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THE INCIDENCE OF PLEURAL EFFUSION IN ARTIFICIAL PNEUMOTHORAX

WITH SPECIAL REFERENCE TO MEDICAL TREATMENT*

BY

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The number and variety of purely medicinal measures advocated in the treatment of pulmonary tuberculosis are themselves indicative of the uncertainty of the results obtained from their use. Recent developments in thoracic surgery, from the modest artificial pneumothorax to the drastic thoracoplasty, have placed in our hands valuable weapons which, however, must be wielded with care to prevent the abuse that so frequently brings useful remedies and lines of therapy into undeserved disrepute. Over the last fifteen years artificial pneumothorax has been steadily finding its correct place in the armamentarium of the physician dealing with diseases of the chest. Undoubtedly, in the early period, the treatment was applied to many cases that were unsuitable. More latterly, the swing of the pendulum has brought us back to a point at which rational appreciation of the limitations of this line of treatment is manifest. Limitations of the application of artificial pneumothorax in the treatment of pulmonary tuberculosis depend on two factors: (1) the stage of the disease, and (2) complications that may arise, due in part at least to the treatment itself. Of these complications, the commonest, and the most upsetting to both the patient and the physician, is the development of a pleural effusion, and it is the purpose of this paper to examine this aspect of the subject.

It has been claimed that benefit may follow the development of a pleural effusion, due to the combined results of mechanical action and serological effects.¹ Personally, I have not observed a case in which any benefit was at all clearly defined, although occasionally a patient may volunteer "feeling better" after the upset associated with the appearance of fluid has worn off. Whilst the presence of pleural fluid in a pneumothorax cavity may be attended by no untoward effects, three undesirable sequelae may be considered.

1. Great thickening of the pleura, preventing satisfactory re-expansion of the lung later. This attains the extreme form in the condition of "opaque pneumothorax."²

2. Premature obliteration of the artificial pneumothorax space by organization of the fibrin in the fluid. (In one case under the observation of Dr. H. James and myself this occurred within the short period of two months from the appearance of a small effusion filling the costophrenic angle, in a well-established artificial pneumothorax.)

3. The fluid may become purulent.

Undoubtedly an uncomplicated artificial pneumothorax is a great boon to the sufferer. The development of fluid introduces an element of uncertainty and danger—at best, it is useful only in helping to maintain the collapse of the lung, and thereby lessening the frequency of refills, an effect beyond control; at worst, it is the precursor of a tuberculous pyothorax.

The numerical incidence of this complication is here reviewed both from a perusal of the literature generally and from a detailed examination of a series of fifty-four cases that have been under my care throughout their course. Admittedly the series is a small one. It includes only cases of pulmonary tuberculosis in which an artificial pneumothorax was induced as a therapeutic measure, and the following cases have been excluded from the review: (1) where artificial pneumothorax was induced for diagnostic purposes; (2) where artificial pneumothorax was established after aspiration of a pleural effusion already present; and (3) where pleural effusion has followed the deliberate insertion into the pleural space of an irritant, such as gomenol, for the purpose of controlling mediastinal displacement or pleural hernia. Detailed pathological examination of the fluid obtained by aspiration was not undertaken.

An attempt has been made to assess the various aetiological factors which may have, either singly or together, played a part in the development of fluid, and the thesis is here advanced that trauma to the pleura, in one way or other, is the main provocative cause.

Reported Incidence of Effusions

Even a cursory examination of the literature shows that there exists a great variation in opinion regarding the frequency of pleural effusion complicating artificial pneumothorax. The discrepancy is partly due to the deliberate exclusion from their figures by some observers of those cases in which only a very small effusion was observed.

Burrell³ reports a series of 309 cases treated by artificial pneumothorax, in which pleural effusion occurred in 128 patients—that is, in 42 per cent. This figure includes only those in which the presence of fluid was observed for at least a week, and in which the fluid covered the diaphragm. He considers that all cases probably develop at least a small transient effusion during the course of an artificial pneumothorax. Of these 128, pus developed in thirty-six cases. In another series of 500 cases, Burrell experienced effusion in 177 (35 per cent.), of which a little over one-third became purulent.

* Read in opening a discussion in the Section of Public Medicine at the Annual Meeting of the British Medical Association, Melbourne, 1935.

Figures quoted by Burrell¹ include:

Riviere—expected effusion in about 50 per cent.

Dumarest and Brette—70.38 per cent. of 265 cases (includes small effusions).

