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THE EPIDEMIOLOGY OF TUBERCULOSIS*

BY

JOHN W. S. BLACKLOCK, M.D., F.R.F.P.S.

(From the Department of Pathology and Bacteriology, the University and Royal Infirmary, Glasgow)

The earliest observation on the contagious nature of tuberculosis occurs in the Ordinances of Manu in India, thirteen centuries B.C. In these, pulmonary consumption and swelling of the glands of the neck are declared to be unclean, incurable diseases. Those who wanted to marry are cautioned not to select a spouse from a consumptive family even though the family had a good lineage and possessed great wealth. These laws show a knowledge of tuberculosis, and as the disease was regarded as an impediment to marriage it seems likely that it was regarded as contagious. In Europe the earliest reference to the contagious nature of tuberculosis was made by the Greek orator Isocrates in his *Aegineticus* (§ 29), written about 390 B.C. In this he states: "The majority of those who had nursed this disease [phthisis] had themselves fallen victims to it." The Hippocratic school, however, did not generally subscribe to this view, preferring the idea of the tuberculous diathesis which has persisted even to the present day. About one hundred years later Aristotle realized that consumption could be spread by close contact with the diseased person. Galen and Avicenna held similar views. It is more than a tragedy that these early Greek observations were disregarded and forgotten in later centuries, for it was only towards the end of the seventeenth century that in Latin countries such as Spain and Italy the contagious nature of the disease was again being recognized. In Britain, Edward Mainwaring was possibly the first to assert that tuberculosis was spread by contact, as in 1667 he wrote: "You must not frequently converse with a phthisical person whose unwholesome breath may infect the sound by drawing in putrid vapours which the other breathes forth, but above all a phthisical bedfellow is most dangerous to affect a sound person and chiefly to be avoided."

Later, in 1694, Richard Morton in his book *Phthisiologia*, which is an outstanding presentation of the symptomatology of tuberculosis, wrote: "A contagious principle also propagates the disease, for, as I have found by experience, an affected person may poison a bedfellow by a kind of miasm like that of a malignant fever." Towards the middle of the nineteenth century, however, leaders of the profession like Bright and Addison (1839), also Graves (1843), almost completely disregarded the contagiousness of tuberculosis, and attached great importance to diathesis. This unparalleled reverence for the past with its diathesis had so dominated men's minds that little or no progress had been made for centuries regarding the true nature of the disease. Laennec (1826), though he unified the whole

concept of tuberculosis by asserting that wherever tubercles occurred the disease was tuberculosis, was of the opinion that at least in France tuberculosis was not usually contagious. That tuberculosis could be produced in animals by inoculation with tuberculous material was shown in 1843 by Klencke, and in 1868 Villemin finally proved experimentally that tuberculosis was an infectious disease. It was Villemin who first showed that tuberculous material from bovine sources was more virulent for rabbits than that from human. In 1867 William Budd, of North Tawton, as a result of a study of the geographical distribution of consumption in past and present times, concluded: "The tuberculous matter itself is (or includes) the specific matter of the disease and constitutes the material by which phthisis is propagated from one person to another and disseminated throughout society." Even after the discovery of the tubercle bacillus by Koch in 1882 we find from the Collective Investigation Record (British Medical Association, 1883) that many British physicians reported that they had never observed a case of probable transmission of the disease from a case of phthisis. Later, Theobald Smith (1896, 1898) reported the existence of "a distinctively human or sputum, and a bovine variety of tubercle bacillus."

Though Koch proved that the tubercle bacillus was the *causa peccans* and stressed the importance of inhalation of infected sputum in the spread of the disease, it is strange how in 1901, while accepting that human and bovine types were different, he yet concluded that the latter was rarely pathogenic for man. Koch (1882) had undoubtedly found the bovine bacillus in human disease, for he had obtained from a case of caseous pneumonia (No. 27) a culture of tubercle bacilli which after inoculation into the anterior chamber of the eye proved virulent for rabbits. In 1911 the British Royal Commission proved conclusively that the bovine bacillus was a definite cause of tuberculosis in man. It is not surprising that Koch went astray when we consider the relative rarity of primary abdominal tuberculosis in Germany as compared with this country. Indeed, Koch himself in his address gave post-mortem statistics from various German sources to support the rarity of this condition. At a later date Ghon and Kudlich (1930) found in 2,114 cases of tuberculosis in children in Central Europe a primary intestinal infection in only 24 (1.14%) and tonsils infection in 2 (0.09%).

Cycle of Infection in Human and Bovine Tuberculosis

The two chief varieties of tubercle bacilli to be considered are the human and the bovine types, as they are almost solely responsible for disease in man and in animals.

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The avian may be dismissed, owing to the rarity of this type of infection in the human subject (Gloyne, 1933; Feldman, 1938; Bradbury and Young, 1946). The human type passes from man to man, more often by droplet infection than through the agency of dried sputum.

