, fluids should be given carefully avoiding overloading. This is best done by recording pulmonary capillary wedge pressure (PCWP) with balloon tipped Swan Ganz Catheter. PCWP should be as low as is compatible with reasonable cardiac output and blood pressure, in view of leaky alveolo-capillary membrane. Moreover, fluid retention may occur via excessive antidiuretic hormone activity when the patient is on ventilator management (Saldeen, 1976). The choice of fluid replacement is controversial. Earlier albumin replacement was advised in these patients with interstitial edema and hypo proteinemia. However, administered colloid may lead into interstitial and alveolar spaces (Appel & Shoemaker, 1981; Holcraft & Trunkey, 1974), and further complicate the problem. Thus, crystalloids are used first and diuretics like furosemide may be used if there is evidence of fluid, overload.

Oxygenation

Primary aim is to maintain adequate oxygen delivery at the lowest inspired fraction of oxygen (Fig2). as oxygen toxicity can itself aggravate ARDS. Safe levels of P_{iO_2} in ARDS is around 0.5 to 0.6 (with greater than 0.6 injury usually occurring after 24-48 hours and at 1.0 in 12-24 hours), the oxyhaemoglobin dissociation curve shows that at P_{aO_2} of 60 mmHg, haemoglobin is 90% saturated. Thus, this is a reasonable objective, as higher levels add little to oxygenation and introduced risk of oxygen toxicity.

In early stages, O_2 supplement with nasal, canulae or Mask is enough to raise P_{aO_2} greater than 60 mmHg. When, concentrations greater than 50%, are needed, endotracheal intubation is usually indicated. In this latter group of patients inadvertent removal of the oxygen mask can cause serious complications and the use of PEEP is indicated; both necessitate the use of endotracheal tube. As a rule, mechanical ventilation is required in ARDS. Moreover, the respiration of the patient may be fast due to reflexes received from intrapulmonary receptors, stimulated by collapse of lung units and a low functional residual capacity.

Mechanical ventilation with tidal volume of 12 to 15ml/kg/body weight and respiratory rate of 12/minute is required when there exists:

1. a respiratory rate of greater than 30 to 35;
2. an a/A ratio of less than 0.35 or A-a O_2 difference greater than or equal to 350 while breathing F_{iO_2} of 1.00);
3. respiratory acidosis with $pH < 7.35$ ($P_{aCO_2} > 45$);
4. tidal volume less than 3.5 ml/kg (by bed-side spirometry) or physiological dead space tidal volume ratio greater than 0.5.

Synchronous intermittent mechanical ventilation (SIMV), is the most popular mode as the patient assumes a proportion of the work of breathing. This may help to reduce mean intrathoracic pressure and minimize hypocarbia. The major disadvantage of this mode is that it sometimes require the patient above that delivered by the ventilator which is unassisted.

'Assist control' is another widely used mode of ventilation. However, the patient may easily exceed the ventilatory output set on the machine by creating a small negative airway pressure. Theoretical possibility of hyperventilation by the patient exists in this mode of ventilation. If P_{aO_2} is still less than 60 mm Hg on F_{iO_2} of 0.6 consider introducing PEEP (Positive End Expiratory Pressure) usually 5-15 mm H₂O PEEP acts by increasing lung volumes, functional residual capacity and opening extra alveolar vessels open, that otherwise may be closed due to oedema. All this improves oxygenation.

Optimal Level of PEEP is one that provides greatest delivery of oxygen to tissues at minimum F_{iO_2} and thus prevents or delays

any further oxygen induced pulmonary damage. PEEP should be increased in increments of 3-5 cm H₂O with careful monitoring and using volume infusions and inotropic agents as necessary to maintain adequate O₂ delivery with FiO₂ not greater than 0.5-0.6. This must be empirically determined in each patient at bedside clinically (skin temperature, cyanosis, features of cerebral hypoxia etc.) and also by measuring lung compliance, maximally obtainable reduction in venous admixture (shunt should be reduced to 25% or less) and by measuring mixed venous PO₂ (MVO₂) by flow directed Swan-Ganz catheter. The latter is the index of efficacy of entire therapeutic regimen as it reflect, oxygen delivery to tissues and hence cardiac output too. A low value (less than 20 mmHg) certainly indicates tissues hypoxaemia irrespective of measured cardiac output and Pao₂. However high value does not exclude serious tissue, especially in gram negative Septicaemia where systemic low resistance shunts develop leaving several capillary beds unperfused. A fall in mixed venous PO₂ while increasing PEEP, indicates decrease in cardiac output which more than offsets any increase in PaO₂ and tissue oxygenation goes down.

High levels of PEEP can decrease cardiac output (due to impeded systemic venous return and geometric changes and intraventricular septal shift decreasing cardiac compliance), impaired left ventricular function, increased chances of barotrauma (pneumothorax, pneumomediastinum) increased extravascular lung water and may sometimes cause a paradoxical decrease in PaO₂ (Qvist et al, 1975; Robotham et al, 1980). PEEP may be given early in high risk patients to prevent ARDS and later (late PEEP) to improve the survival. Today, early PEEP is much more rewarding than the later PEEP (Weigelt et al. 1979; Petty and Fowler 1983).

In patients with adequate ventilatory reserve (Vital capacity greater than 8 ml/kg) who can spontaneously maintain satisfactory PCO₂, continuous positive airway pressure (CPAP) is probably preferable to PEEP as patients are more comfortable and mean airway pressures lower and thus less chance of barotrauma.

Extracorporeal membrane oxygenators (ECMO) have been used where maximal PEEP with FiO₂ of 1.0 does not supply adequate oxygen. A randomized large multicentric trial with 90 patients showed that though it can support gas exchange there was no difference in survival. Thus, experience with this mode of oxygenation has been disappointing (Zapol and Snider, 1980),

Discontinuation of mechanical ventilatory support

Ability of patient to maintain adequate gas exchange without ventilator is heralded by a decreasing FiO₂, requirement of smaller inflation pressures for mandatory or assisted breathing and spontaneous respiratory rate of less than 30 per minute, spontaneous tidal volume of > 8 ml/kg, vital capacity of > 15ml/kg and ability to generate static inspiratory pressure >30 cm H₂O. Despite this, some patients cannot sustain themselves for prolonged periods; so, multiple weaning trials are carried out. Respiratory muscle exercise by synchronised intermittent mandatory ventilation or assisted control ventilation is helpful in increasing patient's respiratory self-sufficiency.

Inhibition of amplification response by corticosteroids

Steroids may prevent complement mediated leucocyte aggregation and superoxide damage to endothelial cells. Capillary permeability following sepsis may be reduced following the use of methyl prednisolone (Coffin et al, 1975; Brigham et al, 1981; Schonfeld et al, 1983).

If methylprednisolone is used, doses should be 30 mg/kg for 1-2 days, given at onset of disease.

Assessment of the patient

Base-line arterial blood gases and chest roentgenograms may be obtained to detect early manifestations of ARDS.

I. *Oxygenation* : Since the level of arterial oxygen varies with concentration of oxygen inspired; a/A O₂ ratio (or A-a O₂ difference) is a better method of assessment of oxygenation especially for patients on ventilators. For example, a patient with a baseline PaO₂ of 60 mmHg on 21 % inspired oxygen concentration has a PaO₂ of 100 mmHg on 40 % oxygen. Is the patient better or worse ? 'A' is the alveolar O₂ and is determined by the following equation:

$$A = FiO_2 (PB - PH_2O) - 1.2 PaCO_2 \\ = FiO_2 (700) - 1.2 PaCO_2$$

$$\text{At } 21\% A = .21 (700) - 1.2(40)$$

$$= 99 \quad a/A \text{ Ratio} = 60/99 = .61$$

$$\text{At } 40\% A = .4(700) - 1.2(40)$$

$$= 232 \quad a/A \text{ ratio} = \frac{100}{232} = .43$$

Thus, the patient is worse than before though arterial PaO₂ is high. The smaller the a/A ratio, the worse is the patient's gas status, reflecting a poor overall oxygen transfer between alveoli and blood.

11. Hemodynamic monitoring : The decision between cardiogenic and noncardiogenic pulmonary edema and hemodynamic situations are best decided by the use of flow-directed Swan-Ganz catheter. A pulmonary capillary wedge-pressure of less than 15 mmHg indicates noncardiogenic origin and wedge pressures of less than 5 mmHg indicate that the patient is hypovolemic/hypotensive. The cardiac-output can also be measured as it is equal to the oxygen consumption divided by the arterial content minus the mixed venous content for oxygen.

$$\text{Cardiac out-put} = \frac{\text{O}_2 \text{ consumption (ml/min)}}{\text{arterial O}_2 \text{ content} - \text{venous O}_2 \text{ content (ml/100)}}$$

Oxygen content is proportional to the amount of hemoglobin in grams/100 ml of blood multiplied by the oxygen saturation of the hemoglobin in percent i.e.

$$\text{Oxygen content} = \text{Hgb} \times \text{Hgb saturation.}$$

The oxygen dissociation is a sigmoid shaped curve and indicates that the PaO₂ in excess of 85 mmHg adds little additional oxygen to the blood while a fall below 50 mmHg leads to large reduction in oxygen content.

The trend of cardiac output can be assessed by estimating mixed venous oxygen tension (PV0₂). If the arterial P0₂ is relatively constant, a decrease in the PV0₂ implies that the cardiac output has fallen and tissue perfusion being inadequate, more oxygen per unit time has been extracted from the blood. When PV0₂ is less than 25-30 mmHg, it indicates tissue oxygenation problems.

Complications

Multi-organ failure and ventilatory and intensive care setting in the management of ARDS can lead to many complications (Pingleton, 1982). Pulmonary complications include pulmonary embolic disease which is difficult to diagnose without a pulmonary angiogram (Table IV). Prophylactic low-dose heparin decreases the incidence of pulmonary emboli (Pingleton et al, 1981). Pulmonary barotrauma includes pneumothorax, pneumomediastinum and subcutaneous emphysema. High inflation

pressures during the use of volume ventilators, high levels of PEEP, high tidal volumes, necrotizing pneumonias and bronchoscopy during mechanical ventilation may lead to barotrauma (Bone et al, 1976).

Gastrointestinal hemorrhage, a fatal complication can be averted by the prophylactic use of antacids (Kahn et al, 1981). Cardiac complications include arrhythmias, hypotension and low cardiac output. Although use of flow-directed balloon-tipped Swan-Ganz catheters can monitor these complications but it may itself be arrhythmogenic. Renal failure and nosocomial infection may be associated with increased mortality in ARDS.

Anticipation of complications, use of prophylactic measures and intensive management is vital for patient management.

Prognosis

ARDS carries a mortality in excess of 50 and it has not changed much in the last decade in spite of important developments in intensive care monitoring and organ support devices. The prognosis, however, depends upon the effectiveness of therapy, of syndrome, or

py and the p

absence of complications and unrelated diseases. Once the patient with ARDS survives pulmonary function may return to near normal in 85 % of patients. Residual sequelae (diffusion

Future

Cyclo-oxygenase blockers, antioxidants (superoxide dismutase, Vit. E) prostaglandin inhibitors (indomethacin, ibuprofen), prostacyclin fission etc. and similar compounds are some of the current approaches under test. Monoclonal antibody technology may be used to prevent neutrophilic aggregation in response to C5a and other chemoattractants. Artificial surfactant might be delivered by inhalation or intravenously as liposomes.

There is also a need to find a marker for ARDS to help identify patients likely to develop ARDS-D-Dimer, a fibrin degradation product is one such possible marker. Evidence of complement activation may also serve as a marker. As life-support systems alone cannot stem the death-toll, innovative pharmacologic approaches must be tested, including possibly multidrug regimens each aimed at a specific pathophysiologic process known to be operating in these patients.

Complications Associated with ARDS

Pulmonary emboli
Pulmonary barotrauma-pneumothorax, pneumomediastinum
Pulmonary fibrosis
Pulmonary complications of ventilatory and monitoring procedures
Mechanical ventilation:
Right main stem intubation
alveolar hypoventilation
Swan-Ganz Catheterization:
Pulmonary infarction
Pulmonary haemorrhage
<i>Gastro-intestinal</i>
Haemorrhage
Ileus
Gastric distension
Pneumoperitoneum
Renal
Renal failure
Fluid retention
<i>Cardiac</i>
Arrhythmia
Hypotension Low cardiac output
<i>Infection</i>
Sepsis
Nosocomial pneumonia
<i>Hematologic</i>
Anaemia
Thrombocytopenia
Disseminated intravascular coagulation
<i>Others</i>
Hepatic, endocrinal, neurological, psychiatric and oxygen toxicity.

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PATHOGENESIS OF COR RCILMONALE IN PULMONARY TUBERCULOSIS

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Summary : A study of the relevant literature on Chronic Cor Pulmonale (CCP) as a complication of Pulmonary Tuberculosis reveals that this complication, infrequent in the pre-chemotherapy era, is now encountered frequently in treated patients. The literature on pathogenesis of Chronic Cor Pulmonale has been critically reviewed and it has been concluded that repeated secondary infections in residual bronchial distortions, cavities and other fibrotic healed lesions play a decisive role in the development of this condition. A short note on the clinical application of the pathology of healing has also been included.

Introduction

Although it was recognised even as far back as the 19th century that myocardial damage can be found on autopsy in patients dying of pulmonary tuberculosis, clinically diagnosable Cor pulmonale was rarely seen as a complication of chronic Pulmonary Tuberculosis.

Huriez (1934) and Brumfiel (1933, 1943) have described circulatory disorders in cases of Pulmonary Tuberculosis, but without CCF. There have been few reports about the occurrence of CCF in such cases in the prechemotherapy era. Nemet and Rosenblatt (1937) saw Right Ventricular hypertrophy (RVH) in 33 of 71 autopsies in patients dying of pulmonary tuberculosis, but the heart, significantly, did not show increase in weight. The clinical features were dyspnoea in 91%, cyanosis 70%, neck vein engorgement 33%, hepatomegaly 42% and moderate leg odema in 45%. but no ascites. They could not clinically label even one third of these cases as having cardiac involvement, as alternative explanations were possible. White (1947) has stated that it is rare to see any deleterious effect of extensive tuberculosis on the heart and even less common to get right ventricular failure. As late as 1951, Bjorkman reported only 7 patients with moderate Right heart strain pattern and one with a definite P pulmonale in serial ECGs on 476 patients of pulmonary tuberculosis. Even cardiac catheterisation did not reveal any significant pulmonary hypertension, and pathological studies by Berblinger (1947), and by Higgins (1944), did not reveal any significant pulmonary vascular disease, although they did find RVH in 56% and 40% of their autopsies, respectively.