Saugman—67.2 per cent. in 238 cases.

Weinstein—70 per cent. of advanced cases; 33 per cent. of moderately advanced cases; and 10 per cent. of mild cases.

Rist and Naveau—52 per cent. cases (excludes small transient effusions).

Brauns—only 5 per cent. of a series of ninety-eight cases.

Morrison Davies⁴ considers that effusion will occur within twelve months in at least 50 per cent. of cases. James⁵ mentions the occurrence of effusion in only two cases of a series of forty—that is, 5 per cent.—and remarks that the normal expectation is about 40 per cent. Sachs⁶ records a batch of 800 cases of artificial pneumothorax, without the occurrence of a single case of empyema! Trail⁷ reports a series of eighty cases, in which one-half developed pleural fluid; in five of these forty the fluid became purulent. He expresses the generally accepted opinion that when pyothorax does not supervene the presence of fluid seldom has a bad effect on the ultimate result of artificial pneumothorax.

Enough has been quoted to indicate that the proportion of affected cases averages about one-half, but until some more careful standardization of results is attempted any accurate forecast will be impossible. With reference to empyema, the incidence appears to vary from one in eight to one in four of those cases that have developed fluid—that is, from 5 to 10 per cent. of patients in whom artificial pneumothorax has been established.

Review of Cases

During the two years from April, 1933, to March, 1935, the number of patients admitted to Gresswell Sanatorium was 629, of whom fifty-four received artificial pneumothorax therapy for the treatment of pulmonary tuberculosis. This is clearly shown in the diagram below.

It is proposed to consider in detail these fifty-four patients with special reference to the occurrence of pleural effusion.

The second diagram shows the number of patients with and without fluid, and for the sake of clarity a special group has been made of those who developed only a small "puddle" of fluid in the costophrenic angle, which occasionally persisted for a very short time only. Without the aid of frequent screening, these would all have been considered as being "without fluid." Thirteen cases showed no fluid at all, although it is recognized that a very small effusion may have appeared and vanished between successive screenings. Some of these patients have been under observation for more than twenty months. This group forms 24 per cent. of the whole. The number of patients who developed a small effusion, sufficient to fill only the costophrenic angle, was eighteen—that is, 33 per cent. In a few of these the "puddle" persisted for many weeks—occasionally for months—with small variation of the quantity of fluid. It will be noted that

these first two groups include 57 per cent. of the total—that is, no effusion of any clinical significance occurred in more than one-half of the cases under review.

The third group consists of the cases in which the quantity of fluid, whilst not sufficient to necessitate aspiration, was great enough to affect the intrapleural pressure, and so modify the routine of refills. The presence of fluid was appreciated by the patient, and could be detected by ordinary clinical examination. At least one aspiration was done in each of these cases to determine the nature of the fluid, which was always serous.

The fourth and fifth groups consist of sixteen cases which needed more active treatment. Some of these

appeared to develop large effusions rapidly, whilst others graduated to their present position in the classification from the second and third groups over a fair interval of time. Of the seven cases of pyothorax, four were successfully treated by conservative methods, one had a thoracoplasty, and two died.

In summarizing, it will be seen that forty-one out of the fifty-four cases developed effusion—76 per cent. If we exclude those in which only a very small "puddle" of fluid, filling the costophrenic angle, formed, the number of effusions was twenty-three, or 43 per cent. of the total.

The presence of adhesions in each case has been carefully looked for, both by fluoroscopy and by examination of radiograph, it being felt that the presence of fluid might be related to this factor.

The occurrence of a febrile reaction at the time of the appearance of the effusion was in each case carefully noted in an attempt to assess the infective, as distinct from the traumatic, factor in the causation of the effusion. It is recognized that these are not mutually exclusive, and that the presence of fever at the time does not exclude trauma, to which it may have been secondary. Table I shows the number of cases with adhesions, and with a febrile reaction at the onset of effusion, in each group.