Infection with the bovine type is found chiefly in cattle, though many other types of animals and also man are liable to be infected. The chief mode of spread in cattle is by droplet infection, and thus, as in man, the primary lesion is most often in the lungs. Man is infected with bovine bacilli chiefly through the ingestion of contaminated milk, though air-borne infection is also possible, as is well exemplified in the cases of bovine conjunctival tuberculosis in milkers reported by Jensen *et al.* (1940). The cycle of infection, however, does not stop there (Fig. 1), as it has

FIG. 1.—The cycle of infection in man and in animal.

been observed that bovine infection may pass back from man to cattle (Magnusson, 1941, 1942; Griffith and Munro, 1944; Plum, 1940; Nielsen and Plum, 1939; Tice, 1944), and also from man to man, as in the five proved cases reported by Griffith and Munro (1935), Munro (1939), Jensen *et al.* (1940), and Hedvall (1942).

The human type of tubercle bacillus may also infect cattle, as it has been observed that cows in contact with a human case of pulmonary tuberculosis, though developing no sign of active disease, may give positive tuberculin reactions. Many of these cases have been proved by the isolation of a human type of bacillus from the tissues of cattle which may show no active disease or minimal lesions in either the respiratory or the alimentary system (Giltner, 1923; Hindersson, 1933; Stenius, 1933; Bang and Jepsen, 1936; Crawford, M. (personal communication), 1936; Plum, 1937; Van der Schaaf and Van Zweiten, 1939; Reid, 1939; Plum, 1940; Nielson and Plum, 1939; Feldman and Moses, 1941; Hillermark, 1942; Rosa, 1942; Magnusson, 1942). Neither Hindersson (1933) nor Plum (1936, 1937) succeeded in isolating human tubercle bacilli from the milk of cows naturally or experimentally infected with the human type. Thus infection of cattle with the human type is more of a nuisance, as it results in confusion at tuberculin-testing: bovine infection, on the other hand, usually gives rise to serious losses. Someone in contact with a previously clean herd should be suspected when many positive reactors suddenly appear at routine tuberculin-testing.

The cycle of infection in man and in animals is thus much more complicated than originally suspected.

A. Infection with the Human Type of Bacillus

1. Respiratory

The chief pathway of infection for tuberculosis in the human subject is via the respiratory system. In a consecutive post-mortem series of 434 cases of tuberculosis in children under 13 years the primary site of infection was found in the respiratory system in 283 (65.2%), in the abdomen in 140 (32.3%), and in the cervical glands in 9 (2.07%); no definite primary portal of infection could be identified in 7. (In 5 of the cases there appeared to be double sites of entry—one in the thorax and the other in the abdomen.)

Respiratory tuberculosis is most commonly caused by the inhalation of infected droplets; occasionally, however, pulmonary tuberculosis may be secondary to tuberculosis elsewhere, as, for example, in the mesenteric or cervical glands, due usually to blood spread from these sites. Tubercle bacilli must, however, be frequently inhaled without producing any recognizable lesion, and it must be assumed that in these cases the tubercle bacilli are destroyed by the resistance of the tissues of the healthy individual. It is thus not the bacillus itself, the presence of which is essential, but the harmonious working together of many factors which results in disease. These factors probably play a more important part in the pathogenesis of the disease than the organism, but the true nature of many of them and their mode of action is still obscure. Tuberculosis is a universal disease and the chances of infection are enormous, and it is a native or acquired resistance, or both, which prevents the disease assuming epidemic proportions. Is this resistance humoral or cellular? It would appear to be more associated with the latter, as Lurie (1942) has shown experimentally that tubercle bacilli phagocytosed by the mononuclear leucocytes of normal animals are not killed, whereas the same cells in actively tuberculous or immune animals have increased bacteriostatic or bactericidal properties which seem to be independent of the body fluids, as these properties remain after the cells have been transferred into a normal animal.

In a series of cases of primary respiratory tuberculosis in children under 13 years we isolated the human type of bacillus from the primary lung lesion or the tracheo-bronchial glands in 160 (96.4%) and the bovine in 6

TABLE I.—Primary Respiratory Tuberculosis; Types of Tubercle Bacilli

Type	0-1 year	1-2 years	2-3 years	3-6 years	6-13 years	Total
Human ..	58	31	21	24	26	160 (96.4%)
Bovine ..	1	2	2	1	—	6 (3.6%)

(Table I). Griffith and Munro (1944) in figures collected from various authors found that the types of tubercle bacilli occurring in the sputum of Scottish patients with pulmonary tuberculosis comprised 2,609 (94.3%) human and 160 bovine strains, and from cases in England, Wales, and Eire 4,113 (98.1%) human and 81 bovine.

