Current Practice

MEDICINE IN THE TROPICS

Ascites in Africa

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Ascites is frequently encountered in the folklore and proverbs of many African peoples. It is widely recognized as a condition with a serious prognosis, and therefore one for which early treatment should be sought. In spite of this many of the simpler folk already have massive ascites of several months' duration when first seen in hospital. The explanation of this seeming paradox is that it is usual for most peasants to consult several native herbalists before finally considering a hospital.

Background

In the approach to ascites in Africa it is essential to bear in mind the general background as well as the environmental peculiarities of the immediate locality.

Malnutrition, malaria, and helminthiasis are widespread in most areas, and working together they lead to a lowering of plasma albumin, an increase in globulins, and a lowering of the plasma albumin/globulin ratio. Edozien¹ found the mean plasma albumin among healthy Nigerians to be 3.35 g./100 ml. (49.5% of total plasma proteins) as against 4.05 g./100 ml. (58.5% of total plasma proteins) for Europeans resident in Nigeria. Similar figures were noted in Kampala among East Africans, where Leonard and Shaper² found the average plasma albumin to be 3.15 g./100 ml.

Though the concept of a critical level of plasma albumin below which oedema is inevitable is not valid in many instances, there is little doubt that hypoproteinaemic oedema and ascites occur most readily when the plasma albumin has already been depleted by malnutrition. There is also a strong clinical impression that liver diseases are most common in the undernourished.

Tuberculosis is very common in most parts of Africa and must always be considered in all cases of chronic ill-health of an obscure nature. Unlike the situation in Europe and the United States of America today, abdominal tuberculosis is still a very important cause of ascites.

Burkitt's lymphoma is the most important cause of childhood malignancy in the more humid parts of the continent. Edington and MacLean³ found that Burkitt's lymphomas accounted for 51% of all malignant diseases seen at Ibadan among patients under 15 years of age. Burkitt's tumour must therefore be kept in mind as a possible cause when ascites is encountered in this age group.

Endomyocardial fibrosis and other obscure cardiopathies are common in most parts of tropical Africa and have been estimated to account for between 25 and 40% of heart disease there. They often present with ascites and other signs of congestive cardiac failure.⁴⁻⁶ Endomyocardial fibrosis must be considered in the differential diagnosis of all patients under 40 years of age who present with ascites and signs of heart disease. Rheumatic heart disease also occurs in tropical Africa, but is not as common as in temperate countries.

Hepatic cirrhosis is widespread throughout Africa, and both the post-necrotic and the nutritional types are common causes of ascites. In areas where it is endemic infection with *Schistosoma mansoni* is sometimes associated with hepatic fibrosis and ascites, but the incidence of serious hepatic involvement in *S. mansoni* infestation outside the Nile Valley is low.

Primary malignant hepatoma is one of the commonest malignant tumours in Africa and is a common cause of ascites. According to figures reported by Edington and MacLean³ the commonest malignant tumours in patients above the age of 15 years in Nigeria are primary carcinoma of the liver and stomach in males, and carcinoma of the cervix, breast, and ovaries in females. Certain fungal parasites of groundnuts and other foods commonly consumed in Africa, such as *Aspergillus flavus*, have recently been shown to be capable of producing carcinogenic metabolites such as aflatoxin.^{7,8} It is tempting to attribute the widespread incidence of hepatic carcinoma in Africa to these substances. However, no clear evidence has so far been adduced in support of this theory, though further work is proceeding.

The nephrotic syndrome is also a frequent and important cause of ascites in both children and adults in Africa. I have the impression that this syndrome is more common among adults in Africa than in Europe, but there are no reliable figures for comparison.

Table I shows the diagnosis made in 91 inpatients over the age of 10 fully investigated for ascites in Ibadan. A completely unselected group, including both outpatients and inpatients, would probably have shown higher figures for patients with heart disease and with ascites of hypoproteinaemic origin, resulting from malnutrition, malabsorption, or helminthiasis. Among children the nephrotic syndrome, abdominal malignancies (including Burkitt's tumours), kwashiorkor, and abdominal tuberculosis are the commonest causes of ascites.

