Where the term embraces minor disturbances in the liver the incidence of malignant change is low, while if the diagnostic criteria are stringent the incidence appears higher (Parker, 1957). For this reason the results in Table II cannot strictly be compared, and serve only to give a general impression. Adopting the same criteria as the present series, Sherlock (1958) found an incidence of carcinoma in cirrhosis of 14%.

Table III shows that malignant change has been recognized more frequently in successive five-year periods, although undue emphasis should not be placed on this increase owing to the small number of patients studied. The incidence of primary liver carcinoma in cases of cirrhosis at necropsy for the last five years was 28.3%. Thus a tumour which is rare in the whole population is common in relation to a small group of patients with cirrhosis. Appreciation of the frequency of the condition will be more likely to suggest the diagnosis than a search for or reliance upon diagnostic signs and tests.

The apparently high incidence of malignant change may be due either to a real increase or to improved methods of recognition. We are not in a position to decide this point.

A feature of interest is the association of peptic ulcer with cirrhosis and hepatoma. Active chronic peptic ulcer occurs in 4 to 8% of all hospital necropsies (Watkinson, 1960). A greater incidence in cirrhosis is well recognized, figures as high as 19.5% being quoted (Lipp and Lipsitz, 1952). In the present series 14.2% of patients dying with cirrhosis were found to have chronic peptic ulcers. Macdonald and Mallory (1958) showed the incidence in hepatoma to be higher (16%) and in the present series the incidence of chronic peptic ulcer in those dying of hepatoma was 23.3%. No explanation for this is offered, but from the clinical standpoint the association may be of some importance, since further investigation of upper

abdominal pain in cirrhosis may be abandoned when an ulcer is demonstrated unless it is appreciated that cirrhosis, hepatoma, and ulcer may often coexist.

Summary

The incidence of primary carcinoma of the liver at necropsy was studied over a period of 23 years (1940-62) at a London teaching hospital.

Among 7,366 necropsies there were 157 cases of cirrhosis and 39 cases of primary hepatic carcinoma.

The incidence of malignant change in cirrhosis was 19.1% over the whole period. Analysis by five-year periods showed an apparent increase to 28.3%. Active chronic peptic ulcer occurred in 14.2% of cases with cirrhosis and in 23.3% of those with primary carcinoma of the liver.

Malignant change in cirrhosis appears to be common.

We are indebted to the physicians of St. Thomas's Hospital for permission to study patients under their care.

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INFECTION DUE TO MYCOBACTERIUM AVIUM

BY

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Disease due to *M. avium*, the avian variety of the tubercle bacillus, has been regarded as very rare in man (Feldman, 1938). Only two well-established cases have so far been reported in Britain (Bradbury and Young, 1946; Furniss *et al.*, 1961), but since *M. avium* closely resembles certain of the "anonymous" mycobacteria in its cultural and biochemical properties, it was decided to investigate anonymous strains collected by the Tuberculosis Reference Laboratory during the last 10 years. The study was confined to 16 isoniazid-resistant thermophilic strains, taken at random from a series of 18 incriminated as pathogens. The case reported by Furniss *et al.* is also described, because the strain belonged originally to the series being surveyed (Case 4).

Material and Methods

The strains in the present series were classified presumptively as pathogenic because of their repeated isolation either from pus in cervical adenitis or from sputum in patients with pulmonary disease in the absence of other pathogens. In each case in which it was possible, histological examination of resected or post-mortem material

supported the diagnosis of mycobacterial infection. Strains were stored at 4° C. but subcultured every three months on Löwenstein medium before their examination as a group in 1962-3.

Strains 40529 and 35445 were submitted for identification by laboratories in England, but the remainder were recovered in the routine work undertaken for Wales.

Fowl Inoculations.—The main experiment employed 16 8-week-old Rhode Island Reds, housed separately. All fowls were shown before use to be tuberculin-negative to 0.05 mg. of avian P.P.D. injected into the wattle. Those which survived 12 weeks were retested. A fully grown culture in Dubos medium was inoculated into a pectoral muscle and intraperitoneally in a dose of 0.5 ml. (about 0.25 mg.) by each route except with strain 35445, for which the dose was 1 ml. Certain additional fowls were inoculated similarly but given 0.002 mg. intravenously as well. Fowls in the main series which survived 12 weeks were killed after their tuberculin test and examined by the methods used for those dying spontaneously. Impression films and sections were made of lung, liver, spleen, and kidney, and portions of these organs were pooled for

culture. Films and sections were stained by the Ziehl-Neelsen method, in the latter case followed by haematoxylin. The additional fowls were examined by individual cultures of the liver and spleen and sections of these organs and the lung.