After the advent of chemotherapy, however, Cor pulmonale began, slowly, to be recognised as a complication in the living

pulmonary tuberculosis. Even in the early era it had been mentioned as occurring, although rarely, in tuberculosis patients who had undergone extensive thoracoplasty etc. However, the first authentic report in a clinical series was by Samuelson (1952) who found that 45 of his patients had this complication. Walzer and Frost (1954) reported an autopsy series in which 60 % of cases of Cor pulmonale were ascribed to pulmonary tuberculosis, and 51 % of pulmonary tuberculosis cases had RVH, while Kozłowski and Maldyke (1955) had full-fledged Cor pulmonale in only 10 of their autopsies on such subjects, against 81 % histological cardiac damage. Corbetta, Pozzi and Scoccia (1955) concluded that early stages of Cor pulmonale were very common in Pulmonary tuberculosis, finding diagnostic ECG change in 43 % of their patients. In this country also, Cor pulmonale had rarely been diagnosed in cases of pul. tuberculosis as can be seen from the reports by Malhotra (1962) and Padmavathi and Pathak (1959). However a Tuberculosis Hospital reported the presence of this complication in 1959 (Kapoor 1959) and a series of 200 cases was reported in 1962 (Kapoor 1962). This complication was seen to occur in 17 of 100 patients of pul. tuberculosis lying in hospital wards on a single day. Subsequently, Padmavathi and Mishra (1969) reported tubercular aetiology in 32 out of 454 cases of Cor pulmonale (7 Y.). Vishwanathan (1969) had similar findings. However, studies carried out among tuberculosis patients again revealed a heavy incidence of Cor pulmonale, e.g., 15.8% by Agarwal et al. (1978) or even 47.5% by Chatterjee et al. (1971). We had reported on 51 cases of Cor pulmonale (Kapoor, Radhakrishnan and Ganesan, 1979) diagnosed from among 279 consecutive admissions into the Tuberculosis ward-an incidence of 18%. This incidence is of the same level as in case of Bronchiectasis and more frequent than in C.B.E. (11 %) and Bronchial Asthma (4%) (Kapoor 1962).

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Pathogenesis

The pathogenesis of Cor pulmonale has been attributed to different factors by different authors, coloured principally by the material studied by them. Even the proportion of various respiratory diseases contributing to its development, as given by different workers, varies widely. To add to the problem, most of the pathological information is from necropsies, not a very reliable indicator of dynamic processes. Biopsy and other studies in the living have been rather few and far between and again have been biased by the material. tuberculosis, being usually treated in specialised hospitals which deal with no other disease, naturally suffers from this bias. However, the pathology of Cor pulmonale in pulmonary Tuberculosis can confidently be stated, based on the work of numerous authors. In brief, the condition is characterised by a selective right ventricular hypertrophy, with relative thickening of the wall and increased rugosity of the musculature without a definite enlargement or increase in heart weight. The earliest and maximum hypertrophy is seen in the outflow tract. The right atrium also shows some thickening with thicker muscular ridges. The above is reflected in the ECG by right atrial dominance in the form of P Pulmonale and inconstant, not very frequent, patterns of right ventricular hypertrophy or bundle branch block. However, vector cardiogram shows a type C RVH pattern, which is characteristic of outflow tract hypertrophy. This also explains the frequent absence of this pattern in scalar ECG, its appearance being dependent upon right ventricular potentials being sufficiently powerful to damp the normally more powerful left ventricle potentials (Radhakrishnan et al, 1979). Although, some authors have postulated about shrinkage of vasculature in the lesser circulation, no definite evidence of vascular hypertrophy has, so far, been adduced (Bjorkman loc cit). However, it would be obvious that, in a destructive disease like tuberculosis, quite a large proportion of the pulmonary vasculature can be destroyed as part of the general destructive process.

The development of Cor pulmonale has been described as secondary to Pulmonary Hypertension. Although all workers are unanimous on this, it is but fair to point out that, among the meagre Cases of cor pulmonale submitted to right heart and pulmonary artery catheterisation, a few odd cases have been noticed where the pulmonary artery pressures were normal or only mildly elevated.

Pulmonary hypertension, in turn; has been attributed among other things, to extensive blockage of pulmonary vascular bed and its destruc

tion and restriction, with consequent impairment of gas exchange, hypoxia and hypercapnoea (Richard and Fishman 1956). Kapoor (1959, 1962) suggested that repeated secondary infections play a dominant role, through raised cardiac output with impairment of gas exchange due to blockage of respiratory passages by exudate and secretions. It is a well known fact that pulmonary tuberculosis, after chemotherapy, frequently leaves a residue of bronchiectasis and bronchial distortion (Mukhopadhyaya 1974) or even the open negative cavity, which are very liable to

repeated secondary infections (Amarchand et al. 1979). The same workers have also reported that Cor pulmonale is about 4 times as frequent (as a late complication) in patients with residual so called 'solid lesions' than in those whose roentgenograms cleared after chemotherapy. It has also been noticed by almost all authors who have reported cases of pulmonary tuberculosis with Cor pulmonale, that the complication was noticed most frequently in those with a disease history of 3 to 5 years. The above evidence would certainly lend support to the above argument. However, it certainly cannot be called conclusive evidence.

In order to verify the above hypothesis, a study was undertaken in 1978 at Perambur Railway Hospital, and findings were presented at the 6th Asia Pacific Conference on Diseases of the Chest (Kapoor, Radhakrishnan and Ganesan 1979). It would probably be worthwhile to reproduce some of the material presented there.

Extent of lung disease (when CPP was diagnosed)

Minimal	11	22%
Moderately advanced	16	
Far advanced	24	

Incidence of CCP in chronic respiratory failure

No. of patients with C.R.F.	40
Evidence of Rt heart disease	18
No. evidence of Rt heart disease	22

Secondary infections and respiratory failure in CCP

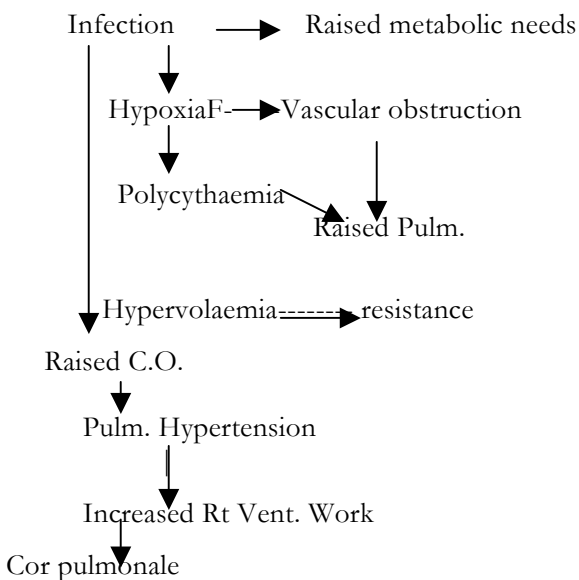
	Cor
Pulmonale	
Sputum above 100 ml/day, multiple or giant cavities, Bronchiectasis etc.	45(80%)
No evidence of severe secondary infections	6 (12%)
Respiratory insufficiency	26(52%)
PaO ₂ within normal	25
Total cases	51

Kapoor had reported (1959) that more than 1/3rd, of cases had disease occupying less than one lobe, and only 1/4th had involvement of area greater than one lung. In the above series also, after a lapse of 20 years, and in a different geographical situation, less than half the cases are seen to have far advanced disease, while as many as 22 % showed minimal lung field involvement. Two of the latter patients showed almost clear lung fields on plain skiagraphy. This would suggest that extent of disease and, as a corollary, shrinkage of pulmonary vascular bed, do not play a significant role in the pathogenesis of Cor pulmonale. A glance at the above statistics would provide a convincing argument that hypoxia by itself can hardly be considered of paramount importance in the pathogenesis of Cor pulmonale, as many as 55% of patients with significant oxygen desaturation having failed to exhibit clinical or electrocardiographic evidence of right heart disease.

The evidence in favour of repeated secondary infections being a principal determinant in the pathogenesis of CCP in pulmonary tuberculosis is, however, seen to be overwhelming as can be readily appreciated from the data presented earlier.

Secondary infections are bound to occur frequently where favourable factors such as cavities, bronchial distortion, tubercular brochiectasis etc. exist, with their potential for retention of secretions. These infections, with the consequent acceleration in metabolic process, increase the cardiac output, which is further accentuated by hypoxia and hypercapnoea consequent upon reduced ventilation, which results from exudation and blockage of air passages. The increase in cardiac output means increased work for the right ventricle, which has to contend with an already reduced pulmonary vascular bed. Repeated such episodes lead to permanent rise in pulmonary artery pressure and right ventricular hypertrophy.

The schema given below represents the above:



It would be pertinent here to refer to a 45 years old man with a history of fully treated tuberculosis 5 years earlier, who was admitted complaining of moderate haemoptysis. Plain skiagram chest showed clear lung fields with a streaky shadow in the right upper zone suggesting a fibrotic strand. ECG, however, showed P Pulmonale with early RVH. He was found to be passing about 60 ml of mucopurulent sputum daily, negative for AFB and, to having cough and expectoration since a long time. PaO₂ was 145, PaCO₂ 31.0 and oxygensaturation 100 %. Bronchogram revealed an irregular pooling in right upper lobe.

Clinical considerations

It has been stressed that Cor pulmonale is difficult to diagnose clinically. However, with modern non-invasive diagnostic aids to cardiology, it is possible to detect most of the cases who have significant pulmonary hypertension and/or right ventricular hypertrophy, complicating the primary disease. Clinical precordial findings in such cases do get modified by lateral and other displacements and by pleural thickening, localised emphysema, etc. The most characteristic auscultatory finding of pulmonary hypertension is accentuation of the second heart sound in the pulmonary area. However, it has already been shown that this accentuation may be a function of displacement. An accentuated P₂ may also get muffled due to overlying emphysema or left ward displacement of the heart, and this happens rather frequently. Similarly, displacement also frequently obscures the cardinal sign of Right ventricular hypertrophy i.e. the parasternal heave. It would be profitable, in such situations, to palpate and auscultate at the subxiphoid region where we can frequently find a heave and an accentuated second heart sound. When present, these can be regarded as diagnostic of CCP, as shown by us in 1971 (Kapoor, Sharma and Rawat). The presence of P pulmonale (tall, peaked P waves of height 2.5 mm or more in lead 2, 3 and a VF) and an upright P in VI, are diagnostic. A pattern of RVH or RBBB is frequently seen, but need not always be present, as shown by Radhakrishnan et al. (loc cit) and Kapoor, Radhakrishnan and Ganesan (loc cit).

A question can arise. How does it help to detect Chronic Cor pulmonale in patients of pulmonary tuberculosis ? To this, there are several important considerations. Firstly, as pointed out earlier, this condition can sometimes be reversed. Secondly, having seen that secondary infections are dominant in the aetiopathogenesis, progress of an already stabilised Cor pulmonale can be arrested or

at least slowed down; and finally, it is possible, once we understand the pathogenesis, to prevent this dreaded complication. In case of established Cor pulmonale, it is important that vigorous chemotherapy be instituted for all secondary infections, especially in patients with residual lesions. In other words, patients of healed tuberculosis have to be followed up for the rest of their lives and educated about the desirability of treating these infections. To prevent Cor pulmonale developing, it is important that the treatment of Chronic pulmonary tuberculosis should be regarded as incomplete if a clear X-ray picture does not result. It is imperative that all removable residual lesions, whether solid looking or cavitory, are eliminated by surgery.

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IMMUNOLOGY OF OCCUPATIONAL LUNG DISEASES CAUSED BY DUST: AN OVER VIEW

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SUMMARY : The lungs are exposed to numerous injurious substances. Such injury may be the result of immunological or non-immunological mechanisms. The lung clears itself of inhaled particles by means of ciliated cells lining the airways and the macrophages. The latter play an important role in the immune process as well. Inorganic particles are ingested by macrophages and if found inert are transported for eventual expulsion. Particles such as silica are poorly handled by macrophages, they not only damage the macrophages but also impair their function. Others, such as asbestos, may stimulate fibrosis. Endogenous factors such as the presence of auto-antibodies (rheumatoid factor or anti-nuclear factor) alter the response of the host to inhaled particles. The pathological changes caused by handling inorganic dusts include interstitial fibrosis, nodular fibrosis or macule formation leading to emphysema. Occupational asthma occurs when individuals are exposed to dusts during the course of their work. The lung responds differently to organic dust. T cells and complement are important elements in handling organic dust. The role of inhaled steroids which have no significant systemic effects in the prevention of certain occupational asthmas is worth evaluating, apart from control measures which minimise the exposure.

The lungs occupy a vulnerable position in the body both structurally and functionally. Since they have to exchange gases they are necessarily exposed to a wide variety of environmental agents such as smokes, fumes, organic and inorganic dusts etc. In fact, next to the skin, the lungs are exposed to the maximum insult from environmental factors. Exposure to such agents may have several consequences. These particles may interfere with the defense mechanisms of the lung or may lead to pulmonary damage as a consequence of an immunological reaction. Further, as the lungs receive the entire cardiac output, they are often the seat of disease when circulating antigens or immune complexes are deposited in the pulmonary capillary bed.

Pulmonary injury is more likely to occur in individuals engaged in occupations which entail exposure to dusts, usually over prolonged periods of time. Host factors also influence the effects of inhaled agents. Genetic determinants clearly influence ciliary action clearance rates of inhaled particles and macrophage function. Afzelius et al, 1989. In addition HLA antigens have been linked to certain occupational lung diseases e.g. HLA B-27 and asbestosis. Airway geometry and breathing patterns, as also the effect of smoking, have recently begun to be recognised as important factors that influence the development of an occupational lung disease (Chamber Ian et al, 1983). Needless to say the immunological make up of the individual by factors such as the presence of an allergic diathesis also play an

important role in the etiology of disease. Individuals with a personal or family history of atopy are liable to hypersensitivity to inhaled antigens in the course; of occupational exposure (e.g. baker's asthma on exposure to wheat flour). However, occupational asthma can also develop in non-atopic individuals-as occurs in exposure to Isocyanate which is a powerful sensitizer. Disability due to airflow limitation may be precipitated or aggravated in individuals with hyperreactive bronchi such as asthmatics on exposure to non-allergic environmental factors like inorganic dust.

