THE ETIOLOGY and AFTER EFFECTS

of

PINK DISEASE

M.D. 1939.

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INTRODUCTION

There are many problems concerning Pink Disease which clinical observations and experiment have failed to solve. Its cause is unknown. Its peculiar age incidence is unexplained. Its pathogenesis is uncertain. In its treatment there is nothing curative that we can exhibit. All that is left is to assist the healing powers of nature. Even so there are contradictory opinions as to how the assistance should be given.

In my work in hospital and in practice I have had an opportunity of studying and treating a number of children suffering from Pink Disease and in this thesis I shall use this clinical experience and also an examination of the literature published to consider the unexplained etiology of the disease. My figures in this thesis are based on the examination of the notes of cases of Pink Disease treated in the Babies' Hospital, Newcastle, during the past fifteen years.

I have also examined a number of cases after recovery from the Pink Disease with a view to discovering any possible after effects.

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HISTORICAL

Although our understanding of Pink Disease depends mainly on the observations and work of Swift, Bilderbeck, Byfield and Feer, the German physician Selter appears to have given the first true account of the disease (called by him Trophodermatoneurosis) when he described his observations on eight cases to the Congress at Cassel in 1903. His contribution, although historically important, is merely a very short paper to a local medical congress whose report was as follows:

Herr Selter (Solingen, 1903) reported eight cases of an illness for which he found no analogy in literature and which he termed trophodermatoneurosis. The malady occurred in girls of 1½ - 2½ years. It was of gradual onset and manifested itself in loss of interest, nervousness and progressive loss of speech. Other features were delirium in sleep, mental disturbances (hallucinations, coprogaphy) and profuse sweating with its consequences (sudamina, eczema and sodden skin). The hands and feet were swollen, reddened and cold. The patients had a constant sense of coldness and itchiness and there was a loss of hair (mostly temporal) sometimes amounting to complete baldness. As clearly secondary phenomena paronychia and boils appeared. The internal organs showed no
abnormality. The illness ended favourably in all cases in weeks or months.

It is interesting to note that Selter in 1934 wrote a much longer paper, giving a fuller description of the symptoms.

After Selter's description of 1903, the first important work came from H. Swift (1914) when he presented to the Australian Congress of the British Medical Association at Auckland, New Zealand, a paper dealing with a malady affecting children from 6 - 16 months. He reported on 14 cases showing cutaneous lesions consisting of generalised eruptions on the hands and feet and gave to it the name Erythroedema. In this paper, he did not come to any conclusion regarding the etiology or discuss after effects. This pioneer work of Swift's is reflected in the eponymous title of Swift's Disease.

Byfield, A.H. (1920) wrote a paper on seventeen cases which he had studied. After a description of the findings, he wrote the following comment:-

"From these findings it seems probably that we are dealing with a primary disease of the nervous system. The falling out of the teeth (in three cases) without a distinct involvement of the gums, the falling out of the hair and a double neurokeratitis (first case) point quite clearly to an involvement of the fifth nerve. The paraesthesia of the extremities
and of the trunk also suggests a sensory nerve involvement, while the coldness and blueness of the finger tips and toe tips point to a vasomotor disturbance. The muscular weakness and atrophy, the diminution of the reflexes and at times their complete absence, suggest involvement of the lower motor neuron even though a complete palsy was not often encountered. In other words there seems to have been a preponderance of sensory manifestations with a mild affection of the motor nerves."

In conclusion, regarding etiology, he says:—
"According to the anamnesis infection rather than dietary error seems to play the more important role as an exciting factor."

In this Byfield does not discuss any after effects of Pink Disease.

In the same year, another important paper came from America, when Bilderback (1920) reported ten cases of Pink Disease and again in 1925 he wrote an article in the Journal of the American Medical Association dealing with his observations on twenty cases of Pink Disease. Bilderback here explains the name Acrodynia, as Pink Disease is called in America, as from the Greek words for extremity and pain. He tells of an epidemic in France in 1830, described by Chardon, and affecting adults with erythematous dermatitis of the palms of the hands and the soles of
the feet, followed by pigmentation. Petren, in Sweden, said that this was probably arsenical poisoning from the vineyards.

In his description of the disease, Bilderback says:

"It is a disease of the skin and nervous systems involving the vasomotor centres, the motor and trophic nerves, but affecting principally the sensory nerves."