In most cases of human infection in childhood the source of infection is usually a near relative, and in a recent series of cases of meningitis of all ages due to the human type of bacillus investigated in Scotland the mother was the most frequent source (Table II). The significance of this familial

TABLE II.—Relationship of Contact to 144 Cases of Meningitis Infected with Human Strains

Mother ..	44	Brother ..	20	Grandmother ..	2
Father ..	22	Aunt ..	12	Grandfather ..	6
Sister ..	21	Uncle ..	6	Others ..	11

infection is important, as it subjects those coming in contact with it to repeated infections, and also to the liability of massive doses of tubercle bacilli. Both these factors may overcome any natural or acquired resistance possessed by a member of a family, more particularly should this resistance be lowered by acute disease, overwork, or malnutrition.

In childhood the primary infection results in the primary lung lesion, originally described by Parrot (1876) though often credited to Ghon (1916). It may also occur in adults, and during the war period we observed typical childhood acute primary pulmonary lesions more often in the adult than formerly, due, I think, to the greater number of rural dwellers coming to work in factories in urban areas. The primary lung lesion in the child is usually small and may

be readily missed unless carefully searched for at necropsy (Blacklock, 1932). It is usually single, but why this should be so in view of the probability of multiple infections—as, for example, in the case of a child with a tuberculous parent—is unknown. The secondary lesion in the tracheo-bronchial glands in the child under 3 years is usually massive. The reason for the greater size of the lesion in the glands as compared with that in the lungs would appear to depend on the degree of hypersensitivity which the child has developed in the interval elapsing between the occurrence of the lesion in the lung and that in the glands. Owing to this hypersensitivity the lesion in the glands is more of an exudative type, and thus massive caseation occurs. In the older child the degree of tuberculosis in the tracheo-bronchial glands is usually less than that in the younger; in fact in older children and adults the glandular lesion may be entirely absent. Terplan (1946) has also noted this. In post-mortem examinations in adults small healed primary lung lesions are often found, and in a series of cases still being studied in the Royal Infirmary, Glasgow, only about 5% show any evidence of tuberculosis in the tracheo-bronchial glands. This relative absence of secondary lesions in the glands of older children may be partly accounted for by the more frequent evidence of healing as judged by the growth of fibrous tissue around the primary lung lesion. This fibrosis increases *pari passu* with age (Table III), and will close lymphatic channels

TABLE III.—Primary Lung Foci in Children: Evidence of Healing

Age	No. of Foci	Percentage Healing
0-6 months	40	0
6-12 "	58	10.3
1-2 years	62	37.1
2-3 "	40	40.0
3-6 "	44	52.2
6-13 "	46	67.4

and thus prevent the spread of the bacilli to the glands. This, however, is not the primary reason, for it is obvious that in order to allow granulation tissue to form and subsequent fibrosis to occur the bacilli must be fixed at the site of infection and prevented from undue multiplication, at least for a time, by some bodily defensive mechanism.

Age is undoubtedly an important factor in determining healing. The longer the primary infection in the child is delayed the greater chance of resolution, particularly in the period between 5 and puberty, but why this should be so is unknown. This probably accounts for the higher mortality in children of the hospital class as compared with those who are better off. In the former there are more opportunities of infection occurring in early life, due largely to the overcrowded conditions under which most of them live, than in the latter, in whom primary infection is usually delayed until school age or later. A further and an important factor is that between 5 and 14 years there is a greater proportion of changes from a positive to a negative tuberculin reaction than at any other age (Zacks and Sartwell, 1942).

If the disease is not localized at or near the site of infection then, in the child, generalization occurs, resulting in acute generalized miliary tuberculosis with or without meningitis. The total human percentage for the latter in Scotland was 82.8 as reported by various workers between 1907 and 1947 (Watt, 1907; Wang, 1916-17; Blacklock, 1932; Griffith, 1934; Blacklock and Griffin, 1935; Macgregor *et al.*, 1935; Macgregor and Green, 1937; Munro and Scott, 1936; National Investigation (Scotland), 1943-4). The proportion of human infections was higher in the older than in the younger age groups (Table IV). The main portal of entry of human strains is via the lungs,

TABLE IV.—Types of Tubercle Bacilli: Cerebral Tuberculosis: Scotland

Date	0-5 years		6-15 years		Over 15 years		Total	
	H.	B.	H.	B.	H.	B.	H.	B.
1907-37	178	72	71	19	30	6	281*	99*
1943-4	193	42	153	15	152	5	498	62
Total	371	114	224	34	182	11	779	161
Human %	76.5		86.8		94.3		82.8	

* Includes 2 cases, ages not stated.

and thus most of these cerebral deaths should be included with tuberculosis of the respiratory system, though by the Registrar-General they are tabulated separately under the heading of "meningeal tuberculosis."