Rabbit Inoculations.—Each strain was injected intravenously into a rabbit in a dose of 0.01 mg. Individual cultures were made of the liver and spleen of animals that died, impression films of these two organs and the lung, and sections of all three, together with the kidney. The minimum of decolorization was used in staining sections by the Ziehl-Neelsen method since *M. avium* decolorizes rather easily in tissues. Animals which survived seven weeks (eight in one case) were killed and examined similarly.

Description of Strains.—As judged by the imperfect criteria available, our 17 strains correspond to the anonymous mycobacteria designated "Battey" organisms and assigned to Group III of Runyon's (1959) classification. They resemble *M. avium* in giving effuse buff growth which emulsifies well—the bacilli usually being short—in growing well at 42° C., and in growing deep in semi-solid medium. Considerable resistance is exhibited to most anti-tuberculosis drugs. A fuller description of the series has been given by Marks and Richards (1962).

Results

Strains from 10 of the 17 patients investigated proved to be *M. avium* on the basis of our pathogenicity tests. Both of the cervical adenitis strains are included and 8 of the 15 from pulmonary infections. Where reference is made below in the text or Table to tuberculosis in fowls or rabbits, the pathological features characteristic of *M. avium* infection are implied unless a qualification is made. The disease in rabbits was largely of the Yersin type. Each strain isolated from the viscera of infected animals was found to have the same cultural properties as that originally inoculated.

The present investigation did not include guinea-pig inoculations, since these had been carried out at the time of isolation. None of the strains produced more than a local abscess in guinea-pigs.

A short account of each case of *M. avium* infection follows, but the corresponding experimental findings are collected together in the Table. In summary, all 10 strains diagnosed as *M. avium* were lethal for fowls, and six were lethal for rabbits. In both species death was clearly due to progressive tuberculosis. The four avian strains that failed to kill rabbits in the experimental period nevertheless produced varying degrees of progressive tuberculosis.

The partial loss of virulence for rabbits in these strains may have been due to their prolonged maintenance in the laboratory before the test.

Case Histories

The date given after the case number is that of the first isolation of the strain or its receipt from another laboratory.

Case 1 (1961).—A girl aged 3 complained of a recent cough. A cervical abscess was found near the right mandibular joint. Aspiration produced 0.5 ml. of pus. No organisms were seen on microscopy, and culture for banal organisms was negative, but acid-fast bacilli resembling *M. avium* in the manner described above were grown (strain 41258). Pus aspirated three weeks later gave a similar result (strain 2268). Three months later a Mantoux test with 10 T.U. of old tuberculin in one forearm and a dose of 0.0002 mg. of avian P.P.D. in the other gave reactions of the following diameter after 48 hours: avian P.P.D.—erythema 24 mm., induration 17 mm.; O.T.—erythema 10 mm., induration 7 mm. There was no history of drinking raw milk or of especially close contact with birds.

Case 2 (1961).—A girl aged 5 had cervical adenitis apparently secondary to a lesion of the gum. Pus from the lymph nodes was negative on guinea-pig inoculation but yielded a growth of acid-fast bacilli resembling *M. avium* (strain 40529). Specimens were similarly positive 9 and 12 days later. The gum lesion was thought to be tuberculous after histological examination of a biopsy.

Case 3 (1960).—A butcher aged 26, in whom pleurisy was diagnosed in 1955, was seen in 1958 for cough and loss of weight, and a small apical lung lesion was found. Little or no change was seen during the next 14 months, but in 1960 a tomogram showed a small cavity. On his admission to hospital six successive specimens of sputum were positive on culture for acid-fast bacilli resembling *M. avium* (strain 10861). Three specimens examined two months later were similarly positive. The lung lesion was resected and found grossly and microscopically to be fibro-caseous tuberculosis; it was not cultured. In the two years following the operation 14 specimens were examined and all found negative. Since *M. avium* infections occur in cattle and pigs it seems likely that this patient contracted his infection through his work.

Case 4 (1960).—A woman aged 60 had a long history of achalasia of the cardia. Aspiration pneumonia may have prepared the ground for her infection, which proved fatal. An account of this case has been published by Furniss *et al.* (1961).