The staple diet in many parts of Africa is rich in carbohydrates and poor in protein. However, no recognizable dietary pattern is discernible among cirrhotics, and the incidence of alcoholism does not seem higher than in the rest of the population. The consumption of "bush teas" or herbal medicines held to be responsible for certain kinds of hepatic disease in the West Indies has not so far been shown to be important in cirrhosis in Africa, but further investigation is required.

TABLE I.—Diagnosis in 91 Inpatients with Ascites Investigated at Ibadan

Diagnosis	No. of Cases	%
Cirrhosis of liver	24	26.3
Abdominal tuberculosis ..	22	24.2
" malignant disease ..	18	19.8
Nephrotic syndrome	18	19.8
Heart failure	8	8.8
Hypoproteinaemia due to malabsorption	1	1.1
	91	100

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Diagnosis : Some Clinical Profiles

The correct diagnosis of the cause of ascites can be reached in most cases by careful consideration of the clinical findings, a chemical and microscopic examination of the ascitic fluid, and some other laboratory and ancillary procedures.

HEPATIC CIRRHOSIS

In ascites due to hepatic cirrhosis the patient is often between the ages of 15 and 50 years, and males are more frequently affected than females.

Some degree of generalized muscle wasting is usually present, and may be marked in the temporals. Sometimes the parotid glands are enlarged. Anaemia due to bleeding varices or haemorrhoids, coexisting hookworms, or malnutrition may be observed. Palmar erythema, gynaecomastia, testicular atrophy, distended abdominal veins, and loss of the masculine hair distribution may be seen, but spider naevi are difficult to identify on dark skins. Jaundice may be present but is not deep till towards the end. Advanced cases may show skin changes frequently seen in hypoproteinaemic states in Africans; the skin especially in the lower limbs is pale and dry and shows a crackled or mosaic pattern, and the hair may lose its normal curliness and some of its normal dark colour.

The liver and spleen are usually concealed by the ascites, but after paracentesis a firm liver edge may be felt in the epigastrium or beneath the costal margin, and a slight or moderately enlarged spleen may become palpable. Liver biopsy and liver-function tests are invaluable in diagnosis. Death may occur from hepatic failure, intercurrent infection, or internal haemorrhage. I have the impression that major bleeding from oesophageal varices is not as common as in the U.S.A. or Europe.

MALIGNANT DISEASE OF THE LIVER

Primary hepatomas may occur alone or in association with hepatic cirrhosis, usually in young or middle-aged males. The history of ascites is usually short, and the liver is hard, nodular and tender. There may be anaemia, and jaundice occurs terminally. Death is usually due to hepatic failure or internal haemorrhage. The clinical picture of secondary carcinoma of the liver, usually from primary disease of the gastrointestinal tract or female genital tract, may be similar to the above except for additional signs of the associated primary neoplasm.

ASCITES DUE TO HEART DISEASE

When ascites is due to heart disease the jugular venous pressure is always elevated, there is oedema of the legs, and triple rhythm or signs of valvular disease can be elicited by clinical examination.

Endomyocardial fibrosis is a disease of obscure aetiology, characterized by carditis, which may be recurrent, and ending in fibrosis of the endocardium and myocardium. Children and young adults of both sexes are affected. Death may occur rapidly during an episode of carditis, or more slowly over a longer period from a combination of the carditis and the haemodynamic consequences of endocardial fibrosis. In right-sided endomyocardial fibrosis the picture may be one of constrictive endocarditis with marked elevation of jugular venous pressure (which may persist after oedema has responded to diuretics), tricuspid incompetence, and ascites which may be resistant to treatment. Abrahams and Brigden⁶ have pointed out that in left-sided endomyocardial fibrosis the picture may be one of mitral incompetence and pulmonary hypertension. Sometimes, however, murmurs are absent or atypical, and only signs of a myocarditis can be detected.