Defense mechanisms of the lung

Most of the larger inhaled particles (5µm or greater) are deposited in the nose or in the dead space proximal to the respiratory bronchioles. Particles less than 3 µm tend to reach the gas exchanging part of the lung.

The lung clears itself of inhaled particles by means of ciliated cells lining the airways. In addition, inhaled harmful agents which reach the lung are also cleared by the aggregates of lymphoid tissue and their effector cells. Within the alveoli, clearance is to a large extent the function of the alveolar macrophage. These highly specialized cells, after ingesting particles, can transport them to the level of the terminal bronchioles from where they can be expelled by the use of the mucociliary escalator. Currently, opinion is divided as to whether such transport occurs along the surface or as a consequence

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of the macrophage transiting through the interstitium to reach the terminal bronchiole.

Immunoglobulins A (IgA) and E (IgE) are associated with secretions and it is not surprising that they play an important role in the defence of the respiratory tract. In fact, secretory IgA (a specialised form of IgA, with a secretory piece) and IgE are the antibodies involved in the primary defence of the lung and they are capable of being synthesised locally by specialized B lymphocytes. On the other hand, T lymphocytes mediate delayed type hypersensitivity reactions which are characterised by granulomata. Such reactions are the hallmark of disorders like tuberculosis and sarcoidosis. Phagocytes and complement complete the rest of the components which make up the defense system of the lung.

It is important to remember that while immune mechanisms play a crucial role in the pathogenesis of occupational lung diseases due to dust, both inorganic and organic, nonimmunological pathways could also initiate occupational lung disease.

Response of the lung to inorganic particles

In the gas exchanging part of the lung, inorganic particles are ingested by alveolar macrophages. The response of the macrophage depends on the type of particle ingested. For example, coal dust and haematite which are inert are sequestered within macrophages which transport them to other sites for expulsion. But a particle like silica causes macrophage dysfunction. Silica is readily ingested by the macrophage but is poorly handled thereafter. This leads to lysosomal injury either by bonding of silica to the membrane or by activation of membrane phospholipases (de shazo RD 1982). The end result is autolysis of the macrophage leaving the particle free to attack a fresh macrophage. This impairment of macrophage function renders the cell incapable of handling other agents such as mycobacteria.

Asbestos has a different effect on the macrophage. Asbestos fibres cause the release of powerful enzymes within the macrophage and also stimulate arachidonic acid metabolism. In addition, they promote the release of fibronectin (a substance which promotes fibrosis) and increase the number of surface receptors such as Fc (for immunoglobulins) and C_a (for complement) suggesting an enhanced macrophage activity (Kagan E, 1981). A postulated defect of antigen presentation by macrophages in certain occupational lung diseases awaits confirmation.

It has also been shown that the immunological

background of the host also influences the handling mechanisms. For example, rheumatoid factor (RF) and antinuclear factor (ANF) have been found in individuals with occupational lung diseases more often than in normals (Turner Warnick, 1979). Rheumatoid factor is found frequently in silicosis, asbestosis and coal worker's pneumoniosis. The relationships of these autoantibodies to occupational lung disease is not clearly defined. While it would appear, on one hand; that the increased incidence of RF is due to the adjuvant effect of silica (Pernis and Paronetto, 1962) other evidence also shows that RF itself is an important factor in the production of silicosis (DeHoratius and Williams, 1972): In addition, depressed responses to Concanavalin A have been observed among silicotics suggesting loss of suppressor T-cells. This might explain the appearance of autoantibodies described in silicosis (Schulyer et al, 1977). The occurrence of these autoantibodies and the immunoglobulin type vary with the type of dust ingested.

Antinuclear factor is a good indicator of the prevalence and severity of disease in coal workers (CWP) and asbestosis. This is based on observations which suggest a high degree of correlation between ANF and the extent of radiological abnormalities and its more frequent occurrence in disease than RF (Lippman et al, 1973).

The pathological changes seen as consequence of handling inorganic dust can be broadly grouped as under.

(a) *Interstitial fibrosis:* This occurs when fibrosis of the alveoli is associated with thickening of the alveolar capillary membrane. This is commonly seen in exposure to dusts such as asbestos, beryllium and cobalt.

(b) *Nodular fibrosis:* is commonly seen in silicosis. Silica is transported by macrophages to the interstitium and lymph nodes where autolysis leads to liberation of enzymes and development of fibrosis. This occurs away from the gas exchanging part of the lung near the respiratory bronchioles.

(c) *Interstitial and nodular fibrosis:* A combination of the above two occurs in exposure to diatomaceous earth.

(d) *Macule formation and emphysema:* When minimally fibrogenic materials such as coal are ingested by macrophages, effective clearance occurs as long as the macrophages are not overwhelmed by the number of particles. When the burden exceeds the capacity of the macrophages, dust particles are deposited around

the respiratory bronchiole. This leads to atrophy of smooth muscle leading to emphysema.

Response of the lung to inhaled organic dust

Initially when immunological mechanisms were involved to explain the pathogenesis of organic dust induced pulmonary disease, it was believed that organic dust induced the production of IgG antibodies (precipitin) which complexed with the inhaled antigens to form immune complexes. It was also believed that the deposition of immune complexes in the lung resulted in complement activation and consequent pulmonary damage (Pepys et al, 1959).

It is now recognised that this may not be the actual event obtaining in extrinsic allergic alveolitis induced by exposure to organic dust.

In these disorders the predominant cell type in most lesions is the lymphocyte and granulomata and giant cells are a predominant feature of such an exposure. Such lesions are characteristic of T-cell mediated immune injury. In addition, however, complement activation occurs either by the classical or by the alternate pathway. It would thus appear that both antibodies (Type III) and cells (Type IV) are involved in the handling of organic dusts (Burrell and Rylander 1981).

A large number of occupational lung diseases, exemplified by disorders such as farmer's lung are caused as a result of such immune mechanisms operating. This usually results in the production of occupational asthma, or alveolitis.

Occupational asthma: Liberation of a variety of mediators from sensitized mast cells and basophils leads to bronchial narrowing resulting in asthma. The usual trigger for such a release is the IgE molecule which on contact with the appropriate antigen initiates a sequence of membrane perturbations culminating in the release of mediators. Some of the mediators are histamine while others such as leukotrienes are synthesized de novo and the release of mediators is controlled by cyclic AMP levels in the mast cells.

Large molecule proteins such as grains, animal derived dust and wood dust provoke asthma which is similar to allergic asthma. It is likely that atopic individuals by their inherent capacity to produce more IgE are affected more often than non-atopic subjects. However, isocyanates resins which have a low molecular weight are capable of inducing occupational asthma in both atopic as well as non-atopic individuals.

Non-IgG mediated histamine release is known to occur in certain occupational disorders. Methyl piperonylate a substance found in cotton bract, is considered to cause by histamine release, symptoms and signs of byssinosis. Adrenergic blockade, which results in lowering of cyclic AMP levels, is probably another mechanism by which occupational asthma can be induced by agents such as toluene di-isocyanate.

An understanding of these mechanisms is likely to help in the prevention and management of some of the occupational lung diseases. For example, since the airways narrowing that occurs in certain occupational asthmas is immune mediated, it has been suggested that prophylactic use of either membrane stabilizing agents such as cromolyn sodium or steroids may prevent or minimise the occurrence of the airways narrowing. The role of inhaled steroids in the prevention of occupational asthmas particularly those based on immunological mechanisms is worth evaluating, besides strict measures for minimising occupational exposure to the agents concerned for e.g. baller's asthma. Prior inhalation of Betamethasone aerosol or taking of an antihistamine orally before entering the work spot has minimised the fall in FEV₁ through the work shift in textile workers (Thiruvengadam et al 1971). In other occupational lung diseases, the development of fibrosis is an important event in the pathogenesis of the disease. Methods to diminish or to prevent the progression of fibrosis are currently under experimental study. This includes the use of Vitamin A analogues in certain occupational lung diseases (Mossman et al. 1980). Clearly, further studies with particular emphasis on the cellular aspects of the tissue response to organic and, as well as inorganic dust injury would help in the development of more effective strategies to combat these disorders.

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NON-TUBERCULOUS LUNG MYCOBACTERIOSIS IN GUJARAT†

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SUMMARY : The isolation rate of mycobacteria other than *Mycobacterium tuberculosis* and their species, from patients admitted in the K.J. Mehta Tuberculosis Hospital, Amargadh, Gujarat, from July 1983 to June 1985, was studied.

The isolation rate of disease-associated non-tuberculous mycobacterial strains was estimated as 0.15 Y., with the back-ground isolation rate (for casual isolates) as 0.25 %. The former consisted of *Mycobacterium kansasii* and *Mycobacterium fortuitum* only.

Introduction

Mycobacterium tuberculosis is the most common mycobacterial pathogen isolated from pulmonary lesions in India. Some other myco bacteria, known as atypical, anonymous or unclassified mycobacteria, have also been isolated frequently. We know now that these species are not atypical of the genus mycobacterium, but have reproducible characteristics that are used for identification. The terms anonymous or unclassified are no longer acceptable. Most appropriate and least objectionable terms proposed are 'non-tuberculous mycobacteria' (NTM) and MOTT bacillimycobacteria other than tubercle bacilli. (Wolinsky, 1979; Good, 1979).

A study is being undertaken at Tuberculosis Research Centre, Amargadh (Gujarat) to determine the frequency of lung diseases due to NTM within the state and to identify their species.

The study is still continuing and the present report deals with the mycobacteria, isolated from July, 1983 to June, 1985.

Material and Methods

The study is based on the patients admitted in the K.J. Mehta Tuberculosis Hospital, Amargadh (Gujarat). Only residents of Gujarat were included and recent migrants to Gujarat from other states were excluded. Out-patients were not included. Relapses, if admitted again in study years, were included only if NTM were isolated, but if tubercle bacilli were isolated again, the patient was not included in the study. When several specimens of sputum from the same patient were examined, the organisms from the first culture were

included. Thus, sputum specimens from a total of 2,945 patients were examined.

Sputum specimens were collected in September, December, March and June of the study year, so as to get a good number of newly admitted patients and also enough time to proceed for the screening and identification of NTM.

Isolation: Isolation of mycobacteria was carried out as follow:

Sputum (max. 4 ml.) was collected in a sterile wide mouth screw capped bottle and equal volume of 4 % NaOH was added.

The mixture was shaken for 5 minutes to homogenize the specimen and then left at room temperature for 15 minutes. This was then centrifuged at 3,000 r.p.m. for 15 minutes and supernatant was discarded. Sterile distilled water was added to the sediment and centrifuged at 3,000 r.p.m. for 10 minutes. Supernatant was discarded. Sediment was inoculated with 4.0 mm. loop into 2 slopes of L.J. medium and incubated at 37° C. Slopes were observed daily for the first week to pick up any rapidly growing strain and then twice a week for eight weeks before discarding them as negative.

Screening: Acid-fast organisms isolated were examined microscopically using the Ziehl-Neelsen method of staining. Screening for non-tuberculous mycobacteria was carried out by three tests (Tsukamura, 1981 a): (i) niacin production test (Konno, 1956), (ii) test for the growth on PNB medium-L.J. medium containing 0.5 mg. of p-nitrobenzoic-acid/ml. (Tsukamura and Tsukamura, 1964) and (iii) test for growth on Hydroxylamine medium-L.J. medium containing 0.125 mg. of hydroxylamine/ml. (Tsukamura, 1965 a,b).

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As shown in Table 1, if the test organisms showed negative niacin production and growth on the PNB and/or Hydroxylamine medium, organisms were considered to be suspicious of NTM, and were subjected to further identification test.

Table 1

Screening of Non-tuberculous Mycobacteria

Organism	Niacin test	Growth on PNB-medium	Growth on Hydroxylamine-medium
<i>M. tuberculosis</i>	+	-	-
<i>M. bovis</i>	-	-	-
<i>Other Mycobacterisa</i>	-	+	+

Identification: Identification of mycobacteria was made following the system of successive differentiation with the use of dichotomous keys. At every step, at least three key characteristics were used and differentiation was decided by taking two or more fitnesses for these characteristics. Final identification was decided by comparison of overall similarity of the characteristics of our isolates with the key characteristics of named species (Tsukamura, 1967; Tsukamura, 1975; Tsukamura, 1981 b). Identification tests were monitored by including standard mycobacterial cultures as known positive and negative controls. A group of standard mycobacterial cultures was obtained from Trudeau Mycobacterial Culture Collection, National Jewish Hospital and Research Centre, Denver, Colorado, U.S.A.

The following tests were performed to identify the strains: (Tsukamura, 1975; Vestal, 1975).

1. Growth at 28° C. and 45° C.
2. Growth within 7 days.
3. Photochromogenicity.
4. Growth on hydroxylamine (0.25 mg. and 0.5 mg/ml.)
5. Catalase test (Semi-quantitative pH 7/68° C.).
6. Growth on 5 % NaCl medium.
7. Iron uptake.
8. Arylsulfatase test (3 days and 2 weeks)
9. Growth on MacConkey's agar.
10. Nitrate reduction test.
11. Tween hydrolysis (7 days and 14 days).

12. Tellurite reduction test.
13. Pyrazinamidase test.
14. Urease test.

Definition off lung disease due to non-tuberculous mycobacteria

Occasional isolation. of these organisms from sputum in the absence of related disease or without any association with the disease, may occur due to temporary colonization in the respiratory tract. These organisms were referred to as causal isolates.

A definite diagnosis of lung disease due to NTM was based on the criteria published by American Thoracic Society. (American Thoracic Society, 1974).

i) Presence of radiographic abnormalities indicating active disease.

ii) Isolation of the same mycobacterial strain repeatedly from the sputum in the absence of other pathogens.