The remaining patients were all coal-miners with pneumoconiosis. The majority, if not all, had had negative bacteriological examinations at various times before the isolation of *M. avium*, but records of these are incomplete.

Case 5 (1953).—A miner aged 49, in whom pneumoconiosis was certified in 1950, complained of cough, dyspnoea, haemoptysis, and lassitude, and was suspended from work in 1954; he did not deteriorate seriously, however, until 1956. A lung

Pathogenicity Tests Identifying *M. avium* Infections in 10 Patients

Case No.	Strain	Fowls: Survival and Post-mortem Findings				Rabbits: Survival and Post-mortem Findings			
		Survival in Days	Degree of Visceral Tuberculosis	A.F.B. Present on Microscopy	A.F.B. Present on Culture	Survival in Days	Degree of Visceral Tuberculosis	A.F.B. Present on Microscopy	A.F.B. Present on Culture
1	41258	33*	+++	+++	+++	27	+++	+++	+++
	2268(a)	36*	+++	+++	+++	23	+++	+++	+++
	2268(b)	(84)	++	+	+				
2	40529	53	+++	+++	+++	23	+++	+++	+++
3	10861	53	+++	+++	+++	26	+++	++	+++
4	35445(a)	35*	+++	+++	+++	(56)	+	+	++
	35445(b)	21	+++	+++	Not done				
5	16515	83	+++	+++	+++	18	+++	+++	+++
6	1150	39	+++	+++	+++	(49)	++	+	++
7	4127	56	+++	+++	+++	(49)	++	++	++
	14148	36	++	+++	+++				
8	2038	60	+++	++	+++	(49)	+	Scanty	++
9	8775	39	+++	+++	+++	28	+++	+++	+++
10	22846	33	+++	+++	+++	31	+++	+++	+++
	1180	21*	++	++	+++				

All the animals died of their infection except five which were killed at the times given in parentheses. Each strain cultured at necropsy was checked by *in vitro* tests for similarity to the strain inoculated.

* These fowls were given 0.002 mg. of culture intravenously in addition to the normal inoculation.

cavity had been noted in 1950. Cultures of sputum made between 1953 and his death in 1956 were positive on 23 occasions for acid-fast bacilli resembling *M. avium* (strain 16515). Smears were mostly positive also. A diagnosis of pneumoconiosis with caseating chronic pulmonary tuberculosis was made at necropsy. Acid-fast bacilli rather longer than *M. tuberculosis* were seen in sections, and cultures from a lung lesion and from a bronchus yielded organisms resembling *M. avium*. A portion of the lesion inoculated into a guinea-pig produced a small local abscess; its viscera appeared normal but were not examined microscopically.

Case 6 (1956).—This patient was a man of 56, in whom pneumoconiosis with cavitation was diagnosed in 1953, several years after ending eight years' work as a miner. Sputum was first cultured in 1956, and from then until the last examination in 1962 it was positive 16 times for acid-fast bacilli resembling *M. avium* (strain 1150); smears were often positive also. There was gradual deterioration in his condition over this period, the symptoms resembling those of bronchitis and emphysema. He died in 1963, quiescent fibro-caseous tuberculosis being found at necropsy.

Case 7 (1957).—A man of 69 ceased work as a miner in 1941 and was compensated for pneumoconiosis in 1947. He was fairly well until 1957, when he developed haemoptysis and lost weight. A cavity on a pneumoconiotic background was found. Sputum was positive on smear, and culture yielded acid-fast bacilli resembling *M. avium* (strain 4127) which have been found in 12 more cultures made up to 1961; smears were mostly positive also. His general condition was noted in July, 1962, as being reasonably good, but *M. avium* was isolated again in 1963 (strain 14148).

Case 8 (1958).—A man of 51 was certified as pneumoconiotic in 1945 after 21 years in mining. In 1948 he complained of a recent cough and dyspnoea on exertion. Progressive massive fibrosis with a cavity was found and sputum was positive on smear. Culture yielded acid-fast bacilli resembling *M. avium* (strain 2038). Five further cultures were similarly positive in 1958, two were negative in 1959, one out of four was positive in 1961, and three were positive in 1963. Haemoptysis occurred in 1959, but otherwise no important change in his condition is recorded.