BURKITT'S LYMPHOMA AND OTHER KINDS OF MALIGNANT ASCITES

When ascites occurs in cases of Burkitt's tumours the cause is usually a deposit of this lymphoma in the kidneys, the liver, or the ovaries, or in the region of the coeliac axis. Sometimes a Burkitt's tumour elsewhere, such as in the jaw, orbit, or thyroid exists at the same time.⁹ Those affected are usually children between 2 and 14 years of age. The tumours are often masked by the associated ascites, but sometimes masses can be felt in the epigastrium, right hypochondrium, loins, or suprapubic region, depending on the site of the tumour. Paraplegia due to an extradural Burkitt's tumour is not uncommon.

In other kinds of malignant ascites, such as those due to non-Burkitt lymphomas and peritoneal secondaries from gastrointestinal or genital carcinomas, enlarged malignant lymph nodes in the neck, axillae, or groins may be present as well as other signs of the primary lesion.

ABDOMINAL TUBERCULOSIS

Patients of all ages and both sexes may be affected, but the typical case is a young woman who is anaemic, feverish, wasted, and often complains of amenorrhoea. Ascites commonly exists without clinical signs of tuberculosis elsewhere. Sometimes, however, pulmonary or glandular tuberculosis coexist, and focal signs of pleural or pulmonary disease may be observed on chest examination.

Enlarged tuberculous lymph nodes may also be noted in the neck, groin, or axilla. Particularly in cases associated with malabsorption, steatorrhoea, or chronic diarrhoea, signs of avitaminoses such as angular stomatitis and glossitis, as well as skin changes associated with hypoproteinaemia, may be observed. At necropsy there is usually a combination of peritonitis with mesenteric tuberculous adenitis or ileocaecal tuberculosis.

NEPHROTIC SYNDROME

In ascites due to the nephrotic syndrome the patient is usually a child or a young adult with a puffy face, generalized anasarca, and heavy proteinuria. Signs of hepatic or cardiac involvement are absent.

MALNUTRITION AND HELMINTHIASIS

Ascites due to hypoproteinaemia from malnutrition alone or more often a combination of malnutrition and helminthiasis is not uncommon. Often there is a social problem in the background with poverty and neglect resulting. The clinical picture often assumes the form of "adult kwashiorkor" with anaemia, generalized anasarca, a miserable countenance, and a scaly, cracked, or mosaic skin, especially over the lower limbs.

Heavy infestations with hookworms and *Strongyloides* are seen frequently in these cases, but *Ascaris* or *Trichuris* may also be present, and recurrent amoebic or *Giardia lamblia* infections are not uncommon.

In cases of proved hookworm anaemia Gilles *et al.*¹⁰ found a distinctly lower mean albumin level than in apparently healthy people, and they also found that each worm caused a loss of 0.05 ml. of blood per day. No comparable studies for *Strongyloides* have yet been carried out but there is no doubt that heavy *Strongyloides* infestation can result in marked hypoproteinaemia.

Examination of Ascitic Fluid

A careful chemical and microscopic examination of ascitic fluid pays dividends in the diagnosis of ascites. The most

useful examinations are an estimation of ascitic fluid protein, and microscopic examinations of both an unstained and a stained smear of the centrifuged deposit. Other useful investigations are an ascitic fluid cell count, and an ether test in suspected chylous ascites.

Protein Determination

For this determination 2 ml. of ascitic fluid is collected in a bottle containing sequestrene to prevent protein coagulation. Estimation of protein is by the biuret method¹¹. The value (and limitations) of ascitic fluid protein determinations are shown in the figures from cases seen at Ibadan (Table II).