Results

Out of a total 2,945 sputum specimens, 2,016 (68.4 %) were culture positive for acid-fast bacilli. Among these, 8 strains (0.4%) were screened out as non-tuberculous mycobacteria. All others were identified as *M. tuberculosis*. The species of NTM isolates are shown in Table 2. Three NTM strains, 2 of *M. kansasii* and 1 of *M. fortuitum*, were found to be associated with disease, giving an isolation rate of 0.15 %. The other 5 strains were found to be

TABLE 2

Kind of Non-tuberculous Mycobacterial species isolated during the study

Species	Number of strains		Total
	Disease Associated	Causal isolates	
<i>M. kansasii</i>	2	-	2
<i>M. fortuitum</i>	1	3	4
<i>M. scrofulaceum</i>	-	1	1
<i>M. gordonae</i>	-	1	1
Total	3	5	8

casual isolates, giving a background isolation rate of 0.25 %.

Discussion

Increasing interest of mycobacteriologists in the non-tuberculous mycobacteria has improved our knowledge about the incidence of lung disease due to NTM. Data on the frequency of lung disease due to NTM are available for several countries. The frequency is 4.6% in Western Australia (Carruthers and Edwards, 1955), 0.1 % in South Africa (Stottmeir, Kleeberg and Blockbergen, 1966), 2.8% in Canada (Gale, 1976), 1.7% in Japan. (Tsukamura et al, 1981), 3.3% in Rhodesia (Tsukamura et al, 1972), 1 to 30%, in various locations of United States (Wolinsky, 1979). In India, the isolation rate varies from 0.7 to 34%. (Thomas et al, 1961; Patel, D' Souza and Sayed, 1966; Choudhri et al, 1979; Ramakrishnan, 1981; Kotian et al, 1981; Das et al, 1982; Hardas and Jayaraman, 1984; Paramsvan et al, 1985). However, most of the reports from India range from less than 1.0 % to as high as 13.1 %, except one, which reports 34 % isolation rate (Pate), D' Souza and Sayed, 1966), which was unusually high. In many reports, there is no distinction between casual isolations and actual cases of disease, or mycobacterial strains were not identified up to the species-level. Merely, the report of isolation rate or number of mycobacteria isolates does not give an exact idea of the clinical significance of various species of potentially pathogenic non-tuberculous mycobacteria.

In the present study, an isolation rate of 0-15% has been obtained, which is quite low, when compared with other reports. Temporary colonization of NTM in the respiratory tract is not uncommon, and about 5 % of the healthy individuals were found to have such colonization (Kotian et al, 1983). In the present study, all the patients were known cases of pulmonary diseases and were taking anti-tuberculous chemotherapy and this may be the reason for the suppression of temporary colonization and hence, very low casual isolation rate of 0.25 % only.

Geographic differences in the occurrence of disease due to a particular non-tuberculous mycobacteria species have been reported. In Europe and the United States, about 50 % of all isolates of non-tuberculous mycobacteria obtained from the patients in Tuberculosis Hospital are *M. Kansasii*. In contrast, *M. avium-intracellulare* strains are in the majority among isolates in Japan, Rhodesia and Australia (as quoted by Tsukamura et al, 1981). In the present study, the number of cases of non-

tuberculous mycobacteriosis was too small to indicate the prevalence of particular type of species. However, *M. Kansasii* and *M. fortuitum* were found to cause the disease, and it was noticeable that no *M. avium-intracellulare* strain was isolated. In other parts of India, however, isolation of *M. avium-intracellulare* from sputum has been reported (Kotian et al, 1981; Das et al, 1982; Paramsvan et al, 1985).

In United States and Japan, it has been noticed that as the number of cases of tuberculosis declines, disease due to other mycobacterial species increases (Good, 1979; Mycobacteriosis Research Group of the Japanese National Chest Hospital, 1983). In Gujarat, with a relatively high morbidity of tuberculosis (about 1.5 % - unpublished data from Tuberculosis Research Centre, Amargadh), the prevalence of lung disease due to NTM appears to be very low.

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DIAGNOSIS OF SMEAR NEGATIVE PULMONARY TUBERCULOSIS BY FLEXIBLE FIBEROPTIC BRONCHOSCOPY

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SUMMARY : Contribution of fiberoptic bronchoscopy and transbronchial biopsy in establishing diagnosis in 33 patients suspected of pulmonary tuberculosis was studied. All patients had radiological lesions consistent with tuberculosis and three sputum-smear examinations were negative for A.F.B. Prebronchoscopic sputum culture, histopathological examination of transbronchial biopsy; smear and culture of bronchial washings and postbronchoscopic sputum examinations were carried out in all cases. Definite diagnosis was established in 25 patients out of which 20 had pulmonary tuberculosis, 2 adenocarcinoma, 2 allergic bronchopulmonary aspergillosis and 1 radiation fibrosis. In 13 tuberculous patients, the diagnosis was established only by one of the four methods of diagnosis while in the remaining 7 patients, more than one source resulted in diagnosis of tuberculosis. Bronchoscopy resulted in diagnosis of 17 patients and diagnosis would have been missed in 11 patients if bronchoscopy was not done. -

Introduction

The initial diagnostic approach to suspected cases of pulmonary tuberculosis is to demonstrate *Mycobacterium tuberculosis* in stained smears of expectorated sputum. However, in a large proportion of patients, repeated sputum smear examination for acid fast bacilli may remain negative in spite of clinical profile and radiological lesions being consistent with the diagnosis of pulmonary tuberculosis. Even the cultures of sputum may be non-contributory. The difficulty is further compounded by the fact that culture of *Mycobacterium* requires 6-8 weeks. Flexible fiberoptic bronchoscopy (FFB) and bronchial washings analysis have an extensive diagnostic potential in pulmonary infections (Kulpati et al, 1980). The high diagnostic yield of bronchial aspirate examination in pulmonary tuberculosis has been reported by many investigators (Denek and Bower, 1979; Sarkar et al, 1980; Uddenfelt and Lundgren, 1981; James et al, 1981 and Funahashi et al, 1983), though some (Kvale et al, 1979) have advised against the culture of bronchial aspirate for *Mycobacteria*. The contribution of transbronchial biopsy (TBB) has not been extensively evaluated in our country (Wallace et al, 1931). The present study refers to the patients admitted with us during the last six years, who were suspected of having pulmonary tuberculosis and for whom three reported stained smears of expectorated sputum failed to reveal *Mycobacteria* or from whom no sputum could be obtained and who were, therefore, subjected to FFB/TBB due to strong suspicion of pulmonary tuberculosis.

Material and Methods

From January 1979 to June 1984, all hospitalised patients suspected of having pulmonary tuberculosis were reviewed for intake into the study. The clinical profile and radiological lesions in these patients were consistent with the diagnosis of pulmonary tuberculosis but either they were unable to produce any sputum on three consecutive specimens of sputum were negative for AFB. All the study patients underwent flexible fiberoptic bronchoscopy. During endoscopic examination, 25 ml of bronchial saline wash, bronchial brushings and trans-bronchial biopsy (TBB) were obtained (Kulpati et al, 1980). Post-bronchoscopy sputum was collected for 24 hours.

All the sputum (both pre and post-bronchoscopy) specimens except transbronchial biopsy and bronchial brushings were sent for smear and culture examination for AFB. The latter were sent for histopathological examination also.

Results

Among the 33 patients, suspected of having pulmonary tuberculosis, in only 20 patients the diagnosis of tuberculosis was finally established. These were 12 males and 8 females. The youngest patient was 13 years old while the oldest was 62 years old. The clinical presentation was mainly with cough (18), expectoration (17), fever (17), chest pain (7), haemoptysis (5) and constitutional symptoms (15). One patient had no symptoms at all

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and only the routine x-ray chest showed pulmonary infiltration. Another patient had only constitutional symptoms but no cough with suggestive chest x-ray. Twelve patients had the illness for less than 2 months and the duration in the remaining was 2-6 months. The radiological diffuse infiltration was observed in 15 patients while in four patients cavitory lesions were present. The remaining one patient had reticulo-nodular shadows. Single cavity was seen in 3 while in the fourth patient two cavities were observed. The lesions were unilateral in 16 patients and bilateral in the remaining 4 patients. Endoscopic examination revealed coating of mucosa of the involved segments with yellowish white secretions in almost all the patients. After bronchial wash, the mucosa revealed generalised mild to moderate hypraemia with whitish patches of variable size in between. In 6 patients the segmental openings were narrowed, edematous and slightly deformed. In all the 4 patients with cavitory lesions, the mucosa was ulcerated.

irregular and swollen with deformed segmental openings. Similar ulcerative lesions were observed in 5 more patients with extensive areas of pulmonary involvement radiologically. Secretions were scanty and bronchial wash was done in all the patients. Specimens, collected during the procedure, included bronchial washings, brushings and transbronchial biopsy from involved mucosa in each patient, and sent for analysis within an hour. Bronchial brushings and biopsy were sent for histopathological examination but not for culture.

Three prebronchoscopic sputum smears were negative for acid-fast bacilli in all the patients but cultures were positive in 6 patients and this was the only diagnostic feature in one patient (Table I). However, the culture of bronchial aspirate was positive for acid fast bacilli in 13 patients. Thus, the diagnostic yield of bronchial aspirate culture in comparison with prebronchoscopic sputum was highly significant ($p < 0.001$). The bronchial aspirate

TABLE I

Final diagnosis of Mycobacterial disease established by various diagnostic techniques in 20 patients

Prebronchoscopic Sputum-culture Positive	Bronchial Aspirate		Histopathology		Post Bronchoscopy sputum		Total No. of Patients
	Smear Positive	Culture Positive	Positive*	Non Caseat- ing granuloma	Smear Positive	Culture Positive	
1	—	—	—	1	—	—	1
—	—	3	—	—	—	—	3
—	—	—	3	—	—	—	3
—	—	—	—	1	1	1	1
—	5	5	—	3	—	—	5
2	2	2	—	1	—	—	2
—	1	1	1	—	—	—	1
1	—	1	—	—	1	1	1
2	—	—	—	1	—	2	2
—	—	1	—	—	1	1	1
6	8	13	4	7	3	5	20

*Histopathology was considered positive if the section showed caseating granuloma or AFB or both.

smears were positive in 8 patients and included 3 patients who did not produce any sputum (Table I). All the positive bronchial aspirate smears were associated with positive cultures also. In 8 patients, smear or culture of bronchial aspirate along contributed to the final diagnosis. The transbronchial biopsy revealed caseating granulomas in 4 patients with acid fast bacilli in 2 patients only. Out of the 4 patients, one had bronchial aspirate positive for acid-fast bacilli. However, noncaseating granulomas were observed in additional 7 patients and were suggestive of tuberculosis. Nonspecific chronic inflammatory changes were the findings in 7 patients and normal histology was observed in the remaining 2 patients. The postbronchoscopic sputum yielded acid fast bacilli in 3 patients and on culture in 5 patients (Table I). In one patient the diagnosis was clinched by post-bronchoscopic sputum culture only. Definite evidence of tuberculosis by study of bronchial brushings was not obtained in any case.

Out of 16 patients in whom chest skiagrams had evidence of diffuse involvement of the lungs, bronchial aspirate was positive in 13 (65%) patients, 4 (20%) on smear and 9 (45%) on culture. In the remaining 4 patients with cavity both smear and culture were positive. Thus, bronchial aspirate was diagnostic on smear in 8 patients and on culture in 13 patients. Out of these 13 patients both smear and culture were positive for acid fast bacilli in 8 patients. Also, cavitory lesions were more often positive than infiltrative disease by bronchial aspirate, while transbronchial biopsy was positive in infiltrative as well as cavitory lesions.

Bronchial aspirate was responsible for establishing diagnosis in 5 out of 7 patients with minimal, 4 out of 9 with moderately advanced and all the 4 with far advanced tuberculosis. It appears that positivity did not depend upon the extent of the disease. Post-bronchoscopic sputum was more often positive for AFB in minimal disease.

No serious complications were encountered during this study except pneumothorax (<10 %) in 2 patients and hemoptysis (<10 ml) in 1 patient. No specific treatment was required to manage these complications.

Bronchoscopy helped to establish the diagnosis in 5 more patients: Adenocarcinoma 2, allergic bronchopulmonary aspergillosis 2 and radiation fibrosis 1 patient. In the remaining 8 patients no diagnosis could be established either because investigations were incomplete or non-contributory.

Discussion

The diagnosis of pulmonary tuberculosis

could not be established in 20 patients included in this study as 3 consecutive sputum stained smears were negative for Myco. tuberculosis or the patients were unable to produce sputum. Flexible fiberoptic bronchoscopy provided material for early diagnosis e.g. bronchial aspirate for smear preparation and transbronchial biopsy for histopathological study. In a similar study, Danek and Bower (1979) and Purohit et al. (1983) demonstrated acid fast bacilli in 34% and 42% respectively while in our study 40% were positive. All these were confirmed by positive culture. Wallace et al. (1981) reported that transbronchial biopsy provided microscopic diagnosis in 30% and was the only diagnostic evidence in 26% of patients. In our study, caseating granulomas were observed in 4 patients (20%) and were the only diagnostic feature in 15% of patients which is a lower diagnostic rate than in the earlier study. In a study by Danek and Bower (1979) granulomatous inflammation was included as diagnostic criteria and bacillary confirmation of diagnosis was present in 41 % of his patients. In our study the diagnostic rate would be 55% if non-caseating granulomas were also considered as diagnostic and this would be comparable to both the earlier studies. Combining stained smear positivity of bronchial aspirate and classical histopathology, the diagnosis was established in 50 % of patients, while it was 48% in the study of Wallace et al, 1981. If granulomatous inflammation too is accepted as sufficient evidence (Danek and Bower, 1979) our results would be 70% as against 75% in their study.