The first infection in the lungs with tubercle is pathologically distinct from all others in that it affects a virgin soil and at its onset is localized. In most cases, particularly in older children and in adults, this localization persists and complete healing results. But the patient has now developed hypersensitivity, the degree of which varies from patient to patient for some years after the initial infection, though it tends to lessen as age advances. For example, in a series of still unpublished Mantoux tests which Griffin and I made in 1932-4 in 1,732 clinically non-tuberculous children, all under 13 years, testing each child first with 0.1 mg. and thereafter, if negative, with 1 mg. and 10 mg. of old tuberculin, we found that of those who did not react to 0.1 mg. the percentage who gave positive reactions with 1 mg. increased as age advanced. The same was true of those who reacted negatively to 1 mg. but positively to 10 mg. (Fig. 2). On

account of this waning hypersensitivity in the older as compared with the younger child there is more of a formative response on the part of the fixed tissues, with resulting localization of the infection. The tissue reaction to reinfection tuberculosis, which in the adult is usually exogenous, depends on many factors such as degree of hypersensitivity and of immunity, dose and virulence of the infecting bacilli.

Of these various factors hypersensitivity is the most easily investigated in the human subject; the others are difficult. Experimentally infected animals in which hypersensitivity has waned have acquired a high degree of resistance to any subsequent infection (Willis, 1928). The same would appear to be the case in the human subject, for in most adults healed primary lesions, often minute, are found post-mortem. It should be noted, however, that this acquired resistance is by no means absolute and may be broken down by acute and chronic disease, overwork, and malnutrition. A high degree of hypersensitivity is an unfavourable factor as demonstrated in animals by Rich and McCordock (1929) and in tissue cultures by Rich and Lewis (1928). These authors have shown that tubercle bacilli *per se* cause little necrosis in normal tissue, though they quickly do so when hypersensitivity is present.

FIG. 2.—Results of a series of Mantoux tests, showing increased percentage of reactions as age advances.

2. Alimentary Infections

Figures for primary abdominal tuberculosis are small. The collected figures from 1914 to 1944 for Scotland (Mitchell, 1914b; Wang, 1916-17; Blacklock, 1932; National Investigation, 1943-4) show a total percentage of human infections of 22.1 (Table V). As most of the abdom-

TABLE V.—Types of Tubercle Bacilli: Tuberculosis of Abdomen and of Cervical Glands: Scotland

Site and Date	0-5 years		6-15 years		Over 15 years		Total	
	H.	B.	H.	B.	H.	B.	H.	B.
Abdomen:								
1914-32 ..	10	51	3	10	2	2	15	63
1943-4 ..	3	5	1	2	2	4	6	11
Total ..	13	56	4	12	4	6	21	74
Bovine % ..	81.2		75.0		60.0		77.9	
Cervical glands:								
1914-35 ..	9	50	13	44	5	2	29*	102*
1943-4 ..	17	30	8	55	27	23	52	108
Total ..	26	80	21	99	32	25	81	210
Bovine % ..	75.5		82.5		43.9		72.2	

* 2 human and 6 bovine cases included; ages not stated, but under 12 years.

inal cases were examined post-mortem, care was taken to exclude any source of infection in the lungs from which the abdomen could have been infected. To account for these primary alimentary lesions human tubercle bacilli must have been swallowed in food contaminated by droplet infection or, in the case of young children, by fingers contaminated from floors on which droplets of sputum may have been present. In the case of children between 9 months and 2½ years Dieudonné (1901) recovered tubercle bacilli from the dirt on their hands in 2 of 15 cases. Still another method is through the imperfect cleansing of eating utensils, as has been demonstrated by Hutchinson (1947) for dysentery bacilli, streptococci, and staphylococci.

Of the cases of primary tuberculosis of the cervical glands investigated up to 1944 in Scotland (Mitchell, 1914a, 1914b; Griffith, 1915, 1929; Wang, 1916-17; Blacklock, 1932; Griffith and Smith, 1935; National Investigation, 1943-4) the proportion of infections with the human type was 27.8%. The human type of bacillus is thus not mainly responsible for tuberculosis of the abdomen and cervical glands.

B. Infection with the Bovine Type of Bacillus

1. Alimentary

Infection with the bovine type of bacillus is mainly through the alimentary system, and accounts for the greater proportion of cases of cervical gland and abdominal tuberculosis in the various Scottish investigations (Table V). The highest proportion of bovine infections is found in early life, and this is probably due to the greater consumption of milk at that age than at any other. There are thus greater opportunities for infection should the milk contain tubercle bacilli. As the mucosa of the intestine and of the nasopharynx is a less favourable site than the lungs for attack by tubercle bacilli, which grow slowly, some coincidental lesion may probably allow the bacilli to invade these mucosae. The more frequent occurrence of acute catarrhal conditions in these sites in childhood as compared with adults may provide a *locus minoris resistentiae* in which tubercle bacilli may gain a foothold. This may partly account for the greater frequency of tuberculosis of the cervical glands and of the abdomen in children than in adults. Further, the possibility of acquired resistance due to an arrested infection in the lungs may also determine the relative infrequency of

alimentary tuberculosis in the adult as compared with the child. This is well exemplified in the case of a phthisical cavity in the adult where, in spite of a sputum containing numerous tubercle bacilli, secondary tuberculous ulcers may not be found in the intestine.

