Case 2

A man of 62, with chronic bronchitis, emphysema, bronchopneumonia, and slight heart failure, deteriorated during the first three days in hospital. He was severely anoxic, but the administration of O₂, either intermittently or continuously, at low flow rates (1-3 l./min.), caused CO₂ narcosis. When he was breathing air his arterial pCO₂ was 74 mm. Hg and O₂ saturation 39%. The administration of O₂ at 7 l./min. by oronasal mask caused the pCO₂ to rise to 140 mm. Hg. A continuous intravenous infusion of 2% nikethamide in 5% glucose was started. There was no clinical response until the rate of administration was raised to 80 mg./min. for 1½ hours. At this time he became fully conscious, coughed up copious quantities of sputum, and became very breathless. Subsequently consciousness was maintained and the arterial CO₂ tension was reduced to 85-90 mm. Hg by a rate of administration of 36-48 mg./min. Attempts to decrease the rate of administration caused unconsciousness, with slow shallow breathing. Stopping the O₂ caused intense cyanosis. Ventilation was maintained with nikethamide in the above dosage for 24 hours, and his clinical condition was satisfactory. He then became unconscious and his breathing became slower and shallower. The arterial pCO₂ rose to 120 mm. Hg and his blood pressure fell abruptly. Increasing the rate of administration of nikethamide produced no improvement. Artificial ventilation by positive pressure through a tracheostomy reduced the pCO₂ to 60-73 mm. Hg, but the hypotension persisted and he died. Necropsy was not performed.

Discussion

These observations show that nikethamide can overcome the respiratory depression in patients with acute ventilatory failure due to O₂ administration. They do not, however, suggest that this drug can be used with ease or confidence in routine practice. The quantities required are very large and the rate of administration is very critical. The effects of overdosage, although short-lived, are distressing and obviously put a considerable additional strain on already very ill patients. Unpublished observations by Dornhorst and Laurence (personal communication) are in agreement with these findings. The hypotension in the second patient may have been due to the drug. Less-detailed observations on two further patients have confirmed that the margin between the dose which stimulates the breathing and that which causes distress is narrow and difficult to judge. We nevertheless feel that the intermittent administration of nikethamide is of value, particularly to stimulate coughing, in patients with ventilatory failure due to chronic lung disease in whom O₂ is essential. The depressant effects of O₂ can be largely avoided by improved methods of O₂ administration (Campbell, in preparation).

Summary

The potential value of nikethamide, aminophylline, and sodium salicylate as respiratory stimulants has been investigated in patients with chronic lung disease and ventilatory failure. As a first step the effect of these drugs on the arterial CO₂ tension was measured with the patients breathing air.

Aminophylline (1 g. intravenously) had little or no effect in six patients.

Sodium salicylate (8 g. intravenously) produced significant and prolonged lowering of the pCO₂ in three patients. Reasons are given why further experience is desirable before using salicylate in routine practice.

Nikethamide (2.5 to 6.25 g. intravenously) produced significant but very transient reduction of the pCO₂ in

three patients with moderate and severe ventilatory failure but not in two patients with mild ventilatory failure.

Further observations are described showing that nikethamide can counteract the respiratory depression caused by O₂, but also showing the difficulties and dangers of trying to maintain ventilation by the continuous administration of this drug.

We thank Professor A. Kekwick, Dr. J. D. N. Nabarro, Dr. F. H. Scadding, and Dr. A. Willcox for permission to study patients admitted under their care.

REFERENCES

- Galdston, M., and Geller, J. (1957). *Amer. J. Med.*, **23**, 183.
 Riley, R. L., Campbell, E. J. M., and Shepard, R. H. (1957). *J. appl. Physiol.*, **11**, 245.
 Samet, P., Rosenthal, A., and Bernstein, W. H. (1958). *Amer. J. Med.*, **24**, 215.
 Sieker, H. O., and Hickam, J. B. (1956). *Medicine (Baltimore)*, **35**, 389.
 Stroud, M. W., Lambertsen, C. J., Ewing, J. H., Kough, R. H., Gould, R. A., and Schmidt, C. F. (1955). *J. Pharmacol. exp. Ther.*, **114**, 461.
 Tenney, S. M., and Miller, R. M. (1955). *Amer. J. Med.*, **19**, 498.
 Wechsler, R. L., Kleiss, L. M., and Kety, S. S. (1950). *J. clin. Invest.*, **29**, 28.
 Wégria, R., Capecci, N., Kiss, G., Glaviano, V. V., Keating, J. H., and Hilton, J. G. (1955). *Amer. J. Med.*, **19**, 509.
 Westlake, E. K. (1954). *Brit. med. J.*, **2**, 1012.
 ———, Simpson, T., and Kaye, M. (1955). *Quart. J. Med.*, **24**, 155.