Case 9 (1959).—A man of 64 who ceased mining in 1942, when certified as pneumoconiotic, was found to have progressive massive fibrosis when seen in 1951 for cough and sputum; two specimens were negative. In 1959 cavitation was noted and the sputum found positive on smear; culture yielded acid-fast bacilli resembling *M. avium* (strain 8775). Ten further specimens were similarly positive in the period to his death a year later. Massive fibrosis, with a tuberculous cavity and tuberculous bronchopneumonia, was diagnosed at necropsy, but no cultures were made.

Case 10 (1960).—A man of 75, who had been a miner for 40 years, complained of haemoptysis, and bilateral lung fibrosis with cavitation was found radiologically. Sputum was positive on smear, and culture yielded acid-fast bacilli resembling *M. avium* (strain 22846); it has been similarly positive on culture, and mostly by smear also, on 20 occasions in the last three years. The most recent positive culture in 1963 (strain 1180) has been tested in a fowl as well as by *in vitro* methods.

Infections Due to Anonymous Mycobacteria

The seven remaining strains inoculated into fowls gave largely negative results. All the patients concerned were men with pulmonary lesions, four having a history of pneumoconiosis. None of the fowls died and all were in good condition when killed after 84 days; by that time six had become reactors to avian P.P.D. One bird had small lesions resembling tuberculosis in the spleen and liver, while acid-fast bacilli were found in small numbers on microscopy and culture. The status of the strain concerned is uncertain at present. Only trivial reactions were found in sections of the viscera of the other six birds, although five gave scanty growths of acid-fast bacilli on culture and rare

bacilli were seen in one spleen section. The rabbits inoculated with the same seven strains were in good-to-excellent condition when killed after seven weeks. No lesions of any significance were found in the viscera and no acid-fast bacilli were seen in the sections or impression smears. Very scanty growths of acid-fast bacilli were obtained from liver in three cases and from the spleen in one case.

Discussion

Griffith (1938) reported his failure to find any avian infections among 7,800 cases of tuberculosis. The incidence of *M. avium* in our routine material has not yet been ascertained exactly, but if cases with pneumoconiosis are excluded as a regional feature it is probably rather less than 1 in 5,000 strains of tubercle bacilli and so not necessarily inconsistent with Griffith's experience. Nevertheless, an increase in the incidence of *M. avium* infections in recent years cannot be excluded, although, as with infections with anonymous mycobacteria, it will be difficult for some time to decide whether any apparent increase is real or due to better recognition. It would not be surprising, however, if the recession of ordinary tuberculosis in Britain offered an opportunity to the less virulent mycobacteria. As changes in incidence are likely to be slow, the problem will best be solved by accurate periodic surveys.

Accounts of avian tuberculosis in man appear more frequently in Germany than in Britain. Nassal (1961) has reviewed the subject in presenting a large series of his own cases, but it is not clear in what proportion the diagnosis of *M. avium* infection was supported by repeated isolation of the organism.

Another epidemiological approach is by means of community tuberculin tests. Recent work with avian tuberculin and allied antigens indicates that subclinical infection with *M. avium* may not be rare and that such infection has to be considered as a possible cause of non-specific reactions to mammalian tuberculin (Flynn, 1962; Hart *et al.*, 1962; Griffith *et al.*, 1963).

An *M. avium* infection associated with pneumoconiosis was reported by Karlson *et al.* (1955). The six cases described above attest to the adverse effect of pneumoconiosis on resistance to invasion by mycobacteria.

It would be of interest to compare the pathogenicity of *M. avium* for man with that of the anonymous mycobacteria, but deductions from the incidence of infection suffer from our ignorance of the relative degrees of exposure. It seems likely, however, that *M. avium* ranks below *M. kansasii* and *M. scrofulaceum* in this respect.

At present *M. avium* cannot be distinguished from certain anonymous mycobacteria except by pathogenicity tests. The development of *in vitro* methods would be an advantage, for a closer watch on infection with these organisms appears desirable in the future.

Summary

Animal tests on a number of strains collected as anonymous mycobacteria at the Tuberculosis Reference Laboratory have disclosed nine cases of *M. avium* infection in addition to one already reported. In all, the series consists of two cases of cervical adenitis in children and eight lung infections in adults. The latter included a butcher, a woman with achalasia of the cardia, and six coal-miners with pneumoconiosis.

As tuberculosis recedes it is possible that infections by *M. avium* and other mycobacteria of low virulence for man may increase.