The rural inhabitant is more liable to bovine infection than the urban, as is shown by the greater incidence of bovine infections in cervical adenitis in country (77.8%) than in urban patients (46.2%) (Table VI). The figures

TABLE VI.—Permanent Residence of Patients: 1943-4 Investigation: Scotland

Site of Disease	Town		Country	
	H.	B.	H.	B.
Abdomen ..	3	6 (66.7%)	3	5 (62.5%)
Cervical glands ..	28	24 (46.2%)	24	84 (77.8%)
Cerebral* ..	306	20 (6.1%)	191	42 (18.0%)

* In 1 case residence not stated.

for abdominal tuberculosis are too small to be significant for comparative purposes; those for cerebral tuberculosis, however, show a bovine percentage three times higher in rural than in urban cases. More detailed analysis of the figures obtained in the 1943-4 investigation further confirms this higher proportion of bovine infections in rural areas. In tuberculous meningitis 8% were infected with bovine strains in the large burghs and cities of Scotland, as against 15.9% in the rural areas of the counties; in surgical tuberculosis 20.1% of the cases in the burghs and cities were caused by bovine infection; in the rural county areas this percentage was more than double—45.4%. Bovine infection is thus more of a rural than an urban problem. This finding is further substantiated by the figures for the western area of Scotland. In this region 56.7% of the entire population of the country reside, Glasgow accounting for 39.8% of the population of the area. In 1914 there were in this area 3,219 (77.5%) of the 4,138 attested herds in Scotland: in Ayrshire, for example, 88.6% of the dairy herds are attested. This large proportion of attested herds in the western area partly accounts for this region having the lowest bovine percentage of all areas in Scotland in the meningitis series and the second lowest in the surgical series (Table VII). It is not the whole

TABLE VII.—Percentage Bovine Infections: Cerebral and Surgical Tuberculosis: Scotland

Area	Cerebral	Surgical
Eastern ..	27.3	54.2
North-eastern ..	26.7	44.1
South-eastern ..	13.4	43.7
Northern ..	8.3	24.0
Western ..	6.1	27.8

explanation, which is more apparent when the figures for the western area are analysed. In the meningitis cases Glasgow had a bovine percentage of 2.3, the large burghs in the Clyde Valley area had together 8.2, and the rural areas in the Western Counties 10.9. The corresponding bovine percentages in the surgical cases for these places were 8.8, 13.6, and 44.4, respectively. In Glasgow 95% of the milk sold for consumption is subjected to some form of heat treatment (45.9% pasteurized under licence, 49.1% heat treated, and 5% sold as raw milk), and this accounts in part for the very low bovine percentage in the city. In the large burghs the proportion of milk subject to some form of heat treatment is lower than in Glasgow, while in the rural districts of the western area from which Glasgow draws its milk supply any form of heat treatment is practically non-existent. Thus in Glasgow, partly owing to the extensive heat treatment of milk, the mortality rate for bovine meningitis is less than one-quarter and the

morbidity rate in surgical tuberculosis due to bovine infection is one-fifth of those in the rural areas of the western counties from which it draws its milk supply. Ruys (1946) has made similar observations in Amsterdam, where during the war practically all the milk was pasteurized, and where there was a decrease in bovine tuberculosis in children, though no such decrease was observed in the surrounding rural areas.

Another factor in this difference in the incidence of bovine infection in urban and rural inhabitants which must be considered is an immunological one. Infection with the human type of bacillus must be less common in the country than in the towns, and the rural dweller therefore escapes this type of infection; he consequently develops no tuberculo-immunity, and thus is more liable than the town inhabitant to bovine infection. Indeed, it has been suggested that the presence of bovine bacilli in milk may serve as an immunizing agent in the human subject. This is, however, a dangerous doctrine, for neither the dose nor the virulence of the bacillus is under control, and tuberculous disease, often fatal, may result. For example, applying the bovine percentage—namely, 11.1—which we obtained in Scotland during 1943–4 for meningitis to the 1,033 meningeal deaths recorded for these years by the Registrar-General (Scotland), it can be computed that 115 of these were due to infection with the bovine bacillus. Similarly applying the bovine percentage of 33.8 for surgical tuberculosis obtained in the same investigation to the 20,433 cases of surgical tuberculosis notified in these years, it is estimated that 6,906 of the cases were caused by the bovine bacillus.

Reinfection tuberculosis due to the bovine bacillus is unusual, as it is not common to find post-mortem evidence of fresh infection in cases of tuberculosis of the abdominal or cervical glands when old lesions already exist. This is in marked contrast to the lung, where the finding of a small healed primary focus, usually without glandular involvement and more recent reinfection tuberculosis, is not uncommon. It is worthy of comment, however, that even in healed cervical and abdominal glands viable tubercle bacilli may still be present; indeed, we have been able to isolate bovine bacilli from calcified abdominal glands. From such an apparently healed focus tubercle bacilli may escape and cause secondary lesions in bones, joints, urogenital system, etc., years after the primary infection in the glands has taken place.