TABLE II.—*Ascitic Fluid Protein Values in Common Causes of Ascites in Africa*

Diagnosis	No. of Cases	Mean Ascitic Fluid Protein (g./100 ml.)	Range	S.D.	Comment
Cirrhosis ..	20	1.4	0.7–2.6	0.6	2 cases had values > 2.5
Abdominal tuberculosis	15	4.3	1.7–6.4	1.4	3 cases had values < 2.5
Nephrotic syndrome ..	15	0.98	0.2–3.3	0.8	1 case had value > 2.5
Ovarian carcinoma ..	4	5.5	3.9–7.0	—	—
Malignant hepatoma ..	5	2.5	1.5–3.9	—	2 cases value 3.9; the other three < 2.0
Burkitt's lymphoma ..	1	3.2	—	—	—

There is little doubt that in most cases of hepatic cirrhosis and the nephrotic syndrome the ascitic fluid is a transudate with a protein of less than 2.5 g./100 ml. However, a small number of cases have higher figures than this. Fortunately the correct diagnosis can usually be reached in these cases by a consideration of other clinical and laboratory findings.

In congestive cardiac failure the fluid is usually a transudate, but where endomyocardial fibrosis is responsible the fluid may be an exudate, and in a series of 10 cases reported by Abrahams¹² the ascitic fluid protein ranged from 3.4 to 5.7 g./100 ml. In tuberculous peritonitis the ascitic fluid is usually an exudate with protein values above 2.5 g./100 ml. In this disease, however, lower values may occasionally be encountered, especially in patients with a low plasma albumin. Malignant ascites tends to produce exudates, except in malignant hepatoma supervening on a previously cirrhotic liver, where a transudate is common.

Microscopic Examination

Five millilitres of ascitic fluid are centrifuged for 10 minutes, the supernatant is discarded, and some of the deposit smeared on a slide, covered with a cover slip, and examined directly under the microscope. Another smear from the same deposit is dried, fixed in a preparation containing 50% alcohol and 50% ether, and stained with either Leishman or Giemsa stain and then examined.

When they are present in the ascitic fluid microfilaria and trypanosomes may be detected in the wet film by their wriggling movements and confirmed in the stained films. The percentage of red cells present in comparison with other cells can often be roughly assessed in the wet or stained film. This is important if a cell count is contemplated, for when large numbers of red cells are present special care must be taken in the interpretation of the cell counts (see below).

The stained film is of value in the differential count of cells in the ascitic fluid. A high lymphocyte count is characteristic of tuberculosis and lymphomas. A high polymorph count suggests non-tuberculous infection. Malignant cells can be identified in stained films examined by an expert.

Cell Counts

Provided there is no serious contamination with blood, as judged by an examination of the wet preparation, a cell count of ascitic fluid often yields useful information. It provides a further clue to the nature of the ascitic fluid, and in cases where protein levels are equivocal or misleading a cell count may point to the true nature of the fluid.

A count is performed as for white blood cells, using the improved Neubauer counting chamber.

A cell count greater than 500/cu. mm. is commonly found in inflammatory and malignant exudates, while a low count below 300/cu. mm. is characteristic of transudates. Some of the higher counts among the transudates—200–300 cells—are seen in some cases of hepatic cirrhosis, and the predominant cells may be lymphocytes, monocytes, or mesothelial cells.

In cases where there is serious contamination with red cells cell counts are of limited value, but a rough idea of the cell population may be obtained by performing a total cell count, using the red cell counting techniques, and comparing it with a separate white cell count in which a white cell diluting fluid is used to destroy red cells. The final ascitic fluid cell count may then be obtained by subtracting one white cell for every 1,000 red cells from the total "white" cell count.

Chylous and Pseudochylous Fluids

Milky or turbid ascitic fluid due to a high fat content is described as chylous. The turbidity in these cases can be cleared by the addition of a few drops of ether, and microscopic examination shows large numbers of fat globules.

Milky ascitic fluid is usually due to abdominal tuberculosis, malignant peritoneal deposits (especially lymphomas and secondary carcinomatosis), or the nephrotic syndrome.

Chylous ascites due to *Filaria bancrofti* infestation does occur, but is probably not as common as previously thought. The turbidity of pseudochylous ascites is usually due to a high cellular content, as in abdominal lymphomas, and the turbidity is not cleared by ether.

When not due to accidental contamination during paracentesis, haemorrhagic ascitic fluid may be seen in hepatoma and other forms of malignant ascites, and less commonly in tuberculous peritonitis and endomyocardial fibrosis.