TABLE I

Group	Adhesions Present in—	Temp. Elevated at Onset of Effusion in—
1. No fluid; 13 cases...	9 cases (69 per cent.)	—
2. Small "puddle"; 18 cases	16 " (90 ")	1 case (5 per cent.)
3. Fluid covers diaphragm; 7 cases	5 " (70 ")	1 " (14 ")
4. Larger effusion (serous or S.F.); 9 cases	9 " (100 ")	6 cases (66 ")
5. Larger effusion (purulent or S.P.); 7 cases	7 " (100 ")	6 " (85 ")

It is manifestly difficult to draw any conclusions from these small numbers, but there is a suggestive association between the occurrence of fluid and the presence of adhesions, particularly in Groups 2, 4, and 5. The comparison of Groups 1 and 3 shows that other factors are

also concerned. Notable, too, is the infrequency of febrile reaction in Groups 2 and 3, and its frequency in Group 5. It is interesting to observe that adhesions of some degree were present in forty-six of the fifty-four cases—85 per cent. These ranged from fine strands to massive bands holding the lung to the chest wall over a considerable area.

Table II presents, in a different way, the association of the presence of adhesions with the development of pleural effusion.

TABLE II

	No Adhesions	Adhesions Present
No fluid	4 (7.4 per cent.)	9 (16.6 per cent.)
Fluid present. Groups 2, 3, 4 and 5	4 (7.4 ..	37 (68.5 ..)

With reference to the time that elapsed from the establishment of the artificial pneumothorax until the appearance of fluid, examination of the figures discloses no suggestive feature, except the tendency to earlier appearance in Groups 2 and 5, the least and most important respectively. Wide variation is noted—from one week to sixty-four weeks. Table III summarizes these figures.

TABLE III

Group	Time of Appearance of Fluid, from Induction of A.P.	
	Average in Weeks	Minimums and Maximums
2. (18 cases)	13	1 week—40 weeks
3. (7 cases)	21	2 weeks—50 weeks
4. (9 cases)	23	2 .. —64 ..
5. (7 cases)	12	4 .. —20 ..

Finally, it is interesting to inspect the figures showing the present position of those in whom artificial pneumothorax was established (see diagram below). Of the fifty-four cases thirty are having refills as required to maintain collapse.

Of the remaining twenty-four, seven were abandoned because adhesions prevented satisfactory collapse of the lung; ten had refills discontinued because of the presence of pleural effusion, together with adhesions preventing satisfactory collapse; and in seven the development of tuberculous empyema required modification of treatment. Where artificial pneumothorax was abandoned for reasons other than the presence of pus, phrenic nerve avulsion was advised, except in one case in which apical thoracoplasty was performed. The only deaths in the series were two of the seven cases of tuberculous empyema.

Possible Aetiological Factors

TRAUMA TO THE PLEURA

This may occur in many ways, separately or together. The chief factors are: repeated puncture of the parietal pleura; introduction of a foreign body into the pleural space; high intrapleural pressure; and rupture of adhesions.

(a) *Repeated puncture of the parietal pleura*, and probably also of the visceral pleura in the early stages of artificial pneumothorax. Burrell¹ does not consider this important, and states that thoracoscopic examination of the pleura shows that there is no inflammation around the site of punctures. However, some patients persistently experience local pain and slight fever after each refill, even in the later stages of the treatment. It seems probable that effusions which appear in the late stages of an artificial pneumothorax when the degree of collapse of the lung is fairly well stabilized are due to this cause. (In my series fluid appeared after forty weeks in six cases.)

(b) *Introduction of a Foreign Body into the Pleural Space*.—Considerable pleural reaction follows the prolonged presence of air in the pleural space. This is shown in two ways: (1) the thickening of pleura that gradually occurs after the artificial pneumothorax has been established a few months, detectable as increased resistance to the passage of the artificial pneumothorax needle, an effect appreciated by both the patient and the physician; and (2) thickening of the pleura, evidenced by less mobility of the mediastinum in the later stages. Theoretically, oxygen, being more rapidly absorbed than air, should be less irritant, but it is generally agreed that the nature of the gas—air, oxygen, nitrogen, or carbon dioxide—has no effect on the frequency of occurrence of effusion. Warming the air before the introduction into the pleural space has been found a valueless refinement, whilst the rate of insertion of air, within reasonable limits, is without any influence. Filtration of the air through a modest "filter" of cotton-wool seems, on general principles, to be desirable, and is the rule in practice. It seems likely that the very small effusions which tend to occur early in any series of refills are due to this cause.

(c) *High Intrapleural Pressure*.—This tends to cause stretching of the pleura, particularly in the presence of adhesions. Attempts to "compress" the lung by the use of positive pressures, when the degree of collapse has been unsatisfactory, are sometimes followed by the development of effusion, even without the rupture of adhesions. Morriston Davies⁴ notes the not infrequent occurrence of contralateral effusion, associated with excessive intrapleural pressure and mediastinal displacement.