2. Respiratory Infections

Respiratory tuberculosis of bovine origin is rare, accounting for 3.6% in our necropsy series in children (Table I), and for 5.7% of cases in Scotland and 1.9% in England, Wales, and Eire in the collected figures for all ages reported by Griffith and Munro (1944). In our series bovine bacilli were isolated from the primary lung foci or related tracheo-bronchial glands; thus there is little doubt that the infection was of respiratory origin. Infection in these cases was probably derived from open cases of pulmonary tuberculosis due to the bovine bacillus.

Conclusion

The duty of every medical man is first to prevent disease; if that is not possible, to cure; and if that is impossible, to alleviate. How is this dictum to be applied to tuberculosis? As regards prevention—human infection is the more difficult to control as there are so many known and unknown carriers of the disease in our midst. As Osler (1905) remarked: "The germ of tuberculosis is ubiquitous; few reach maturity without infection, none reach old age without a focus somewhere." It is obviously impossible to segre-

gate all those who may spread the disease; but in factory, in workshop, in school, and in college mass radiography together with adequate clinical examination can play an important part in excluding foci of infection, especially among the young susceptible 15-to-25-years age group, in which tuberculosis is the main cause of death. But mass radiography applied indiscriminately to the population at large will achieve little if we cannot admit to hospital all those who are liable to disseminate the disease, both the young incipient and the old chronic case. Little is eventually to be gained in the control of the disease by dismissing from hospital the old chronic to provide a bed for the young case: that will only result in further spread of the disease. All this is a problem for preventive medicine. Higher standards of living, housing, nutrition, and recreation must also play their part: these are problems for social medicine. These measures may help to reduce the incidence of the disease but will not completely eradicate it.

Bovine infection is the easier to control, and in this agriculturists and veterinarians have already accomplished much. The ideal, of course, is that all milk for human consumption should come only from attested herds; but this is a long-term policy, and in the meantime some universal form of adequate heat treatment seems to be the only solution, particularly in view of the bulking of our milk supplies. This is no counsel of despair, as it must be emphasized that in addition to tuberculosis there are many other equally important milk-borne diseases which are preventable by heat-treatment, even though all milk eventually comes from attested herds.

Prophylactic vaccination with B.C.G. is still a controversial question, and over 20 years of trial has left the medical profession in a state of confusion as regards its efficacy. Many reports, chiefly from Scandinavia and more recently from America (Aronson and Palmer, 1946), and the recent Memorandum to the Minister of Health (Tytler, 1946) testify to the advisability and the adequacy of this measure. It is uncertain, however, that in a mixed population such as ours the same results would hold as elsewhere, particularly as tuberculosis is such a prevalent disease with us, and frequent infection must be the lot of us all. The discovery by Petroff *et al.* (1927–8) that B.C.G. could dissociate into avirulent R and virulent S forms raised doubts in the minds of many regarding the use of a living vaccine. No definite case of tuberculosis has, however, yet been proved as resulting from the use of properly prepared B.C.G. vaccine. Vaccines of killed bacilli have been employed with apparent success by Goodwin and Schwenker (1934), Opie *et al.* (1939), and Wells *et al.* (1944). As in all tuberculosis research, it will be long before we can assess and pass a final judgment on the efficacy of B.C.G. vaccination. This interval must be at least 15 to 25 years in order to allow us to judge its efficacy in the young adult age group, in which at present tuberculosis is such a serious problem. Meanwhile, B.C.G. may serve a useful function until chemotherapeutic or immunological research provides us with something as reliable for the cure of tuberculosis as penicillin has been for pyogenic infections. In his Memorandum Tytler (1946) has given all the essentials for a scheme of prophylactic vaccination. It is hoped that those in authority will carefully consider his suggestions, as the disaster at Lübeck is still fresh in our minds.

With regard to the cure of established tuberculous disease, nothing can be added to the valuable contribution which D'Arcy Hart (1946) has made to the chemotherapy of tuberculosis. Streptomycin is still under trial as a curative agent, and the results of these trials are awaited with interest.