The results of stained smear examination of bronchial aspirate were confirmed by culture in 68% but in other similar studies, Danek and Bower (1979), Sarkar et al. (1980) and Uddenfeldt and Lundgren (1981) the rates were 95%, 87% and 83% respectively. In our study the positive culture rate was 65% only. Kvale et al. (1979) could grow AFB only in one third of their patients of suspected tuberculosis. Kato et al. (1978) reported that higher concentration of lidocaine had an inhibitory effect on mycobacterial growth. Though we did not culture the biopsy material, the bacilli were grown in 20% (1 out of 5), 60% (3 out of 5) and 41% (12 out of 22) in studies of Wallace et al. (1981), Funahashi et al. (1983) and Danek and Bower (1979). But this was not the only diagnostic evidence in any patient in any of these studies and did not influence the diagnostic contribution of other methods. The exclusively positive diagnostic results were provided by culture of pre-bronchoscopic, bronchoscopic aspirate and postbronchoscopic specimens in 29%, 9%, 9% and in 5%, 46%, 13% in other studies while in our study these results were

10% and 5% respectively. Thus, the diagnosis of mycobacterial disease would probably not have been confirmed, had bronchoscopy not been performed in 10% to 40% of suspected cases of pulmonary tuberculosis. Wallace et al. (1981) and Danek and Bower (1979) have reported 95% culture positivity of specimens obtained by FFB and therefore negative culture provided strong evidence against tuberculosis. FFB is also helpful to diagnose associated diseases and to obtain specimens in patients who are unable to produce sputum or produce very scanty sputum. Post-bronchoscopic sputum studies provide excellent collaborative evidence in smear negative tuberculosis. Flexible fiberoptic bronchoscopy in combination with TBB provided early diagnosis (60 to 85%) in smear negative pulmonary tuberculosis in other studies. In our study, it also provided the exclusive diagnosis in 40 % of patients on culture of bronchial aspirate obtained by FFB.

Our study suggests that fiberoptic bronchoscopy (FOB) can provide excellent material for diagnosis of suspected cases of pulmonary tuberculosis from whom smears of expectorated sputum do not reveal mycobacteria or from whom no sputum can be obtained. Secondly, FOB combined with transbronchial lung biopsy may provide early diagnosis of tuberculosis. Thirdly, in cases of diffuse infiltrative tubercular disease, main stress should be on transbronchial lung biopsy while in cavitary tuberculosis bronchial washings are more likely to be diagnostic. Efforts should be made to get the post-bronchoscopic expectorated sputum. It is advisable to culture the biopsy material or bronchial brushings.

Acknowledgement

Our sincere thanks to Dr. K.B. Sharma, Dean, Maulana Azad Medical College, New Delhi, for permission to publish these data. We are also thankful to the Pathology and Microbiology departments and ICMR Cytology Centre, M.A.M. College and various other hospitals for their contribution in the present study.

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REVERSIBILITY OF CLUBBING IN PULMONARY TUBERCULOSIS

A Case Report

B.K. KHANNA AND K.S. KHARE

Summary : A case of pulmonary tuberculosis, with advanced clubbing of left index finger nail, showing a total reversal of clubbing, (by subjective observations and by measurement of hyponychial angle from finger cast) following 11 months of antituberculosis chemotherapy, has been reported

Clubbing has been Reported in pulmonary tuberculosis in less than 1 % (Weirman, Clagett, and McDonald 1954) to 90% cases (Pyke 1954). Almost, all the studies have been based on clinical observation alone. Mellins and Fishman (1966) recommended the use of alginate impression material for production of accurate casts of digits. The method is accurate, reproducible and provides an objective reference material (Regan, Tagg and Thomson 1967; and Bently, Moore & Schwachman 1976).

During our study on subjective and objective assessment of clubbing in patients suffering from pulmonary tuberculosis, we came across a case of advanced clubbing which completely reversed with cmotherapeutic treatment. The case is being presented below.

Case Report

A male patient, aged 32 years, was admitted to our hospital on 10-8-1983. The duration of symptoms was said to be about five months before reporting to us. His sputum was positive for acid fast bacilli on smear examination. Clinical and radiographic examination of the patient revealed no other pathology except for bilateral pulmonary tuberculosis. Four lung zones were involved and the disease was mainly fibro-cavitary.

Detailed clinical examination of left index finger nail revealed evidence of advanced clubbing e.g, increased curvature of finger nail and marked swelling of nail bed. The tissue surrounding the nail bed was warm, red and shiny. A finger cast was taken and measurement of hyponychial angle by shadow graph (Mefarlane, Ibrahim and Tor-Agbidye 1979) revealed it to be 205°.

The patient was administered streptomycin (Ig/lmi OD) isoniazid (300 mg/day after breakfast) and PAS (5 g twice a day after meals). He was discharged after 2½ months of stay in the hopsital, by which time, his clinical condition had improved considerably. Clinically, the curvature of the nail and swelling of the nail bed had reduced markedly. Warmth, shinyness and redness of the tissue at the nail bed had also decreased. At his home, the patient continued to take PAS and isoniazid (in the same dosage). At the end of 11 months of total treatment, he had improved clinically, radiographically and bacteriologically. Skiagram of the chest showed marked improvement. Cavity was reduced in size and its wall had become thinner. Furthermore, all evidence (subjective and objective) of clubbing had disappeared. A repeat finger cast of the same finger revealed a hyponychial angle of 185° (Figure 1).

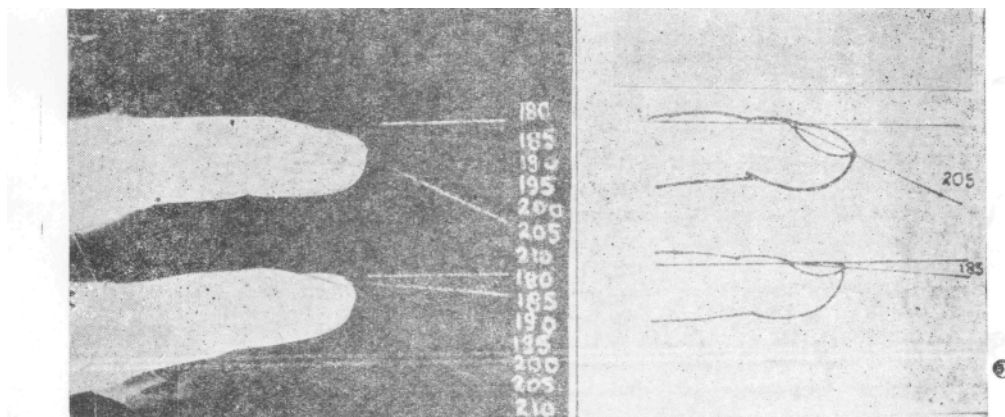


Fig. 1. Shows reversal of clubbing after 11 months of chemotherapy.
Upper—before treatment. lower—after treatment.

Discussion

Hyponychial angle, as an objective criterion of clubbing, was chosen by us because it has been found to be independent of age, sex, height and weight of the patient. It incorporates measurement of two different parameters e.g. profile angle and curvature of the nail (Sly et al 1973 and Macfarlane, Ibrahim & Tor-Agbidye 1979). Left index finger was chosen by us because its nail is less likely to chaff or crack in our right-handed subject. In a study of left index finger casts from 30 normals, upper limit of the Hyponychial angle is 185° which is similar to that recorded by Regan, Tagg & Thomson (1967) (187°) and Bentley, Moore and Shwachman (1976) ($180.1^\circ \pm 4.2^\circ$).

Weirman, Clagget and McDonald (1964) were probably the first to report reversal of clubbing on subjective evidence in a case of tuberculous emphysema following its management with pneumonectomy and subsequent thoracoplasty on the affected side. Similarly, reversal of clubbing on subjective evidences following surgical management of bronchogenic carcinoma (Pneumonectomy) was reported by Stenseth, Clagget, and Woolner (1967). To the best of our knowledge, our case is the first to be reported where subjective reversal of clubbing in pulmonary tuberculosis following satisfactory medical treatment only was confirmed objectively also.

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MILIARY TUBERCULOSIS IN ASSOCIATION WITH SCROFULODERMA

G.S. THIND* AND R.S. BEDI**

Summary : A rare association of miliary tuberculosis with scrofuloderma is reported. Attention is drawn to the diagnostic importance of skin involvement in cases with suspected miliary tuberculosis.

Introduction

Before the introduction of anti-tuberculosis chemotherapy, various cutaneous lesions were seen during the course of miliary tuberculosis, but such lesions did not occur very often. These lesions used to be macular, papular, vesicular, purpuric and haemorrhagic bullous eruptions (Wilkinson, 1972). In developed countries, due to the advent of anti-TB drugs, improved living conditions and nutrition, overall prevalence of tuberculosis including miliary and cutaneous forms has declined and their association has become still rarer. Now-a-days, one may occasionally come across a case report describing miliary tuberculosis in association with solitary skin lesions usually related to underlying suppurative foci (Sahn and Neff, 1974; Bateman et al, 1980). However, in developing countries, prevalence of all forms of tuberculosis is still high.

Scrofuloderma is a subcutaneous tuberculous process, secondary to underlying lymph node, bone or joint tuberculosis leading to cold abscess formation and a secondary breakdown of the overlying skin.

This case report describes a patient of miliary tuberculosis along with scrofuloderma, a rare association, which prompted us to present this case

Case Report

A 20 year old male farmer was admitted with complaints of low grade fever, cough and malaise of two months' duration. He also complained of ulcers in groins and left thigh of the same duration. Skin lesions had started as small reddish papules with slight itching, gradually increasing in size and ultimately breaking down within a month to form ulcers with dirty white discharge. The patient also gave a history of having had papular lesions on the medial aspect of the left upper arm

which also ulcerated but healed with some indigenous treatment.

On examination, he was moderate in built and nourishment and was febrile. Chest examination revealed no abnormal physical signs and choroidal tubercles were not seen.

Dermatological examination was as follows:

Left inguinal region showed ulcerated, warty red out-growths covered with dirty white *slightly* foul smelling discharge. The ulcer had inverted undermined edges and the floor has covered with soft, uneven granulation tissue which did not bleed on touch. There was no sinus formation and three inguinal glands were moderately enlarged but non-tender. Adjoining area of the thigh revealed areas of scarring and hyperpigmentation. Scarring was present in the right groin also and one tender, pedunculated flesh-colored outgrowth was seen in the central area. In addition, one sinus was seen on the right side. Thin atrophic scars, not adherent to underlying structures, were present on the medial aspect of the left elbow. The skin lesions were suggestive of clinical diagnosis of scrofuloderma.

Haemoglobin was 12 gm% and total and differential white cell counts were within normal limits. Mantoux test with PPD ITU was negative. Chest X-ray showed miliary mottling throughout both lung fields. His sputum and discharge from ulcers were negative for acid fast bacilli. Biopsy taken from left groin lesions revealed destruction of skin with evidence of non-specific abscess formation in the centre (Fig 1). In peripheral portion, tubercular granulomas of varying size consisting of caseation, lymphocytes, epithelioid cells and giant cells of Langhans type were seen (Fig. 2). Acid fast bacilli were not found. The findings were consistent with histopathological diagnosis of scrofuloderma.

Treatment was started with streptomycin,

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isoniazid and ethambutol in conventional dosages. There was remarkable clinical improvement and skin lesions healed by scarring within one month. He took this treatment regularly for one month only and thereafter became

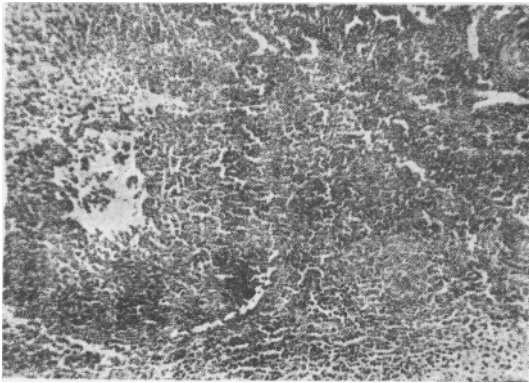


Fig. 1

Showing non-specific cutaneous abscess (arrow)

irregular and stopped drugs altogether after another 2 months. He again attended this hospital after 4 months with complaints of malaise and recurrence of skin lesions. In addition, similar skin lesions were also seen in left axilla and behind left ear. Retreatment was started with rifampicin, pyrazinamide,

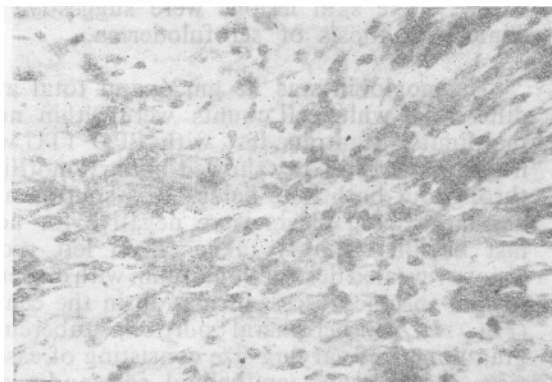


Fig. 2

Tubercular cutaneous granuloma showing Langhans giant cells and epithelioid cells

PAS and isoniazid. He showed gradual recovery and skin lesions completely healed with thin atrophic scars. Anti-T.B. drugs were stopped after one and a half years and the follow up was uneventful.

Discussion

In scrofuloderma, the skin lesion usually starts as a bluish red nodule overlying the infected gland or bone and soon breaks down to form undermined ulcers. Progression and scarring produces irregular adherent masses, densely fibrous in places and fluctuant or discharging in others. Excessive granulation tissue may give rise to fungating tumours (Wilkinson, 1972). Histologically, necrosis and abscess formation found in the centre of the lesion are non-specific. However, the periphery of the abscesses shows tubercular granulomas with caseation necrosis. Tubercle bacilli may, with diligence, be found at the periphery.

The clinical appearance of the skin lesions in our patient was that of scrofuloderma and histological appearances were very suggestive of scrofuloderma. The diagnosis was further confirmed by clinical improvement with specific anti-tubercular therapy and worsening when the patient stopped the drugs. In retrospect, it appears that cutaneous lesions on medial aspect of the left elbow, which were now represented by thin atrophic scars, were also of tuberculous aetiology which had healed spontaneously. Spontaneous healing is known in scrofuloderma, though the usual course is a protracted one. Kennedy and Knowles (1975) reported a case of miliary tuberculosis presenting with cutaneous lesions and emphasized that cutaneous abnormalities may not only accompany but may even precede the other evidence of miliary tuberculosis.

Tuberculin test is usually positive both in miliary tuberculosis and cutaneous tuberculosis. However, it may be negative in patients with over-whelming disease. In our patient, who was not critically ill, the negative reaction may have reflected temporary specific anergy to tuberculin as the test became positive subsequently.