A culture of ascitic fluid may yield the offending organism in infectious cases. In tuberculous peritonitis the result is frequently disappointing.

Other Investigations

Apart from general clinical examination, a routine blood count and examination of urine and faeces are essential in the investigation of ascites. In this way cases of anaemia, nephrotic syndrome, and heavy parasitic infections may be suspected and subsequently confirmed by more specific investigations.

X-RAY EXAMINATIONS

Bilateral elevation of the diaphragm is characteristically seen in ascites. A chest x-ray film may also reveal active or old tuberculous foci when tuberculosis is responsible for the ascites. Sometimes a tuberculous pleural effusion is present. More often, however, the chest is clear. Calcified foci seen in chest x-rays are not always tuberculous. Some are due to calcified guinea worms in the chest wall: these often show a coiled appearance. In ascites of cardiac origin there is usually a large heart shadow (except in constrictive pericarditis), and pulmonary congestion or frank hydrothorax may be evident. In endomyocardial fibrosis the heart shadow is large and may show configurations suggestive of

pulmonary hypertension or a giant right atrium. When ascites is due to a malignant intra-abdominal lesion such as a gastric carcinoma pulmonary metastases may be seen in the chest. In Burkitt's tumour, however, pulmonary metastases are rare.

A straight x-ray of the abdomen may rarely show calcified tuberculous nodes. Care must be taken, however, to distinguish these foci from calcified helminths (for example, porocephalus or guinea worms) and phleboliths. In Burkitt's tumour an x-ray of the jaw may show the characteristic x-ray findings of multiple foci of bone resorption or large osteolytic areas with displacement of teeth.

Barium studies of the gastrointestinal tract may reveal oesophageal or gastric varices in cases of cirrhosis or hepatoma. Dilatation of the small bowel is commonly seen in tuberculous peritonitis, while segmental narrowings in the ileum and filling defects in the caecum may be seen in ileo-caecal tuberculosis. In cases of malignant ascites due to primary lesions in the gastrointestinal tract, the tumour may be located by barium meal or enema.

TUBERCULIN TEST

A negative tuberculin test may occur in up to 10% of patients with proved abdominal tuberculosis. A negative test therefore does not rule out abdominal tuberculosis, though it counts against it. When the test is negative it should be repeated before any firm conclusions are drawn.

PLASMA PROTEINS

A determination of the total and differential plasma proteins is essential for an understanding of the precise mechanism of ascites. Hypoproteinaemia with a low albumin/globulin ratio is usually associated with ascites and oedema in malnutrition, kwashiorkor, nephrotic syndrome, and many cases of hepatic cirrhosis. A low level of plasma albumin may explain an unexpectedly low ascitic fluid protein in abdominal tuberculosis or hepatoma.

LIVER-FUNCTION TESTS

The most useful test of liver function is the bromsulphalein (B.S.P.) test. Five milligrams per kilogram body weight of B.S.P. is injected intravenously, and estimations of blood level of the dye are made 5 and 45 minutes respectively after the injection. Values of 6% retention and below after 45 minutes are regarded as normal. In hepatic cirrhosis and malignant hepatoma values well above 10% are usual. In abdominal tuberculosis the B.S.P. test is usually normal. Values between 10 and 20% may be seen in some cases of endomyocardial fibrosis.

The biochemical tests of liver function usually give results suggestive of hepatocellular involvement in cirrhosis and hepatoma—abnormal thymol turbidity and thymol flocculation tests, normal or slightly elevated values for the alkaline phosphatase levels, slight to moderate elevation of transaminase levels, and normal values or slight elevation of serum bilirubin levels. On the whole these tests are somewhat less consistent than the B.S.P. test, and are occasionally normal in some cases of proved hepatic cirrhosis.

BIOPSY

A liver biopsy is of particular value in the diagnosis of cirrhosis or hepatoma. When malignancy supervenes on an already cirrhotic liver, however, the biopsy needle may miss the malignant nodules and give misleading results.