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REFERENCES

- Aronson, J. D., and Palmer, C. E. (1946). *Pub. Hlth. Rep. Wash.*, **61**, 802.
- * Bang, O., and Jepsen, A. (1936). *Medlemsbl. danske Dyrlægeforen*, **19**, 229. Abstr. in *Vet. Bull.*, 1937, **7**, 104.
- Blacklock, J. W. S. (1932). *Med. Res. Cncl. Sp. Rep. Ser. No. 172*, London.
- and Griffin, M. A. (1935). *J. Path. Bact.*, **40**, 489.
- Bradbury, F. C. S., and Young, J. A. (1946). *Lancet*, **1**, 89.
- Bright, R., and Addison, T. (1839). *Elements of the Practice of Medicine*, p. 280, Longmans, London.
- British Medical Association (1883). *Collective Investigation Record*, p. 91, B.M.A., London.
- Budd, W. (1867). *Lancet*, **2**, 451.
- Dieudonné (1901). *Munch. med. Wschr.*, **48**, 1439.
- Feldman, W. H. (1938). *Avian Tuberculosis*, p. 357, Baillière, Tindall and Cox, London.
- and Moses, H. (1941). *Amer. Rev. Tuberc.*, **43**, 418.
- Ghon, A. (1916). *The Primary Lung Focus of Tuberculosis in Children*, translated by D. Barty King; J. A. Churchill, London.
- and Kudlich, H. (1930). *Handbuch der Kindertuberkulose*, Engel, S., and von Pirquet, C., **1**, 20, Leipzig.
- Giltner, L. T. (1923). *North Amer. Vet.*, **4**, 622.
- Gloyne, S. R. (1933). *Bull. Hyg.*, Lond., **8**, 39.
- Goodwin, T. C., and Schwentker, F. F. (1934). *J. Pediat.*, **5**, 475.
- Graves, R. J. (1843). *A System of Clinical Medicine*, p. 277, Fannin and Co., Dublin.
- Griffith, A. S. (1915). *Lancet*, **1**, 1275.
- (1929). *J. Path. Bact.*, **32**, 813.
- (1934). *Lancet*, **1**, 1382.
- and Munro, W. T. (1935). *British Medical Journal*, **2**, 147.
- (1944). *J. Hyg.*, Camb., **43**, 229.
- and Smith, J. (1939). *Lancet*, **2**, 1339.
- Hart, P. D'Arcy (1946). *British Medical Journal*, **2**, 805.
- Hedvall, E. (1942). *Acta med. scand. Supplm.*, **135**, 1.
- * Hillermark, R. (1942). *Skand. vet. Tidskr.*, **32**, 442. Abstr. in *Vet. Bull.*, 1944, **14**, 332.
- * Hindersson, R. (1933). *Suomen. Elain-lehte*, **39**, 154. Abstr. in *Vet. Bull.*, 1934, **4**, 642.
- Hutchinson, R. I. (1947). *British Medical Journal*, **1**, 134.
- Jensen, K. A., Lester, V., and Tolderlund, K. (1940). *Acta tuberc. scand.*, **14**, 125.
- Klencke (1843). Quoted by W. Osler in *Tuberculosis*, ed. A. C. Klebs, 1909, p. 6, Appleton and Co., London and New York.
- Koch, R. (1882). *Die Aetiologie der Tuberkulose*, Berl. klin. Wschr., **19**, 221.
- (1901). *Trans. Brit. Congr. Tuberc.*, London, **1**, 23.
- Laennec, R. T. H. (1826). *Traité de l'Auscultation Médiate*, **1**, 641, J. S. Chaudé, Paris.
- Lurie, M. B. (1942). *J. exp. Med.*, **75**, 247.
- Macgregor, A. R., and Green, C. A. (1937). *J. Path. Bact.*, **45**, 613.
- Kirkpatrick, H. J. R., and Craig, W. S. (1935). *Edinb. med. J.*, n.s., **42**, 138.
- * Magnusson, H. (1941). *Svensk. vet. Tidskr.*, **12**, 390. Abstr. in *Vet. Bull.*, 1942, **12**, 482.
- (1942). *Acta med. scand. Supplm.*, **135**, 201.
- Mainwaring, E. (1667). *A Treatise on Consumption*, T. Basset, London.
- Mitchell, A. P. (1914a). *Edinb. med. J.*, **13**, 209.
- (1914b). *British Medical Journal*, **1**, 125.
- Morton, R. (1694). *Phthisiologia*, Smith and Walford, London.
- Munro, W. T. (1939). *Edinb. med. J.*, **46**, 165.
- and Scott, H. (1936). *Lancet*, **1**, 393.
- National Investigation, Scotland (1943-4). Report to Medical Research Council (in press).
- * Nielsen, F. W., and Plum, N. (1939). *Beretrn. 5 nord. Vet. mode. Kbh.*, **116**. Abstr. in *Vet. Bull.*, 1940, **10**, 820.
- Opie, E. L., Flahiff, E. W., and Smith, H. H. (1939). *Amer. J. Hyg.*, **29**, 155.
- Osler, W. (1905). First Ann. Rep., Henry Phipps Institute, Philadelphia.
- Parrot (1876). *C. r. Soc. Biol.*, Paris, 308.
- Petroff, S. A., Branch, A., and Steenken, W. (1927-8). *Proc. Soc. exp. Biol.*, N.Y., **25**, 14.
- * Plum, N. (1936). *Skand. vet. Tidskr.*, **26**, 645. Abstr. in *Vet. Bull.*, 1937, **7**, 207.
- * — (1937). *Maanedsskr. Dyrlæg.*, **48**, 609. Abstr. in *Vet. Bull.*, 1938, **8**, 9.
- * — (1940). *Medlemsbl. danske Dyrlægeforen*, **23**, 21, 41. Abstr. in *Vet. Bull.*, 1942, **12**, 328.
- Reid, J. (1939). *J. comp. Path.*, **52**, 318.
- Rich, A. R., and Lewis, M. R. (1928). *Proc. Soc. exp. Biol.*, N.Y., **25**, 596.
- and McCordock, H. A. (1929). *Johns Hopk. Hosp. Bull.*, **44**, 273.
- * Rosa, A. (1942). *Nuova Vet.*, **20**, 239. Abstr. in *Vet. Bull.*, 1946, **16**, 38.
- Royal Commission on Tuberculosis (1911). Final Report, London.
- Ruys, A. C. (1946). *Mon. Bull. Min. Hlth.*, **5**, 67.
- Smith, Th. (1896). *Trans. Ass. Amer. Phys.*, **11**, 75.
- (1898). *J. exp. Med.*, **3**, 451.
- * Stenius, R. (1933). *4. Nord. Veterinärmötet, Helsingfors*, 30. (Quoted by Feldman and Moses, 1941.)
- Terplan, K. (1946). *Amer. Rev. Tuberc.*, **53**, 393.
- Tice, F. J. (1944). *Cornell Vet.*, **34**, 363.
- Tytler, W. H. (1946). *Lancet*, **2**, 138.
- * Van der Schaaf, A., and Van Zweiten, M. (1939). *Ned. ind. Bl. Diergereesk*, **51**, 16. Abstr. in *Vet. Bull.*, 1940, **10**, 650.
- Villemin, J. A. (1868). *Etudes sur la Tuberculose*, Baillière et Fils, Paris.
- Wang, C.-Y. (1916-17). *J. Path. Bact.*, **21**, 131.
- (1916-17). *Ibid.*, **21**, 248.
- Watt, J. P. (1907). Ann. Rep. Med. Off. Hlth., Aberdeenshire, 19.
- Wells, C. W., Flahiff, E. W., and Smith, H. H. (1944). *Amer. J. Hyg.*, **40**, 116.
- Willis, H. S. (1928). *Amer. Rev. Tuberc.*, **17**, 240.
- Zacks, D., and Sartwell, P. E. (1942). *Amer. J. publ. Hlth.*, **32**, 732.