Although cutaneous tuberculosis is now very rare in developed countries, similar situation may not exist in our country and one of the purposes of this report is to emphasize its continued occurrence. Further, more and more cases of miliary tuberculosis are being reported in cryptic forms lately, which are not very easy to diagnose. In such cases, material from conventional sources is often not helpful in confirming the tuberculous aetiology. All cases with suspected miliary tuberculosis should be carefully examined for skin lesions, as material obtained from such lesions provide high diagnostic yield for miliary tuberculosis. Munt (1972) described a series of 69 patients of miliary tuberculosis of which 3 had associated cutaneous lesions

and diagnostic material confirming diagnosis of miliary tuberculosis was obtained from all these skin lesions. Although cutaneous lesions are rarely encountered in association with miliary tuberculosis, but when they are found, their diagnostic significance should not be overlooked.

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TUBERCULOUS PERFORATIONS OF THE SMALL INTESTINE

V.K. KAPOOR*, A.K. KRIPLANI,* T.K. CHATTOPADHYAY** AND L.K. SHARMA***

SUMMARY : Perforation is an uncommon complication of Abdominal Tuberculosis and is associated with high mortality. Six cases of tuberculous perforation of the small intestine with closure of the perforation, resection anastomosis of strictures, peritoneal toilet and drainage with no mortality are reported. Difficulties in diagnosis and guidelines for diagnosis and management are discussed.

Introduction

Abdominal tuberculosis is still common in the developing countries. Patients usually present with intestinal obstruction, subacute or acute. Perforation is an uncommon complication of intestinal tuberculosis. Correct pre-operative diagnosis is difficult, management controversial and mortality high. We have managed 6 cases of tuberculous perforation of the small intestine with no mortality. Based on our experience we suggest criteria for diagnosis and suggest guidelines for treatment.

Material, Methods and Results

During a 3-year period, 45 cases of abdominal tuberculosis were managed which included 6 cases of perforation of the small intestine. The cases are summarised in Tables 1 and 2. In all cases, tuberculosis was proved on histopathological examination (epithelial cell

granulomas with Langhans giant cells and caseation necrosis) of the resected segments of the small intestine or mesenteric lymph nodes. There was no mortality. The average hospital stay was 15.5 days.

Discussion

Perforation is an uncommon complication of intestinal tuberculosis. The incidence of perforation in abdominal tuberculosis has been reported from 7.5% (Bhansali, 1972) to 12.2% (Kakar et al, 1983). We found perforation in 13.3% of our cases of abdominal tuberculosis. Lai et al (1984) collected 150 cases of tuberculous perforation of the small intestine reported till 1984; 25 more cases have been reported since then (Aston and De Costa, 1985; Kakar et al, 1983). Previous history of subacute intestinal obstruction may be present (Bhansali et al, 1968). It was present in 4 (66%) of our cases. Two of these were diagnosed to have

TABLE I
Tuberculous Perforations of the Small Intestine

Case No. (Years)	Age	Sex	Clinical diagnosis	Duration of symptoms	Previous history of abdominal tuberculosis
1	25	M	Acute Peritonitis	6 days	—
2	31	M	Intestinal obstruction, ascites.	2 days	6 months
3	19	M	Acute peritonitis	1 day	—
4	20	F	Acute intestinal obstruction	2 days	12 months
5	17	F	Acute peritonitis	1 day	3 months on anti-TB treatment
6	22	F	Acute peritonitis	1 day	6 months on anti-TB treatment

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TABLE 2

Tuberculous Perforations of the Small Intestine (contd.)

CaseNo.	Chest X – ray	Abdomen X-ray	Operative findings	Operative procedure*	Hospital stay
1	Fibrocalcific lesion (inactive)	Free air	Ileal perforation, stricture.	Resectin-anastomosis	15days
2	Blunted costo-phrenic angle	Loculated air	Extensive adhesions, perforation not found	-	17days
3	Pleural effusion (fresh)	-	Extensive adhesions, perforation not found	-	9days
4	Active parenchymal lesion sputum negative for AFB.	Free air	Ileal perforation, stricture	Closure of perforation Resection-anastomosis	30days; Fecal fistula
5	Normal	-	Ileal perforation, strictures.	Closure of perforation Resection-anastomosis	11 days
6	Normal	-	Ileal perforation, stricture	Resection-anastomosis	11 days

* Peritoneal toilet and drainage performed in all cases.

ileal strictures on barium meal follow through and were receiving antitubercular treatment. An increased incidence of perforation with antitubercular treatment has been noted (Bahari, 1978). Chest X-ray showed evidence of tuberculosis—active or healed in 4 (66%) cases. Correct preoperative diagnosis of tuberculous perforation of the small intestine is not possible (Kakar et al 1983). We suggest that the diagnosis of tuberculous perforation should be strongly suspected in patients with peritonitis who have previous history of subacute intestinal obstruction and/or show evidence of tuberculosis on chest X-ray. All our cases fulfilled one or both of these criteria.

Surgical treatment of tuberculous perforation is controversial. Closure of the perforation with or without bypass has been reported to give poor results (Bhansali et al, 1968). Resection—anastomosis is therefore, recommended (Aston and De Costa 1985). Irrespective of the surgical procedure adopted, however, the mortality is high 30% (Aston and De Costa 1985; Bhansali et al 1968) to 45% (Kakar et al 1983). Tuberculous perforations are often associated with strictures—these must be resected along with closure of the perforation (as was done in cases 4 and 5). Perforations adjacent to strictures should be included in the resected segment of the intestine (cases 1 and 6). In the presence of extensive adhesions,

no attempt should be made to locate the perforation (cases 2 and 3) as injury to the adherent intestinal loops is likely and focal fistula may result in the post-operative period. Peritoneal toilet and drainage should always be performed. We have successfully managed 6 cases with these guidelines of treatment and advocate them for the management of tuberculous perforation of the small intestine.

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TUBERCULOUS PERITONITIS PRESENTING AS ACUTE ABDOMEN

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Summary : Tuberculous peritonitis usually presents insidiously. Two cases of peritoneal tuberculosis presenting as acute peritonitis are reported.

Introduction

Tuberculous peritonitis is the most unusual form of abdominal tuberculosis. Bhansali (1972) reported 19 cases in a series of 300 cases of abdominal tuberculosis—an incidence of 6.3%. Tuberculous peritonitis accounts for 1.5% of all reported cases of tuberculosis (Vyravanathan & Jeyarajah, 1980). The onset is usually insidious and majority of the cases present with chronic abdominal symptoms. Presentation is sometimes acute—the onset resembling acute peritonitis so closely that the abdomen is opened (Rains & Ritchie, 1984). We have encountered 2 cases of tuberculous peritonitis which presented as an acute abdomen and the diagnosis was revealed at laparotomy.

Case Reports

Case 1. A 20 year old woman presented with abdominal pain, vomiting and diarrhoea for 2 weeks, associated with fever. She looked ill and was dehydrated. Abdomen was distended with generalised guarding and tenderness. X-rays revealed dilated loops of small intestine with air-fluid levels. A clinical diagnosis of acute peritonitis due to enteric perforation was entertained. Laparotomy, however, revealed ascites and multiple peritoneal tubercles. The intestines were normal and no perforation was seen. Ascitic fluid was removed, peritoneal biopsy performed and abdomen was closed without drainage. Histopathological examination revealed tuberculosis.

Case 2. A 22 year old male presented with 4 days' history of abdominal pain, distension and vomiting. Abdominal examination revealed distension, free fluid and tenderness. X-rays revealed features of ileus. With a clinical diagnosis of acute peritonitis, laparotomy was performed. Ascites, peritoneal tubercles and adhesions were found. Intestines were normal. Peritoneal cleansing, lysis of adhesions and omental biopsy were performed and the abdomen was closed without drainage. Histopathological diagnosis was tuberculosis.

Discussion

Clinical features of tuberculous peritonitis are many and varied. There are usually long symptomatic intervals prior to the diagnosis (Singh et al, 1969). In one series more than 85% of the patients had symptoms for more than 1 month (Vyravanathan & Jeyarajah, 1980). Rarely, tuberculous peritonitis presents acutely and may simulate an acute abdominal condition (Dineen et al, 1976). None of the patients in three large series of 31 (Gonella & Hudson, 1966), 32 (Borhanmanesh et al, 1972), 35 (Vyravanathan & Jeyarajah, 1980) and 47 (Singh et al 1969) had an acute presentation. Only 6 out of 100 cases reported by Sochocky (1967) had a sudden onset. Tuberculous peritonitis with an acute onset may mimic acute appendicitis or acute cholecystitis (Dineen et al, 1976). It may also present as pyogenic peritonitis (Addison, 1983); a patient who presented with acute abdominal symptoms was diagnosed as perforated duodenal ulcer (Lambrianides et al, 1980). Diagnosis in these cases is established at laparotomy. Treatment includes evacuation of ascitic fluid and omental/peritoneal biopsy; abdomen should be closed without drainage to prevent the formation of fistula (Yampolski et al, 1984). All patients must receive anti-tuberculous treatment; steroids may be added to prevent formation of adhesions (Singh et al, 1969).

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HEPATIC TOXICITY DUE TO ISONIAZID

S.K. SARKAR*, HARMEET SINGH**, AJIPAL SINGH** AND T.N. SHARMA***

SUMMARY : A 65 years old non-alcoholic tuberculous patient developed isoniazid induced hepatitis. Jaundice recurred after challenge with isoniazid.

Introduction

Prophylactically administered isoniazid may produce mere hepatocellular abnormalities with elevation of serum transaminase values, or it may precipitate any other liver disorder (Graham and Dundas 1979).

A US study (Kopanoff et al, 1978) had shown that drinking alcohol increased the risk of hepatitis significantly and the incidence of hepatitis was maximum between the ages of 35 & 60 years, but in the six decade the incidence dropped.

A case is reported where jaundice was caused by Isoniazid in a non-alcoholic.

Case Report

A 65 year old male patient of pulmonary tuberculosis weighing 54.5 Kg. with sputum positive for acid fast bacilli, was referred to the Hospital for Chest Diseases and Tuberculosis, Jaipur with complaints of anorexia, nausea and deep jaundice on 26th November, 1984.

The past history revealed that he started taking anti-tubercular drugs in a combination of streptomycin, isoniazid and ethambutol 6 years back for the first time. Streptomycin was withdrawn 3 days after initiation of chemotherapy as he developed severe tinnitus. He took only ethambutol and isoniazid for the next 2 months after which PAS was also added. After 3 months of chemotherapy the patient developed jaundice. At this stage the patient stopped taking all drugs and switched over to some indigenous drugs.

On 6th November, 1984, he had frank haemoptysis. Sputum was positive for AFB, and he was put on four drugs, namely ethambutol, isoniazid, pyrazinamide and rifampicin. On 26th November, 1984, the patient developed weakness, anorexia and malaise followed by deep jaundice. The investigations revealed SGOT 50 units, SGPT 36 units, total serum bilirubin 11.0 mg%, and direct bilirubin 6.75 mg%. The urine was positive for bile salts

and bile pigments. The anti-tuberculosis drugs were stopped at this stage and the patient was treated symptomatically for jaundice without any cortisone. Within a fortnight he started improving and regained appetite.

The patient did not take alcohol and interrogation did not reveal any other condition which could have been the cause of jaundice

On 10th December, 1984, the serum bilirubin level was almost normal (1.25 mg% total) and SGOT and SGPT levels had also decreased markedly to 38 and 24 units respectively. The patient's clinical condition had also improved considerably. It was decided at this stage to restart anti-tubercular drugs (rifampicin 450 mg, ethambutol 1 gm and pyrazinamide 2 gms per day). The patient was also given 400 ml of 25 % glucose intravenously daily for next 15 days along with anti-tubercular drugs.

The patient did not develop jaundice even after 15 days (from 12th December to 25th December, 1984) of this regimen. Since isoniazid was the only drug left out from among the previously started 4 drugs, isoniazid 300 mg/day was added on 25th December, 1984. Two days after starting isoniazid, the patient again developed fatigue, anorexia and high grade fever. Deep jaundice appeared on the third day. The laboratory investigations on 29th December, 1984 revealed increased serum transaminase values (SGOT 58 units, SGPT 46 units) and raised serum bilirubin levels (Direct 7.25 mg% and total 12.2mg%).

All the drugs were again stopped and the patient was put on symptomatic treatment, along with Tab. betamethasone 0.25mg. 3 times daily. Patient responded satisfactorily to this treatment and jaundice subsided by the end of second week and serum bilirubin level touched almost normal values (Total 1.8 mg% Direct 1.0 mg%).

Discussion

Isoniazid has been a successful therapeutic agent for the treatment of tuberculosis because

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of its high therapeutic efficiency and good acceptability by the patients (Goodman and Gillman 1970). Although isoniazid had been implicated as a possible hepatotoxic agent in a small number of cases (Cohen et al 1961; Davies and Glowinski 1961; Gellis and Murphy 1955; Gillis and Texler 1960; Haber and Osborne 1959; Merrit and Fatter 1959; Randolph and Joseph 1953), the patients who developed hepatitis were also taking other drugs. Only in 1969, Scharer and Smith showed conclusively that isoniazid alone is also capable of inducing hepatocellular injury.

There is a close relationship between alcoholism and isoniazid-induced hepatitis (Kopanoff et al 1978), but there was no history of alcohol intake in our patient.

Accelerated recurrence of severe hepatitis and jaundice as reported by Meddrey et al 1973, was also observed in our patient who developed recurrence of jaundice within 72 hours after addition of isoniazid to the other drugs which he was already taking. Non-development of jaundice with other drugs, namely, rifampicin, ethambutol and pyrazinamide and appearance of jaundice when isoniazid was added were sufficient to establish isoniazid as the hepatotoxic drug in our patient.

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NEWS & NOTES

37TH TB SEAL CAMPAIGN

The 37th TB Seal Campaign organised by the Tuberculosis Association of India and its affiliates in the States, was inaugurated on 1st October, 1986, by Giani Zail Singh, President of India and Patron, Tuberculosis Association of India, at a special function held at Rashtrapati Bhawan, New Delhi. He also released a Souvenir, brought out by the Tuberculosis Association of India, on the occasion. The function was attended by the President and members of the Tuberculosis Association of India and representatives of the Delhi TB Association.