In hepatic fibrosis due to *S. mansoni* the characteristic "pipe stem" fibrosis may be recognized on liver biopsy, and *S. mansoni* ova may be obtained by digesting a small piece of liver tissue.

In abdominal tuberculosis the liver is either normal or shows evidence of fatty change. Rarely a tuberculosis nodule in the liver may be diagnosed by liver biopsy.

Renal biopsy may confirm the diagnosis of membranous glomerulonephritis or amyloidosis in cases of nephrotic syndrome with ascites. The value of lymph-node biopsies needs no further elaboration. Peritoneal biopsy may provide evidence of peritoneal tuberculosis, or more rarely of malignancy. However, because serious internal haemorrhage may occasionally complicate blind biopsies of internal organs, these admittedly valuable procedures should be carried out only where adequate laboratory facilities exist for estimating prothrombin time and for providing an efficient blood transfusion service if the need arises.

Management

Diagnosis is the key to a rational management of ascites. While it is true that some improvement may be expected in all forms of ascites when a negative sodium balance is induced by dietary restriction and diuretics, lasting improvement is more often the result of specific therapy or the subsidence or alleviation of a critical precipitating factor—for example, gastrointestinal haemorrhage or severe malnutrition.

For diagnosis and in the early stages of treatment admission into hospital is advisable.

Abdominal Tuberculosis

This is the most gratifying form of ascites to treat. The result of treatment is so satisfactory in all but late cases that a therapeutic test with antituberculous drugs for several weeks is justified in all patients with ascites, pyrexia, and loss of weight who have no obvious hepatic, renal, cardiac, or malignant disease.

Whenever possible all three standard antituberculous drugs should be used in the first few weeks, or at least for the duration of the patient's stay in hospital. The drugs are streptomycin 1 g. daily by injection; paraaminosalicylic acid 5 g. thrice daily by mouth; and isoniazid 300 mg. daily by mouth.

After the patient's discharge from hospital treatment should be continued with P.A.S. and isoniazid daily for a period of 18 months. When pulmonary tuberculosis is also present the period of streptomycin therapy should be at least 6–12 weeks. This is followed by isoniazid and P.A.S. for 18–24 months.

Where signs of malnutrition are present pyridoxine 150 mg. daily should also be given. Iron and folic acid may also be required for anaemia, and a good nutritious diet also hastens recovery.

The consequences of failing to take the drugs regularly should be explained to all patients and re-emphasized during the monthly follow-up visits.

Anaemia and hypoproteinaemia in abdominal tuberculosis are sometimes partly a result of coexisting heavy hookworm infestation; and recurrent diarrhoea may be due to strongyloidiasis, amoebiasis, or giardiasis. Where the response to treatment, as judged by fall in temperature, rise in haemoglobin, fall in sedimentation rate, decrease in the girth of the abdomen, and increase in weight (after the resolution of the ascites), are unsatisfactory after six weeks' treatment, further investigation for other coexisting diseases should be undertaken and specific therapy instituted where necessary.

Hepatic Cirrhosis, Cardiac Disease, and the Nephrotic Syndrome

Certain general principles are applicable in the management of ascites due to cardiac, renal, or hepatic diseases. A low sodium diet should be given. This can be arranged easily in well-staffed hospitals by the dietitian. In less fortunate institutions this can be achieved for practical purposes by avoiding salt in the cooking, avoiding salted foods, butter, and

tinned foods, and relying as much as possible on a diet made up of fruits, sugar, boiled rice, and fresh vegetables.

A simple diuretic such as hydrochlorothiazide 50 mg. b.d. should be supplemented in resistant cases with spironolactone 25 mg. four times daily; potassium supplements such as potassium chloride 15 g. t.d.s. are usually required to prevent hypokalaemia. In addition to the measures mentioned above, digoxin may be required in cardiac disease.