OXYGEN POISONING IN MAN

BY

KENNETH W. DONALD, D.S.C., M.D., M.R.C.P.

Late Senior Medical Officer, Admiralty Experimental Diving Unit; Chief Assistant, Medical Professional Unit, St. Bartholomew's Hospital

PART II

Signs and Symptoms of Oxygen Poisoning

The available knowledge of the signs and symptoms of oxygen poisoning in man at the beginning of these experiments was extremely scanty. Only about 12 separate exposures where acute toxic symptoms had occurred had been described. It is not certain that Bornstein suffered from oxygen poisoning (see below). All these experiments were in compressed air, and with the exception of Bornstein all subjects were seated and at comparative physiological rest. The British Naval instructions at this time (1941) read as follows: "Symptoms: Tingling of the fingers and toes and twitching of the muscles, especially round the mouth (warning symptoms). Convulsions followed by unconsciousness and death if a remedy is not taken." The U.S. Naval instructions stated: "The first signs of oxygen toxicity are the flushing of the face, nausea, dizziness, and muscle-twitching. A feeling of being irritable and a sense of excitement may follow. As the pressure is increased nausea, vertigo, and, finally, unconsciousness and convulsions ensue."

It was inevitable, with the limited data available, that these instructions were brief and not altogether accurate. Tingling of the fingers and toes had not been reported in any experiment, but was inferred from its occurrence in the aura of idiopathic epilepsy. In the first large series of human experiments, described in this article, a more complete picture of the syndrome of oxygen poisoning in the human has resulted. Most of the signs and symptoms described in the pre-convulsive stage, in the auras, or in the non-convulsant equivalents of epilepsy have been encountered. As in that disease, the total of signs and symptoms is now known. Yet—again as in epilepsy—the individual pattern of signs and symptoms varies enormously within this framework. Signs and symptoms as experienced when the subjects were breathing pure oxygen in compressed air are first described, as the subjects' environment was more normal and careful direct observation was possible.

Facial pallor usually occurs a few minutes after the beginning of the exposure. It varies from person to person in degree and time of onset. The degree of facial pallor is in no way indicative of the subject's sensitivity or of an impending end-point. Fasciculation of the lips or face is often seen early in the experiment and intermittently throughout the exposure. This has been partially attributed to fatigue caused by the mouthpiece and a not unnatural nervous tension. It is a common occurrence when patients