In a message issued on the eve of the inauguration of the Campaign, the President said:

"I convey my greetings and good wishes to the Tuberculosis Association of India and others associated with it. The basic aim of TB Seal Sale Campaign is to focus public attention on the plight of TB patients. It is my earnest wish that all possible facilities should be extended to those who are working in the field for the relief of the unfortunate sufferers from this disease. It is a fitting tribute to the memory of Mahatma Gandhiji that the Tuberculosis Association should have chosen his birthday for launching the Sale Campaign and I appeal to all sections of people to come forward generously and contribute their mite for providing better treatment. I am sure that the TB Seal Sale Campaign will be a great success and involve a large number of people in the Campaign.

I wish the Campaign all success".

Messages wishing the Campaign success were also received from Shri R. Venkataraman, Vice-President of India, Shri Rajiv Gandhi, Prime Minister, Shri P. V. Narasimha Rao, Minister for Health and Family Welfare, Shri H. L. Kapur, Lt. Governor of Delhi and Shri S. Ranganathan, President, Tuberculosis Association of India.

Dr. M.D. Saigal, Chairman, Tuberculosis Association of India, in a personal communication addressed to the Directors of Health Services in the States appealed for their full support and cooperation in making the 37th Seal Campaign a great success.

REFRESHER COURSES IN TUBERCULOSIS

Andhra Pradesh : Three refresher courses in

tuberculosis for general practitioners were held on 7th and 26th July and 31st August, 1986 in Shamirpet, Guntur and Ongole respectively. The courses were jointly organised by the State TB Association and the respective District TB Associations in collaboration with the local branches of the Indian Medical Association. In all, about 200 doctors attended these courses.

Gujarat : Three courses were held on 23rd March, 4th May and 21st June, 1986 in Ahmedabad, Vadagam and Rajkot respectively.

Himachal Pradesh : Under the auspices of the Tuberculosis Association of India, the Department of TB and Chest Diseases of the Indira Gandhi Medical College, Shimla, the Himachal Medical Officers' Association (Solan branch) organised a refresher course at Barog on 7th September, 1986. The course was inaugurated by the Hon'ble Minister for Health and Family Welfare of Himachal Pradesh. Dr. S.P. Pamra, Honorary Technical Adviser, Tuberculosis Association of India, addressed the audience and also gave a talk on 'Differential Diagnosis of Tuberculosis'. The course was attended by 68 doctors and was sponsored by the National Academy of Medical Sciences.

Maharashtra : The Maharashtra State Anti-TB Association, in cooperation with local branch of the Indian Medical Association and Unichem, organised a refresher course at Vita on 29th June, 1986. Sixty three doctors attended the course.

Meghalaya : Under the auspices of the Tuberculosis Association of India, the TB Association of Meghalaya, in collaboration with the local branch of the Indian Medical Association, organised a refresher course at Shil-long on 19th July, 1986. The course was sponsored by the National Academy of Medical Sciences and it was attended by 133 doctors.

Orissa : The TB Association of Orissa organised two refresher courses, one in Jagatsinghpur and the other in Dhenkanal, on 12th and 24th August, 1986 respectively. In all, 77 doctors attended these courses.

AWARDS

Ranbaxy-Robert Koch Oration : Dr. K. Styblo, Director, Scientific Activities of the International Union Against Tuberculosis, Paris, has been selected by the TB Association

of India for the Ranbaxy-Robert Koch Oration for the year 1986. He will be delivering his Oration at the time of the 41st National Conference on TB and Chest Diseases to be held in Hyderabad (Andhra Pradesh) in October, 1986

Wander-TAI Oration : Dr. R. Prabhakar, Director, Tuberculosis Research Centre Madras, has been selected by the TB Association of India for the Wander-TAI Oration award for the year 1986. The Oration will be delivered at the 41st National Conference on TB and Chest Diseases to be held in Hyderabad in October 1986.

Junior Award : The cash award of Rs. 500/- instituted by the TB Association of India for the best Essay by a senior medical student on "The Basis, Technique, Interpretation and Scope of the Tuberculin Test" has been won by Shri Arun Peter Chindripu, final year student of the Andhra Medical College, Visakhapatnam. The award will be presented to Shri Chindripu at the inaugural session of the 41st National Conference of TB & Chest Diseases.

Shri R.C. Garg Memorial Award : The R.C. Garg memorial cash prize of Rs. 1,000/- for the best article published in the Indian Journal of Tuberculosis during 1985 has been awarded for the article entitled "Sero-diagnostic Tests in Tuberculosis" by Drs. A.M. Samuel, G.V. Kadival and M.D. Ashtekar of the Radiation Medicine Centre, Bombay, published in the January 1985 issue of the Indian Journal of Tuberculosis. The award will be presented to the authors at the inaugural function of the 41st National Conference on TB & Chest Diseases on 25th October, 1986.

UTTAR PRADESH STATE CONFERENCE

The VHIth Uttar Pradesh State Conference on Tuberculosis and Chest Diseases was held at the M.L.N. Medical College, Allahabad on 16th and 17th March, 1986. The Conference was inaugurated by Dr. P.C. Vyas, Pramukh Nideshak, Chikitsa Swasthya Avam Pariwar Ka,lyan and presided over by Dr. M. L. Mehrotra, Ex-Director-Professor of the TB Training, Demonstration Centre and Chest

Institute, Agm. Prof. S.R. Singh, Principal, Medical College Allahabad welcomed the delegates and Guests. Dr. M.M.S. Siddhu, Honorary Secretary of the U.P. TB Association spoke on 'Voluntary efforts in Tuberculosis' and Dr. K.B. Varshney, J.D. Allahabad Division released the Souvenir brought out on the occasion. Dr. K.B. Kharey, Joint Director (TB) Medical & Health Services, U.P. and Organising Secretary of the Conference proposed the Vote of Thanks. The Scientific Sessions included the 4th "Robert Koch Centenary Oration" by Dr. M.M. Singh on IMMUNE RESPONSE IN TUBERCULOSIS, and papers on "Short-Course Chemotherapy of Tuberculosis", "TB Meningitis", "Allergy", "Case-finding Camps" and assorted papers on various aspects of tuberculosis. A cultural programme was also organised.

HEALTH CHECK-UP CAMP

Under the auspices of the TB Association of Andhra Pradesh and TB Association of Ranga Reddy District, a general health checkup camp was organised by Sree Satya Sai Organisation at Ramakrishna Vidyalaya (School) Sainikpuri, Secunderabad on 10-8-1986, in which about 50 specialists took part. Dr. G. Narsing Rao, former Principal of the Osmania Medical College and Convenor of Sree Satya Sai Organisation, inaugurated the Camp. The Principal Secretary to Medical & Health, Sri P.L. Sanjiva Reddy, and Principal Secretary to the Irrigation Department, Sri Natarajan, visited the Camp. A total of 1,250 persons were checked up and 9 were found to be sputum positive.

TB CAMP

Under the joint auspices of TB Association of Andhra Pradesh, Distt. TB Association, Nalgonda, Lions Club of Taranka, Hyderabad and Cross Regional Centre, Turkapally, a TB Camp was organised at Turkapally, Nalgonda District on 5th and 6th July, 1986. Sri N. Narsih-mulu, Hon'ble Minister for Power, inaugurated the Camp. The whole expenditure of the camp was borne by Regional Cross Centre, Turkapally, Nalgonda. A total of 349 persons attended the camp; 70 were found X-ray positive and 11 sputum positive.

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ABSTRACTS

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Do Prostaglandins Have a Role in Breathlessness?

Paul A. O'Neill, et al; American Review of Respiratory Diseases; 1985, 132, 22

The effects of indomethacin on the relationship between breathlessness and minute ventilation during exercise have been determined in a double-blind, randomized study on 6 normal subjects. Indomethacin did not significantly alter ventilation or oxygen uptake either at rest or during submaximal exercise. Breathlessness was assessed with visual analogue scales, and, when compared with placebo, the sensation was significantly reduced in relation to ventilation ($P < 0.02$). These findings provide evidence of a possible role for prostanooids in the mechanisms that give rise to breathlessness.

Long-term Oxygen Therapy Can Reverse the Progression of Pulmonary Hypertension in patients with Chronic Obstructive Pulmonary Disease (COPD)

E. Weitzenblum, et al; American Review of Respiratory Diseases; 1985, 131 (Suppl No. 4), 458.

One of the aims of long-term oxygen (LTO) therapy in patients with COPD is to improve pulmonary haemo-dynamics and/or right ventricular function. Sixteen patients with severe COPD underwent three right heart catheterizations. The first one was performed 47 ± 28 months before onset of LTO, the second just before onset of LTO and the third after 31 ± 19 months of LTO. Oxygen therapy was prescribed on usual criteria. The results suggest that LTO for 15 to 18 hours per day can reverse the progression of pulmonary hypertension in a high percentage of severe COPD patients but normalisation of pulmonary artery mean pressure is rarely observed.

The Relative Role of Computed Tomography (CT) in the Diagnosis of Centrilobular Emphysema

W.L. Foster, et al; American Review of Respiratory Diseases; 1985, 131 (Suppl. No. 4), A 60.

Centrilobular emphysema is a common

cause of COPD in middle aged and elderly smokers. The clinical diagnosis is difficult to make and separate from small airway diseases. Symptomatology, pulmonary function tests and chest radiography are generally thought to correlate poorly with pathologically proven emphysema. Over a period of 5 years, 650 post-mortem lungs were evaluated and graded for Centrilobular emphysema. Twenty-five of these patients had undergone chest CT as well. There was poor correlation between pathology ratings and pulmonary density gradient; fairly good correlation between pathology and the following criteria : central intraparenchymal low attenuation areas, pulmonary vascular pruning and pulmonary vascular distortion. Using these three criteria, CT demonstrated a sensitivity of 80% and a specificity of 90% in diagnosing emphysema. CT was much more specific than pulmonary function testing and as specific as chest radiography.

Prediction of Therapeutic Response in Steroid treated Pulmonary Sarcoidosis

Wayne M. Hollinger, et al; American Review of Respiratory Diseases, 1985, 132, 65.

To find a pretreatment predictor of steroid responsiveness in pulmonary sarcoidosis, 21 patients were studied before and after steroid treatment by clinical evaluation, pulmonary function tests, bronchoalveolar lavage (BAL), gallium-67 lung scan serum, and angiotensin-converting enzyme (SACE) level. Although clinical score forced vital capacity (FVC), BAL percent lymphocytes (% lymphs) quantitated gallium-67 lung uptake, and SACE levels all improved with therapy, only the pretreatment BAL% lymphs correlated with the improvement in FVC ($r=0.47$, $p < 0.05$). Pretreatment BAL% lymphs of $\geq 35\%$ predicted improvement in FVC of 10/11 patients, whereas among 10 patients with BAL% lymphs $< 35\%$, 5 patients improved and 5 deteriorated. Clinical score, pulmonary function parameters, quantitated gallium-67 lung uptake, and SACE level used alone in combination with BAL % lymphs or in combination with each other, did not improve this predictive value. Thus, steroid therapy improves a number of clinical and laboratory parameters in sarcoidosis, but only the pretreatment BAL% lymphs are useful in predicting therapeutic responsiveness.

Aspirin as Bronchodilator

Marjan Fortuna; The Journal of Yugoslav Association of Phthiology and Pneumology; 1985, 37, 221.

A case is reported of a patient with bronchial asthma in whom the effect of aspirin was strongly bronchodilator. The theoretical basis of this effect of aspirin and other non-steroid anti-phlogistic drug on the tone of smooth muscle of bronchial wall are described. The frequency of broncho-constrictive effect of aspirin is emphasized together with the extreme rarity of counter-effect, the mechanism of which is not clear.

Palliative Treatment of Endobronchial Tumors : Laser and Afterloading (Iridium-492).

Emslander H.P., Heintz K.W., et al; Giornale Italiano Delle Malattie Del Torace (Italian Journal of Chest Diseases; 1985, 39, 351.

122 patients, mostly with bronchial stenoses due to tumors, were treated with laser therapy 80% in local anesthesia, with the rigid bronchoscope. A good immediate improvement was observed in 72/82 patients with malignancy, but severe complications were observed in 4 patients (1 died). Long-term results were not so good. In conclusion, laser therapy should be used only when resection cannot be suggested.

Calcium and Calcium-antagonist action in the bronchomotor tonus regulation

A. Baronti, et al; Giornale Italiano Delle Malattie Del Torace (Italian Journal of Chest Diseases); 1985, 39, 361.

Calcium acts as intermediary of stimulus-contraction coupling in myocardium and smooth muscular tissue. This contraction comes from calcium penetrating the cellular cytoplasm. The channels letting calcium into the cell are blocked by calcium antagonist drugs, whose effects on the myocardium and blood vessel smooth muscle are well known. The role of calcium as a unifying agent of different mechanisms responsible for bronchial hyperreactivity has been suggested by the experimental data showing the relaxing action of calcium-antagonists on the smooth muscular bronchial tissue. Although there is no unequivocal evidence on human subjects, a direct bronchodilating action of these drugs seems to be unlikely. However, several studies show that these drugs can reduce the bronchial constriction induced by metacholine, histamine, allergens and exercise. In addition, the bronchodilating action of Beta_2 agonist may be facilitated by calcium-

antagonist drugs. Furthermore, the use of calcium antagonist drugs has permitted new studies on bronchospasm physiopathology.

Mucolytic Treatment with Mucosolvin oral

H. Durschmied et al; Studia Pneumologica et Phthiologica Cechoslovaca; 1985, 47, 454.

Oral treatment with Mucosolvin (N-acetylcystein) has some advantages in comparison with its use in the form of aerosol, especially in the out-patient treatment. But it is not effective in all cases so that both the oral and the aerosol form must be available. Our own experience with the oral treatment is discussed and compared with the literature. In accordance with the literature we found a very good or good response to Mucosolvin oral in 93% of the treated patients in a double blind study.