In the nephrotic syndrome steroids are sometimes effective. A high protein diet—100 g. of protein a day—is required in malnutrition, nephrotic syndrome (without azotaemia), and in hepatic cirrhosis (provided signs of hepatic precoma are absent). Vitamin supplements are also useful in malnutrition and states of suspected undernutrition. Alcohol is forbidden in all patients with hepatic cirrhosis.

Paracentesis

The removal of ascitic fluid is often required for diagnostic purposes and for the relief of discomfort in patients with massive ascites. Because of serious complications like hypotension, oliguria, hyponatraemia, and hepatic coma, which have sometimes followed massive evacuation of ascitic fluid, it is wise to limit the fluid removed on each occasion to 2–3 l.

Malignant Ascites

The treatment of ascites due to malignant disease is usually unrewarding, but in the lymphomas, including Burkitt's tumour,

chemotherapy with nitrogen mustards and related agents may occasionally produce surprising results and should be given a trial wherever feasible.

The drug used most often in these cases is cyclophosphamide, which is given intravenously in doses of 30–40 mg./kg. body weight.¹³ One or two doses are often adequate to produce remissions lasting from months to several years in responsive cases of Burkitt's tumours. These drugs are marrow depressants, and should be used only by those who are familiar with their side-effects.

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TODAY'S DRUGS

With the help of expert contributors we publish below notes on a selection of drugs in current use.

New Drugs against Tuberculosis

Capreomycin and ethambutol are new antituberculosis drugs undergoing clinical trial. They are the subject of a recent monograph published by the New York Academy of Science.¹

Capreomycin

Capreomycin is a peptide antibiotic derived from *Streptomyces capreolus*. There is no cross-resistance with streptomycin but there are varying degrees of cross-resistance with viomycin and kanamycin. Patients who have received previous treatment with either of these drugs may have organisms resistant to capreomycin.

The toxicity of capreomycin is similar in type to that of streptomycin. In the usually recommended dose of 1 g. daily vestibular disturbance, deafness, and renal impairment have occurred. The incidence of ototoxicity appears to be no greater than that with streptomycin. The reported incidence of nephrotoxicity has varied, and more needs to be known about its long-term effects. Regular observations of renal function should be maintained during capreomycin therapy.

Used as the only companion drug to either P.A.S. or isoniazid, capreomycin appears to be less effective than streptomycin in the treatment of pulmonary tuberculosis. Given in combination with both P.A.S. and isoniazid in a controlled trial in Japan, capreomycin was as effective as streptomycin. However, capreomycin has no place in the initial

treatment of new cases of tuberculosis except to replace streptomycin in patients with intractable streptomycin hypersensitivity. The main indication for capreomycin is as a secondary drug for the treatment of drug-resistant tuberculosis. Capreomycin is less toxic than viomycin and kanamycin, and may be used in preference to these. It is of no value in treating infections other than tuberculosis. It is a relatively expensive drug.

Capreomycin is marketed under that name by Dista Products Ltd. The basic N.H.S. cost of 5 vials of 1 g. is 58s. 10d.

Ethambutol

Ethambutol is a synthetic compound whose chemical structure ((+)-NN'-Di-(1-hydroxymethylpropyl)ethylenediamine) differs from all other antituberculosis drugs. It is active against *Mycobacterium tuberculosis*, *M. bovis*, and some anonymous mycobacteria but is inactive against other organisms. No cross-resistance with other antituberculosis drugs has been observed.

Studies in which ethambutol has been given as the only drug have confirmed a favourable effect in human pulmonary tuberculosis. The emergence of ethambutol-resistant organisms in many of these patients indicates the need to combine ethambutol with another drug to prevent resistance.

Controlled studies in pulmonary tuberculosis comparing ethambutol and isoniazid with P.A.S. and isoniazid have been made in Japan and the U.S.A. The results suggest that ethambutol 25 mg./kg. body weight in a single daily dose may be as effective as P.A.S. as a companion drug to isoniazid. Ethambutol has proved promising as an addition to the armamentarium of secondary drugs for the treatment of patients whose organisms are resistant to the primary drugs streptomycin, isoniazid, and P.A.S. Ethambutol in doses of up