RESECTION FOR PULMONARY TUBERCULOSIS*

BY

J. R. EDGE, M.D., M.R.C.P.

AND

D. E. BOTTRILL, M.R.C.S., L.R.C.P.

High Carley Hospital, Ulverston, Lancashire

The bacteriological findings in tuberculous lesions resected from 100 consecutive patients, related to the type of chemotherapy given before operation, have already been described (Bottrill and Edge, 1957). The recovery of positive cultures, the incidence of bacterial resistance, and the surgical morbidity and mortality were very much greater in patients who had interrupted or inadequate chemotherapy than in those who had "satisfactory" chemotherapy, according to the regimes recommended by the Medical Research Council (1952, 1955).

The purpose of this paper, which describes the experience of these 100 and our next 70 consecutive patients whose resected specimens were examined bacteriologically, is to correlate the laboratory findings with the subsequent clinical course of the patients; and to assess the value of these findings in defining the place of resection in the management of pulmonary tuberculosis at the present time.

Clinical Material

This series of 170 consecutive patients has been followed up from fifteen months to four years after resection. They are divided into two groups according to the type of antibacterial treatment given. Group 1 (satisfactory chemotherapy) comprised 95 patients who had continuous treatment, in one course of at least six months before operation, in the following minimal

*From a paper presented to the North-West Thoracic Society at Aintree Hospital, Liverpool, on April 16, 1958.

daily dosage with at least two of the three standard drugs: streptomycin, 1 g., with isoniazid 200 mg.; isoniazid, 200 mg., with P.A.S. 10 g.; streptomycin, 1 g., with P.A.S. 15* to 20 g. Group 2 (unsatisfactory chemotherapy) consisted of 75 patients who were given treatment falling short of that laid down for Group 1 (either single drug or intermittent regimes, or repeated short courses).

Extent of Disease

Table I shows a higher proportion of patients with cavitation greater than 5 cm. in group 2 (35%) than in group 1 (14%); similarly, 39% of patients in group 2 had four or more zones involved by disease, compared with 28% in group 1.

TABLE I.—Extent of Disease

Total Cavity Diameter	Group 1	Group 2	Zones Involved	Group 1	Group 2
Less than 2 cm.	14%	4%	1	17%	4%
2 to 5 cm.	72%	61%	2 to 3	55%	57%
More than 5 cm.	14%	35%	4 or more	28%	39%

These figures suggest that selection may have a bearing on the results, as the patients who had unsatisfactory chemotherapy also had more extensive disease. We believe that this is not so, because: (1) None of the 13 patients in group 1 who had cavitation greater than 5 cm. produced culture-positive specimens, whereas the specimens of 65% (17 of 26) of those with similar cavitation in group 2 proved to be culture-positive. (2) Many of the patients in group 2 had relapsed, and thus developed more extensive disease or larger cavities—an occurrence which might have been prevented, at least in a proportion, by giving adequate and continued chemotherapy in the first instance.

The age distribution in the two groups is similar.

Bacteriological Findings

The routine of examination and bacteriological technique, and the criteria for resistance, were as described by Bottrill and Edge (1957).

Table II shows that only 15% of specimens were culture-positive in group 1, compared with 52% in group 2. In contrast, the incidence of patients whose

TABLE II.—Bacteriological Findings in 170 Resected Specimens

	Group 1	Group 2
Culture positive	15%	52%
Smear positive, culture negative	52%	33%
.. and culture negative	33%	15%

lesions proved smear- and culture-negative was twice as high in group 1 (33%) as in group 2 (15%).

52% of group 1 and 33% of group 2 specimens were smear-positive but culture-negative. The significance of these visible but evidently non-viable bacilli is not yet proved, though current opinion tends to the view that they are probably dead (F. W. Turnbull, 1958, personal communication).