(d) *Rupture of Adhesions*.—As previously remarked, adhesions were present in forty-six out of the fifty-four cases—85 per cent. These ranged from fine strands, seen only with difficulty, to dense bands anchoring the lung to the chest wall. Fine strands may rupture with little or no effect, probably during a fit of coughing or sneezing. Spontaneous rupture of adhesions may be associated with severe pleural shock. The effect will vary with the nature of the adhesions. Thus, when they are of the fine fibrous type, rupture may give rise to no untoward results, and be found only by x-ray examination. More often effusion forms, usually small, but sometimes the basis of a larger collection. The cause here is trauma. With firmer bands, having their "base" on the lung, rupture may expose a subpleural tuberculous focus, giving rise to a larger effusion. This is usually serous throughout the course, but it may become purulent. Here the state of affairs is due to trauma with added tuberculous infection. Finally, a band may include pulmonary tissue, which may contain a cavity. The effects in such a case may be slight, with effusion.

It has been pointed out that a rise of intrapleural pressure may precede the appearance of an effusion, and that the rise in pressure associated with an effusion is frequently disproportionate to the quantity of fluid. It

is suggested that rupture of the lung through a small and perhaps temporary opening, giving rise to a spontaneous pneumothorax, may be a not infrequent cause of effusion. Hutchinson and Blair⁸ report several cases in which lung rupture occurred, followed by large effusion. Effects are frequently serious—spontaneous pneumothorax may become superadded on the artificial pneumothorax, with marked mediastinal displacement and great distress. Effusion rapidly develops and becomes purulent, either purely tuberculous or with pyogenic organisms as well. Broncho-pleural fistula may result. Here the cause is trauma, with added infection—tuberculous only, or with pyogenic organisms as well.

Rupture of adhesions may be intentional, as is the purpose of the Jacobaeus operation, with the use of the thoracoscope. Pleural effusion is recognized as one of the three complications of this operation, but as I have only a theoretical acquaintance with this procedure I merely mention it.

TUBERCULOUS INFECTION

Few, if any, cases of pulmonary tuberculosis run their course without some degree of pleurisy, and the subjects of artificial pneumothorax therapy can expect no exemption. It may be suggested, therefore, that the effusions are the result of tuberculous pleurisy, and this is the explanation accepted by Burrell, Morriston Davies, and others. In favour of this it is pointed out that effusions are rare in non-tuberculous cases of artificial pneumothorax, that the cytology of the fluid shows it to be an exudate, and that effusions are more likely in advanced or acute cases than in mild or chronic cases, the acuteness of the infection being more important than the amount of lung involved.¹

On the other hand it might be noted that pleural adhesions are also less frequent in those non-tuberculous cases for which artificial pneumothorax is used—for example, non-tuberculous bronchiectasis—and that the fluid from an inflammatory process, due to trauma *plus* infection, would also have the characters of an exudate. The presence of organisms in the fluid would then depend on the occurrence of a breach of the pleural surface of the lung. That some, at least, of these effusions are infective is evident from the mode of onset. In the series here reviewed, only two cases out of the twenty-five comprising Groups 2 and 3 showed an elevation of temperature with onset of effusion, whilst in Groups 4 and 5 fever occurred in twelve of the sixteen cases (Table I). In some of these it was possible to demonstrate some disturbance at the pleural surface of the lung, as has been shown on the screen; and, in each of these sixteen, adhesions were present.

Let us turn for a moment to the group of patients who were not subjected to artificial pneumothorax over the period under consideration. This includes 541 cases of pulmonary tuberculosis. Examination of the records shows that, of these, thirty-three had pleurisy with effusion (at some time during their stay in sanatorium) *recognized as such*. Obviously, many cases of pleurisy with effusion must be overlooked in patients who are very ill and febrile, and pains of pleuritic type were commonly encountered. In this number—thirty-three—are included twenty-two cases in which pleurisy with effusion was the *only* manifestation of pulmonary tuberculosis. Thus thirty-three out of 541 cases—less than 7 per cent.—had pleural effusion, whilst the “parallel” artificial pneumothorax group had fluid in twenty-three of fifty-four cases, excluding the very small effusions—that is, 43 per cent.

It is therefore felt that there is some justification for considering that pleural effusion in artificial pneumothorax is *not* solely due to tuberculous pleurisy.