II Cancro Del Polmone Nella Donna: Aspetti Epidemiologici, Clinici E Prognostici Attuali

E. Baldini et al; Lotta Contro la tubercolosi e le malattie Polmonari Sociali, 1985, 3, 527.

Results of a clinical and epidemiological investigation of 250 women patients of lung cancer in Italy are reported. Smoking was less frequent in these patients than among males, while the co-existence or the previous presence of various pulmonary pathologies were more frequent (47.7% of patients). Anaplastic cancer was more frequent than adenocarcinoma and epidermoidal tumour. The tumour was operable only in 21 % cases because of long delay in diagnosis. None of patients with 'oat-cell' tumour survived more than 36 months irrespective of therapeutic procedures while 22% anaplastic and 14% adenocarcinomas types survived more than five years.

Pulmonary Function in Intrathoracic Sarcoidosis

M. Mayer, et al; Studia Pneumologica et Phthiologica Cechoslovaca: 1985, 45, 534.

The values of static and dynamic pulmonary volumes, diffuse capacity of the lungs for CO and blood gases in a group of 152 patients (mean age 36 years) with intrathoracic sarcoidosis were analysed. With regard to the X-ray finding the patients were divided into three groups: 1st group (64 patients) with bilateral hilar lymphadenopathy without changes of the pulmonary parenchyma, 2nd group (64 patients) bilateral hilar lymphadenopathy and infiltration of the lungs, 3rd group (24 patients) bilateral lesion in the pulmonary parenchyma without hilar lymphadenopathy. Normal values of functional lung tests were

recorded in 57 of 152 patients (38%); in group I in 50 %, in group II in 28 % and in group III in 29 %. A reduced DLCO assessed by the steady state method was recorded in 63 (41 %), in group I in 38%, in group II in 48% and in group III in 33%. Reduced D.L.C.O. assessed by the single breath method was recorded in 46 (30%), in group I in 14%, in group II, in 38%, in group III in 54%. Signs of obstructive ventilation disorders were found in one quarter of the examined subjects, most frequently in group III. In the discussion the authors draw attention to the discrepancy between a clear X-ray picture and normal values of functional lung tests including the diffuse capacity of the lungs in groups II and III with sarcoidosis which is of diagnostic and differential diagnostic importance.

Late Fate of Unconfirmed Peripheral Pulmonary Lesions

I. Krejbich *et al*; *Studia Pneumologica et Phtiseologica Cechoslovaca*; 1985; 45, 551.

In the years 1977 to 1981, 31 patients with an average age of 62 years with X-ray evidence of peripheral pulmonary lesions were hospitalized. It was not possible to confirm the aetiology of the lesion even with invasive methods. The fate of these patients was investigated by means of questionnaires after an average period of four years. The group comprised 81% smokers, the average number of consumed cigarettes being 2,50,000. In the course of the investigated years 13 patients died, including 4 from confirmed and 5 from very probable bronchogenic carcinoma; 4 died from other diseases. Two patients were operated and a benign tumour was revealed. Sixteen patients still survive, but the aetiology of their pulmonary lesions has not yet been established. In four of these a small progression has been noted.

On analysis of all factors in this group from the diagnostic and therapeutic aspect with regard to bronchogenic carcinoma, older age groups who are heavy smokers and where the peripheral lesion is extensive must be considered risk groups.

Simultaneous Occurrence of a Foreign Body and Bronchogenic Carcinoma in the same Lobar Bronchus

I. Tyce, *et al*; *Studia Pnuemologica et Phtiseologica Cechoslovaca*, 1985, 45, 562

A case is reported of a 67-year-old patient admitted because of respiratory distress, where during the first bronchoscopy a chronic foreign body (a pea) was detected and removed from the upper lobar bronchus on the right side.

As the X-ray finding persisted, the bronchoscopic examination was repeated and a stenosis of the segmental bronchus for the apical segment of the upper right lobe was detected and cytological examination proved a bronchogenic carcinoma. Poor functional parameters did not permit a surgical approach and the negative attitude of the patient, at the time symptom-free, to the necessity of irradiation therapy caused delay during which metastatic dissemination into both lungs occurred and he died one year after establishment of the diagnosis.

The concurrent independent occurrence of a foreign body and bronchogenic carcinoma is rare and during the last 15 years and has been reported only twice in the literature.

Pneumoconiosis and Carcinoma of the Lungs

I. Kohout, *Studia Pneumologica et Phtiseologica Cechoslovaca*, 1985, 45, 568.

Analysis of the causes of death of 161 patients suffering from pneumoconiosis who died in 1976-1980 carcinoma of the lungs was recorded in 25 patients (24 men and one woman), i.e. in 15.5% of the group. Carcinoma was the cause of death in 12. In the remaining 13 it was detected post-mortem. Carcinoma of the lungs was more frequently detected in more advanced forms of pneumoconiosis; the average age of those who died of carcinoma of the lung was only slightly lower than that of the whole group. As to histological types, squamous-cell carcinoma predominated markedly. None of the patients worked in uranium or metal ore mines.

Pareses of the Diaphragm in Chronic Bronchitis Detected by Regional Ventilation

B. Simeckova, *Studia Pheumologica et Phtiseologica Cechoslovaca*, 1985, 45, 589.

In the course of 1037 densitometric examinations of the regional ventilation in 207 patients with chronic bronchitis, phrenic nerve paresis was detected in four patients (not discovered before by the attending clinician). In one patient it was a complication of lower lobectomy on account of bronchiectasis and in another it was most probably a complication of surgical treatment of goitre. In both patients paresis of the diaphragm promoted substantially the development of global respiratory insufficiency.

These findings provide evidence that densitometric examinations of the regional ventilation are of great use in obstructive bronchopulmonary disease not only as regards

selection of a suitable therapeutic procedure but also from the diagnostic aspect and for evaluation of the prognosis of the revealed pathological changes.

Tissue Angiotensin - Converting Enzyme Activity in Various Tuberculous Lesions

Tomiyasu Tsuda, et al; Kekkaku; 1985, 60, 625.

Since serum angiotensin-converting enzyme (S-ACE) has been reported to be elevated in sarcoidosis and other granulomatous diseases but normal in pulmonary tuberculosis, tissue angiotensin-converting enzyme (T-ACE) activity in tuberculous lesions obtained by operation and biopsy (pulmonary lesion, cervical lymph node and pleural specimen) was studied by ACE substrate film method. T-ACE activity was higher in epithelioid cells than in the necrotic center of the granulomas. This suggests that T-ACE is of no value in distinguishing tuberculous epithelioid cells from sarcoid epithelioid cells.

Epidemiological Study on Pulmonary Tuberculosis and Lung Cancer

Kunio Aoki; Kekkaku; 1985, 60, 625.

Co-existence of lung cancer and pulmonary tuberculosis has been reported frequently. A study was undertaken in Japan to determine correlation, if any, between these two conditions and to detect common and/or specific risk factors. The results of the study are:

(1) In death certificates from lung cancer, advanced tuberculosis was present in significantly higher rate in Japan and U.S.A.

(2) In the autopsy series (1974-1982) also the rate of advanced pulmonary tuberculosis amongst cancer deaths was significantly higher than amongst deaths from other diseases such as gastric cancer, heart and cerebro-vascular diseases, etc.

(3) Estimated combined rate of tuberculosis and cancer was about 20% amongst cohorts born between 1950 and 1975 for males and 15% for females. The proportion in U.K. and U.S.A. is similar.

(4) The death rate from tuberculosis decreased markedly between 1950 and 1980 while the rate from cancer increased steeply. The death rate of cancer of other organs has, however, remained stable or showed only minor changes.

(5) Lung Cancer patients had a significantly

higher rate of previous history of pulmonary tuberculosis in Japan and U.S.A.

(6) Significantly high incidence of lung cancer was seen in new tuberculous patients registered to from 1979-1982 in Japan, USA and Denmark.

(7) Tuberculosis preceded lung cancer.

(8) No specific correlation was observed between cancer and INH administration.

(9) Proportion of smokers in lung cancer patients was somewhat higher than in general population. It was difficult to explain excess incidence of lung cancer among the tuberculous patients due to smoking alone.

The above results suggest that increased incidence of lung cancer among tuberculous patients is not deniable, but the causative mechanism does not seem to be simple. Two hypotheses are offered. There may be increased genetic susceptibility to both tuberculosis and cancer or those who have had advanced tuberculosis in earlier life may have high probability to succumb not only to tuberculosis but also to cancer because of distorted immune response or modified metabolic processes. Definite proof is lacking for both hypotheses.

Nostra esperienza Clinico-terapeutica in Tema di legionellosi: Casi Epidemici!, Sporadici! E Nosocomiali

P.M. Gritti, et al; Lotta contro la tubercolosi e le malattie polmonari sociali; 1895, 55(4), 916.

Clinical and therapeutic studies on 8 epidemics, 4 sporadic and 5 nosocomial cases of pneumonia caused by *Legionella pneumophila* are reported. Rifampicin with Erythromycin which are synergistic appear to be the treatment of choice. Rifampicin with Doxycycline is the next best combination. Resolution of pulmonary lesions as seen on x-ray films lagged behind markedly as compared to relief from symptoms.

La Funzione Respiratoria Nelle Toracoplastiche Di Vecchia Data.

M. Fabbri, et al; Lotta contro la tubercolosi e le malattie polmonari sociali; 1985, 55(4), 1095.

Pulmonary functions were studied in 19 patients who had undergone thoracoplasty for pulmonary tuberculosis. Conventional spirometry and arterial gas analysis were performed on each patient before thoracoplasty and before the patient was discharged after thoracoplasty. Spirometric data showed mixed

impairment of lung function with obstructive pattern predominating. There was no significant improvement after thoracoplasty, thus confirming the impairment to be irreversible. Alteration of arterial gas analysis was present in 16 out of 19 patients when admitted. Most of them were in a condition of moderate respiratory insufficiency. Fifteen of these improved after thoracoplasty.

Human Alveolar Macrophages Suppress Lymphocyte Function Via Prostaglandin E₂ (PGE₂)

J. Glazier, et al; American Review of Respiratory Diseases; 1985, 131 (Suppl. No. 4), A 218.

Human alveolar macrophages are known to suppress lymphocyte proliferation, possibly via the secretion of PGE₂. The purpose of these studies was to quantitate by radioimmunoassay the secretion of PGE₂ by normal human alveolar macrophages and to determine if these amounts of PGE₂ suppress lymphocyte proliferation. The results suggest that alveolar macrophages release sufficient amounts of PGE₂ to suppress lymphocyte proliferation. PGE₂ appears to suppress lymphocyte proliferation, in part, by interfering with the effect of Interleukin-1.

Diagnosis of Pulmonary Amyloidosis by Transbronchial Biopsy

Lewis R. Kline, et al; American Review of Respiratory Diseases; 1985, 132, 191.

Previously reported cases of pulmonary parenchymal amyloidosis were diagnosed by open lung biopsy or postmortem examination. Three patients who were found to have amyloid deposits within the lung parenchyma by flexible fiberoptic bronchoscopy are described. In each case, the diagnosis was suspected when a waxy eosinophilic substance was observed within the alveolar walls of transbronchial biopsy specimens stained with hematoxylin-eosin. When stained with Congo red and examined under polarized light, this amorphous material exhibited the apple-green birefringence characteristic of amyloid fibrils. We suggest that a diagnosis of pulmonary amyloidosis can be made by transbronchial biopsy provided the appropriate histologic stains are employed. Special stains for amyloid should be obtained whenever histologic sections from transbronchial biopsy specimens reveal amorphous eosinophilic material within the alveolar septa or within the walls of small vessels.

Application of Silhouette Sign of Lateral Radiographs

C.M. Tsai, et al; American Review of Respiratory Diseases; 1985, 131 (Suppl. No. 4), A 121.

The purpose of this study is to devise techniques to identify by lateral chest skiagram as to which side of the chest is involved in certain parenchymal or pleural lesions and to evaluate the accuracies of these techniques. The silhouette which has been elucidated chiefly on the PA skiagram can be applied to the lateral skiagrams also. For basal lesions, a positive silhouette sign of the inferior vena cava indicates the lesions within the right hemithorax. For upper lesions, a positive silhouette sign of the right pulmonary artery indicates the lesions on the right side and a positive silhouette sign of the left pulmonary artery and/or aortic arch and descending aorta indicates the lesions on the left side. In cases of unilateral intrathoracic lesions where one hemi-diaphragm is obscured on a lateral skiagram, observation of the silhouette of the inferior vena cava is the most applicable and reliable technique to identify which hemidiaphragm is intact.

Cigarette Smoking Divided by Professional Groups in Beijing

Lin Wan-sheng, et al; Chinese Medical Journal, 1986, 99(1), 15.

Smoking among workers, doctors, college faculty members and students was surveyed, including 3,253 subjects, 1,538 male and 1,715 female. They were divided into 5 age groups. It was found that 48.3% of the males and 2.2% of females smoked. There were significant differences in smoking rates among people of different occupations. The smoking rate of workers was the highest (86.4%), followed by that of doctors (38.7%), college faculty members (31.2%) and students (22.6%). The smoking rate of female workers was 4.6%, female college faculty members 1.0% and female doctors 0.2%, but none of the female college students smoked. The smoking rate does not increase with age, but there is evidence that smoking is more prevalent among young men.

The stopped smoking rate varied among people of different professions. In contrast to the smoking rate, the stopped smoking rate of male college students was the highest, followed by male college faculty members, male doctors and female and male workers.

Most smokers began cigarette smoking before the age of 30. Workers started to smoke earlier than doctors and college faculty members. The number of years of smoking

increased with the smokers' age. In all the four professions, most of the smokers consumed less than 10 cigarettes per day. Those who consumed 11-20 cigarettes daily were much more numerous among male workers than others.

Adenosine Deaminase Activity in the Diagnosis of Lymphocytic Pleural Effusions of Tuberculous, Neoplastic and Lymphomatous Origin.

Inma Ocana, et al; Tubercle; 1986, 67, 141.

The activity of adenosine deaminase was

studied in 74 lymphocytic pleural effusions which were divided into four groups according to the aetiology: tuberculous (38 cases), neoplastic (17), lymphomatous (7) and miscellaneous (12). The mean enzyme value was significantly higher in the tuberculous cases (93.81 ± 29.56 U/l) than for the other three groups and significantly higher in pleural effusions of lymphomatous origin than in the neoplastic and miscellaneous groups. Based on the lowest value of enzyme activity found in the tuberculous group (50 U/l), the test had a sensitivity of 1 and a specificity of 0.97.