Sensitivities of Specimen Cultures

Group 1.—Of the 14 culture-positive specimens only 4 were fully sensitive; 3 were resistant to all three drugs; and 7 were resistant to one drug only. It is of

*The Medical Research Council (1952) demonstrated that 20 g. of P.A.S. with streptomycin 1 g. daily is adequate in preventing emergence of resistant strains, but that 10 g. is inadequate. Intermediate doses were not investigated. Many of our patients could not tolerate 20 g. of P.A.S. and were given the maximum tolerated dose, usually 15–18 g.

interest that one specimen showed total, and three partial, resistance when no positive had ever been recovered from the patient, in spite of adequate investigation. This development of bacterial resistance during satisfactory chemotherapy might be explained in either of two ways. Firstly, the patient could have been infected *de novo* with primarily resistant organisms: such resistance was found in some 5% of untreated patients by Oakley, Warrack, and Batty (1954) and by Selkon (1958). Secondly, we are not certain that all these patients were in fact taking their P.A.S., as this feature was not specifically investigated by us; the work of Dixon, Stradling, and Wootton (1957) demonstrated that this may be an important factor.

Group 2.—Positive cultures were recovered from the specimens of 39 patients: only 5 of these were sensitive to all three drugs, 15 were resistant to all three, 13 were resistant to two, and 6 resistant to one.

The sensitivity levels on comparing the specimen cultures with the pre-operative cultures were remarkably consistent in both groups. The association of drug resistance with the recovery of positive cultures is confirmed.

Indications for Resection in the Light of the Bacteriological Findings

Group 1.—Of the 95 patients, 31 had smear- and culture-negative specimens; in these, it seems that surgery was not required. 50 specimens were smear-positive but culture-negative, so that surgery was only doubtfully necessary. 14 were culture-positive, of whom 4 were fully sensitive and would no doubt have responded to continued chemotherapy; 3 were fully resistant, so that surgery was indicated because further help could not be expected from continued antibacterial treatment; and 7 showed partial resistance, surgery being only doubtfully necessary, as improvement might have continued on a three-drug regime. Because pre-operative cultures were consistently negative, bacterial resistance was not recognized in four patients until specimen cultures were examined. In the absence of surgery these patients would have carried a high risk of relapse, which could not have been predicted.

Group 2.—Of the 75 patients, the cultures of 11 were smear- and culture-negative, suggesting that surgery was not necessary: 25 were smear-positive but culture-negative, so that surgery was only doubtfully necessary. There were 39 with positive cultures, of which 5 were fully sensitive and therefore did not require surgery; 15 were totally resistant and definitely required surgery; whilst the remaining 19 were partially resistant, the position remaining uncertain.

Follow-up

Follow-up of the 170 patients for fifteen months to four years after operation showed that 94 of group 1 are well, none has active disease, and there has been one death (Table III). In contrast, 62 patients in group 2 remain well, 6 (8%) have active disease, and 7 (9%) are dead. Thus the giving of inadequate chemotherapy

TABLE III.—Follow-up of 170 Patients (15 Months to 2 Years, 59; 2 to 3 Years, 66; 3 to 4 Years, 45)

	Group 1	Group 2
Well	94	62 (83%)
Disease still active	—	6 (8%)
Dead	1	7 (9%)

has been followed by death, or failure to control the disease, in 17% of the patients in group 2, in contrast with a 1% mortality in group 1.

Of the six patients who still have active disease in group 2, one had fully sensitive organisms, but stopped his drugs three months after operation; one had organisms resistant to all three; and the remaining four had organisms resistant to two antibiotics.

Mortality.—The one death in group 1 occurred in a patient with sensitive organisms, a man of 55 who died suddenly of acute dilatation of the stomach the day after operation. The organisms of six of the seven patients who died in group 2 showed significant resistance. One died of uncontrollable haemorrhage after a lobectomy, believed to be due to hypoprothrombinaemia, and one died during operation of ventricular fibrillation. The other four died of tuberculous complications (broncho-pleural fistula in two, and uncontrollable spread of disease in two). The specimen of the seventh patient, who died of respiratory insufficiency, was culture-negative.

Discussion

The high incidence of bacterial resistance in the culture-positive specimens very strongly suggests a causal relationship. It appears that the principal indication for resection is the persistently positive sputum culture where bacterial resistance has been demonstrated; notwithstanding that a small proportion, less than 5%, of patients having good chemotherapy may develop resistance which cannot be recognized as clinically their cultures remain negative.