EXACERBATION OF CONTRALATERAL DISEASE

It has been stated¹ that an acute exacerbation of disease in the opposite lung will often be followed by an effusion, and that the sudden development of fluid should make one look for activity in the uncollapsed lung. If this were frequent the development of fluid would be itself an indication for reviewing the treatment. No such association was observed in this series.

CLIMATIC EFFECT

Some observers consider that effusions are more common in the cold, damp weather. The climatic variations in this region are considerable, but no definite seasonal relationship to effusion has been observed.

Calcium deficiency, the final factor, is considered in detail in the next section.

Calcium Therapy as a Preventive of Pleural Effusion

My attention was directed by Dr. J. Bell Ferguson to some work of Pisani and Smejkal on the prophylactic administration of calcium preparations in cases of artificial pneumothorax as a preventive of pleural effusion.⁹ Briefly, these workers suggest that pleural effusion as met in these cases is due to the following causes: (1) Increased permeability of the capillaries, because of oxygen lack. (2) Increased osmosis. (3) Higher concentration of H ions. (4) Calcium deficiency of the pleura. (5) Aspirating effect of the endopleural negative pressure.

Any condition which causes a sudden drop in blood pressure—instances of which are “colds, over-exertion, psychic depression, and influenza”—acts as an important contributory factor. This explanation, it is emphasized, is intended for application only to non-inflammatory transudates. The suggested remedy is some preparation of calcium which inhibits (1), (2), (3), and (4) above. Using calcium gluconate, results were obtained which led the investigators to the conclusion that the treatment might be useful “as a preventive measure for pleural effusion.”

The main objections to this hypothesis are: (1) There is no definite lowering of the blood calcium content in pulmonary tuberculosis. Ellman^{10 11} has shown that the calcium content of the blood in this disease is within normal limits (9 to 12 mg. per 100 c.cm.), and that the administration of calcium or parathyroid extract can increase the blood calcium only within these limits. It is difficult to see, therefore, how the administration of calcium can raise the calcium content of the pleura. (2) The theory applies only to transudates. It is generally considered that the fluid in these cases has the characters of an exudate. In the cases under review no aspiration was attempted in those with only a very small effusion. In the larger effusions the nature of the fluid aspirated showed it to be an exudate. Should the smaller effusions be shown to have the features of a transudate, the line of treatment suggested would still have a very limited field of application. (3) Low blood pressure is commonly met with in sufferers from pulmonary tuberculosis.

Author's Own Series

A small series of cases was treated with calcium gluconate, as suggested by Pisani and Smejkal. In this group (the last thirteen of the fifty-four) calcium was given to every alternate patient, the intervening cases serving as controls. No selection was made. Seven served as controls and six received intramuscular injections of calcium gluconate (calcium Sandoz). The dosage was 10 c.cm. of 10 per cent. solution of calcium gluconate thrice weekly for two months, twice weekly for two months, and thence once weekly. The preparation was found to be painless and without reaction.

The results obtained are shown in full in Table IV.

TABLE IV

Case No.	Calcium Gluconate	Fluid	Adhesions
1	No	None	None
2	Yes	Needed aspiration	Present
3	No	Small quantity	Present
4	Yes	Needed aspiration	Present
5	No	None	None
6	Yes	Small quantity	Present
7	No	None	Present
8	Yes	Small quantity	Present
9	No	Small quantity	Present
10	Yes	Small quantity	None
11	No	Needed aspiration	Present
12	Yes	Small quantity	Present
13	No	Small quantity	None

These results are summarized in Table V.

TABLE V

Group	No Fluid	Small Quantity	Needing Aspiration
Controls (7)	3	3	1
Calcium gluconate (6) ...	—	4	2

While it is readily admitted that the number of cases is very small—too small to justify the drawing of any conclusions—the results do not suggest this line of therapy to be efficacious in the prevention of effusion in artificial pneumothorax.

Conclusions

The occurrence of pleural effusion in artificial pneumothorax is due to the combination of the factors of *trauma* to the *pleura* (using the term in its most comprehensive form), and *infection*, which may occur separately or together. It is supposed that: (1) small effusions are due to *trauma* only, and are "reactionary"; (2) larger effusions are due to *trauma plus infection*; and (3) a relatively small proportion of effusions is due to *tuberculous pleurisy*. (It might be mentioned that the question of infection from without has been purposely omitted from the discussion. Under ordinary working conditions this should never occur.)