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ORAL SYMPATHOMIMETIC AMINES IN TREATMENT OF ASTHMA

BY

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Since the work of Barger and Dale (1910) adrenaline has been one of the most effective remedies in certain forms of acute asthma. It has usually been given by subcutaneous injection or by inhalation as a wet or dry aerosol. Its obvious value has led to much research by pharmaceutical firms into the development of sympathomimetic analogues that could be given by mouth in tablet form. Obviously the most desirable analogue would be one with the following properties: (1) it would be active—that is, relieve asthma—when taken by mouth; (2) it would be without undesirable side-effects, especially pressor side-effects such as tachycardia, palpitations, and hypertension; and (3) its action would be more sustained than the transient action of adrenaline by injection or inhalation.

Four sympathomimetic amines with adrenaline-like properties have been investigated—namely, ephedrine sulphate, isoprenaline sulphate, methoxyphenamine hydrochloride ("orthoxine"), and orciprenaline ("alupent"). Crude ephedrine has been known to Chinese medicine for some five thousand years, and since the work of Chen and Schmidt in 1924 ephedrine sulphate has been widely used for the treatment of asthma, but has often caused undesirable side-effects, such as palpitations, sleeplessness, and dysuria. Of the newer sympathomimetic drugs, isoprenaline sulphate has been used extensively during the past ten years in the form of sublingual tablets and was reported to have a quicker but shorter action than ephedrine (Konzett, 1940). More recently still, methoxyphenamine has been given by mouth in the treatment of asthma. Curry *et al.* (1948) reported that they found methoxyphenamine to be at least as effective as ephedrine, and in roughly 30% of the cases more effective than ephedrine in the treatment of "mild spontaneous asthma." These authors also found that a number of patients who were "jittery" on ephedrine were free from this complaint when treated with methoxyphenamine. Ten years later Pearson (1958) reported that the bronchodilator effect of methoxyphenamine and ephedrine was approximately the same but the great majority of patients had a preference for methoxyphenamine, and that there was no advantage in giving methoxyphenamine in doses larger than 100 mg. t.d.s. (Pearson, 1957).

The most recent oral antispasmodic with sympathomimetic properties to come on the market is orciprenaline. Preliminary continental clinical trials on patients with chronic bronchitis and asthma (Günthner, 1961; Zidek, 1961) reported that orciprenaline had a spasmolytic effect when given by mouth or inhalation. These preliminary reports of the efficacy of orciprenaline by mouth, by

inhalation, and by subcutaneous injection have been confirmed (Kennedy, 1963).

The purpose of the comparative trial which is reported here was to study the effects of these different preparations in asthmatic individuals who were known to have usually a consistently good response to aerosol adrenaline. It has been reported (Kennedy, 1961) that individual asthmatics react very differently to aerosol adrenaline, and for this reason only individuals who were known to respond to adrenaline were chosen for the comparative trial, as it is rather pointless to assess the effect of sympathomimetic drugs in individuals who do not benefit from them.

Material and Methods

Twelve asthmatics (five women and seven men) were chosen for this trial; their ages ranged from 16 to 64 years. Most of them had had perennial asthma for many years. Eight of the 12 were receiving supportive therapy in the form of oral corticosteroids or intramuscular corticotrophin at the time of the trial. Earlier studies in these patients had shown that usually they had a consistently good response to aerosol adrenaline. The magnitude of the response varied from individual to individual—adrenaline inhalations usually effected an improvement of 20% or more in the indirect maximum breathing capacity (M.B.C.).

The effect of the individual drugs was assessed by the indirect M.B.C. test (Kennedy, 1953)* before the start of the trial and at half-hourly intervals after the administration of each drug for a period of four hours. At the end of that period an inhalation of adrenaline was given and a further assessment of the indirect M.B.C. was made.

Sympathomimetic Amines Investigated.—The dose of the drugs under trial was as follows: (1) ephedrine 30 mg. by mouth, (2) isoprenaline 10 mg. sublingually, (3) methoxyphenamine 100 mg. by mouth, (4) orciprenaline 10 mg. by mouth, (5) orciprenaline 20 mg. by mouth, (6) a placebo tablet consisting of lactose by mouth. Tests with the various drugs were carried out on different days and were started at 9 a.m. and carried on until 1 p.m. Apart from the respiratory physiological indices, serial recordings of the pulse were taken and the incidence of untoward side-effects was noted.

Results

The results have been analysed in two ways. (1) An analysis of the behaviour to the different test substances was made by preparing separate charts for each individual patient on which were plotted the serial indirect M.B.C.

*Indirect M.B.C. $\equiv$ F.E.V._{0.75} $\times$ 40.