Patients showing bacterial resistance are widely recognized as carrying an increased risk of complications following surgery; so that further assessment is required of the value of antibiotics, other than the three standard ones, as effective cover for resection in this type of case.

The results of continued satisfactory chemotherapy, followed by resection during the first course of treatment, are excellent; on the bacteriological evidence, however, it appears that operation was definitely necessary in only 3, and probably necessary in another 7, of the 95 patients so treated.

Summary

The bacteriological findings in resected tuberculous lesions from 170 consecutive patients are described; the recovery of positive cultures with resistant organisms, the surgical mortality, and the continued activity of the disease were all substantial in patients having prior chemotherapy falling short of the standards laid down by the Medical Research Council. In contrast, there was only one surgical death and no other morbidity in patients having satisfactory chemotherapy.

The bearing of the findings on the indications for surgical resection is discussed.

Our thanks are due to Mr. J. S. Glennie and Mr. P. Jewsbury, who operated on the patients. The expenses of the work were defrayed by a grant from the Research Subcommittee of the Manchester Regional Hospital Board.

REFERENCES

- Bottrill, D. E., and Edge, J. R. (1957). *Tubercle (Lond.)*, **38**, 303.
 Dixon, W. M., Stradling, P., and Wootton, I. D. P. (1957). *Lancet*, **2**, 871.
 Medical Research Council (1952). *Brit. med. J.*, **1**, 1157.
 — (1955). *Ibid.*, **1**, 435.
 Oakley, C. L., Warrack, G. H., and Batty, I. (1954). *J. Path. Bact.*, **67**, 485.
 Selkon, J. B. (1958). *Proc. roy. Soc. Med.*, **51**, 810. Quoted in *Lancet*, 1958, **1**, 513.

INDIAN CHILDHOOD CIRRHOSIS

BY

AMARJIT SINGH, M.D., M.R.C.P.

Professor of Medicine

S. S. JOLLY, M.D.

Senior Registrar

AND

M. BALASUBRAHMANYAN, M.D.

Professor of Pathology

Medical College, Patiala, Punjab, India

Ever since its first description by Sen (1887), cirrhosis of the liver in infants and young children has been extensively reported from all parts of India. There is, however, no authentic report from the Province of Punjab, where Jelliffe *et al.* (1957) believe it to be rare. The object of the present paper is to focus attention on certain clinical aspects of the disease as seen in this province and to elucidate certain points of its aetiology.

Methods and Material

Thirty-three cases admitted over a period of about one and a half years were studied. Investigations on each case included a thorough history and physical examination, liver-function tests, needle biopsy of the liver, and tests for evidence of haemolytic disease.

All the cases included in this series conformed to the definition of the disease enunciated by the liver diseases subcommittee of the Indian Council of Medical Research (1955): "Infantile cirrhosis of liver is a disease peculiar to India, affecting infants and young children, with a tendency to run in families. It is characterized in the early stages by enlargement of the liver, which is felt to be hard, and usually also of the spleen, with ascites and vague symptomatology, course variable but generally rather slow and termination usually fatal. Its aetiology is unknown." Cases with a definite aetiology like congenital syphilis, infective hepatitis, rhesus incompatibility, or various inborn errors of metabolism were not included.

Observations and Comments

Age and Sex Incidence.—Patients varied in age from 9 months to 7 years, being predominantly confined to the 1–3 years age group. All but three were males. This significant male preponderance is in striking contrast to the hospital admission for other diseases, and agrees with the findings of Srivastava and Aikat (1954) and Mukherjee *et al.* (1954). However, Achar and Raju (1951) observed no difference in incidence in the two sexes.

Racial and Religious Factors.—This report covers a geographical area which is predominantly inhabited by Sikhs in the villages, yet only 7 out of 33 patients were Sikhs. The rest were Hindus, out of whom as many as 20 were confined to a particular sect, Aggarwal Bania—a strictly vegetarian community for generations.

Family History.—More than one sibling in the family was affected in 11 cases (33%). This is within the previously reported limit of 20–40%.

Clinical Features.—The majority of cases could be classified clinically into two groups—acute and subacute. The acute type had a superficial resemblance to the