Treatment is divisible into preventive and curative. (a) Preventive. (1) No medicinal treatment. (2) Careful selection of cases for artificial pneumothorax. (3) Care in refills when artificial pneumothorax is established, regular screening being regarded as essential. Positive pressures, or attempts to "compress" the lung, should be avoided. (4) Artificial pneumothorax should be abandoned if collapse is unsatisfactory before complications occur. (b) *Effusion present*: (1) There is no medicinal treatment of proven value. The use of calcium has again been invoked. Foix and Grunwald,¹² on the basis of three cases so treated, advocate the use of calcium chloride orally, together with a low salt diet, claiming that calcium is "essentially the medicament of inflammation in general, and of pleural inflammation in particular." On the contrary, Gordon and others¹³ state that there is no evidence that any favourable effect on pulmonary tuberculosis is obtained from maintaining a high calcium content in the circulating blood. (2) If the quantity of fluid is small and not disturbing the patient, refills should be continued with careful observation, and there should

be occasional aspiration of a small quantity of fluid to note possible change in character. (3) If a large effusion is present, one should aspirate and replace with air as *infrequently* as necessary. If collapse is poor, artificial pneumothorax should be abandoned in favour of other surgical measures. If the fluid does not constantly reaccumulate, and collapse is good, refills should be continued as required. (4) If the fluid is—or becomes—purulent, the treatment is surgical.

I wish to acknowledge my thanks to Dr. J. Bell Ferguson, State Director of Tuberculosis, Victoria, for permission to utilize the records from which the material here presented was derived; and to Dr. H. M. James, clinical tuberculosis officer, Central Tuberculosis Bureau, Melbourne, for kindly taking the x-ray photographs of the patients who had been discharged from the sanatorium, and for general assistance during the preparation of the paper.

REFERENCES

- ¹ Burrell, L. S. T.: *Artificial Pneumothorax*, London, 1932.
- ² Mattina, M.: *British Medical Journal Epitome*, February 2nd, 1935, para. 97.
- ³ Burrell, L. S. T.: *Recent Advances in Pulmonary Tuberculosis*, London, 1929, p. 193.
- ⁴ Davies, H. Morriston: *Pulmonary Tuberculosis*, London, 1933, p. 251.
- ⁵ James, H. M.: *Med. Journ. of Australia*, 1933, ii, 269.
- ⁶ Sachs, W.: Quoted in the *Medical Annual*, 1932, p. 549.
- ⁷ Trail, R. R.: *British Medical Journal*, 1934, i, 183.
- ⁸ Hutchinson, R. C., and Blair, L. G.: *Tubercle*, 1926, vii, 417.
- ⁹ Pisani, V. V., and Smejkal, F. J.: *Ibid.*, February, 1934, p. 216.
- ¹⁰ Ellman, P.: *Ibid.*, January, 1928, p. 162.
- ¹¹ Idem: *Ibid.*, March, 1929, p. 251.
- ¹² Foix and Grunwald: *Presse Méd.*, January, 1934, p. 3.
- ¹³ Gordon, B., Roark, J., and Lewis, A. K.: *Journ. Amer. Med. Assoc.*, 1926, lxxxvi, 1683.

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WITH SPECIAL REFERENCE TO AUSTRALIAN EXAMPLES*

BY

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There has been a certain uniformity in the process by which the natural history of different infectious diseases has been elucidated. The first stage has always been the gradual disentanglement of a specific disease syndrome from other infectious processes; in most of the more important human diseases this had been fairly accurately accomplished by acute clinical observers from Sydenham onward before the opening of the bacteriological era in the 'eighties. With the development of bacteriology and the experimental investigation of infectious disease the process of sorting out the various maladies was accelerated and rendered more efficient. In particular it offered invaluable aid in the recognition of the mild case, the specific cause of which could on clinical grounds only be deduced from its association with outbreaks of the classical disease.

In very general terms we may say that by about 1914 clinical and bacteriological study had resulted in a clear demarcation of the great majority of infective human diseases. We have still some important diseases of presumptive micro-organismal origin the aetiology of which is still undetermined, but, practically speaking, there have been no important recognitions of new clinical entities among infective diseases since the war. By that time it was clearly recognized that, in addition to the frank epidemic with typical syndromes and a characteristic mortality, most infective diseases showed mild atypical cases occurring simultaneously with epidemics of the typical disease, and also that sporadic cases were more or less continually occurring in interepidemic periods.

* Read in opening a discussion in the Section of Pathology at the Annual Meeting of the British Medical Association, Melbourne, 1935.