He asks: "Is it a new disease in the U.S.A.?" and goes on to say: "It does not seem possible that it could have existed previously and not been recognised. While there are variations in the severity of the symptoms in different patients, the clinical picture as a whole is classical. It is as clear cut and definite as poliomyelitis or meningitis."

In his discussion on the etiology, Bilderback says: "Most of the cases coming under my observation have been from the small towns or farms in Oregon where an exceptionally good environment existed, and in no case has the food seemed deficient."

Dealing with the cause, he says: "It is probably an infection or the aftermath of one . . . " Many of the children give a history of having been ill a few weeks earlier, at which time the distinctive feature has been fever. Some, but not all, may have had a coryza concurrent with the fever . . . . The portal of entry may be the pharynx as it is in many diseases,
such as poliomyelitis and meningitis, but we have no definite proof. He does not discuss any after-effects of the disease.

In Australia, the subject naturally continued to excite profound interest and after a paper, read by Swift in 1914, nothing further was published owing to the Great War, until Wood, A. Jr. (1921) made a review of the signs, symptoms, prognosis and treatment, based on the study of 91 cases.

In this paper, Wood describes in his discussion on etiology how the faeces of numerous cases were examined, but no light was thrown on the subject. With regard to the length of the disease, he says: "I think it is shorter in the young babies than it is in older children."

In 1935 came what is probably the best contribution to the problem of pink disease by Wood, A.J. and I. from the Annual meeting of the British Medical Association in Melbourne. They have seen over 200 cases in Australia and all have been under 4 years of age. In discussing the aetiology and pathology, they say: "At present we prefer to maintain an open mind as to the site of attack of the noxious influence and would rather visualise it as a toxin which is diffusely distributed throughout the body rather than acting entirely through the medium of the nervous system." As regards the theory of causation, they do
not agree with the vitamin deficiency theory and the light hypersensitivity theory of Braithwaite, but say: "The infecting organism may be a virus which is widely spread throughout the community in a non-pathogenic state. These carriers would perhaps react slightly to the virus from time to time and thus immune bodies would be produced. On rare occasions, the organism would assume a pathogenic role in a highly susceptible individual, usually a child aged between 8 - 18 months and an attack of Pink Disease would result. This theory would explain the infrequency of transmission by direct sporadic cases in isolated parts of Australia."

In discussing prognosis they give some very interesting mortality figures:

Treated at home . . . . . . . . . . . 3% mortality
" in hospital (Melbourne) . . 30% "
" " " (Sidney) . . . . . 29% "

Braithwaite (1933) has put forward the theory that Pink Disease is due to an abnormal reaction to sunlight in a child who has suffered from a recent acute infection. He declares that most cases commence in the Springtime, and he has treated them in a darkened room with success.

It is interesting to compare the paper by Bruton Sweet from Australia in 1936 with Braithwaite's theory.
He claims good results in treatment with a mercury vapour lamp, which is exactly opposite to Braithwaite's reaction to sunlight theory.

Numerous papers have come from the South West of France. Writers from there describe the disease as coming in "epidemic outbreaks" and being found mostly along the river banks.

Day, Smith and Klingman (1939) in a recent article in the American Journal of the Diseases of Children, write: "Clinical evidence of the involvement of the sympathetic nervous system is universally recognised, but no observations on quantitative sympathetic disfunction." They have carried out tests concerned with the pulse rate by placing small lead pellet electrodes over the apex of the heart and taking recordings graphically. Response to various stimuli, such as placing the foot in cold water, evoked very little alteration in the heart rate, whereas in the healthy child it was quite marked.

Summarising the article they say:-

"A clinical procedure is described which demonstrated graphically the hypertonicity of the sympathetic division of the vegetative nervous system in patients with acrodynia and the absence of this hypertonicity after recovery."

The writers suggest that this failure to respond may be that in acrodynia the sympathetic nervous system is already overstimulated and cannot respond any
further to stimulation. They injected atropine sulphate to paralyse the vagus and got an increase in the heart rate showing that the vagus is still acting in acrodynia and that the tachycardia is not due to paralysis of the vagus.

Among the names which have been given to Pink Disease are:

Acrodynia in America. (Still used)
Tropho-dermato-neurosis . Selter.
Erythoedema . . . . . . Swift, and also known as Swift's disease in Australia.
Feer's Disease, or as described by Feer as a "neuritis of the vegetative nervous system."
Erythoedema polyneuritis. Paterson and Greenfield.

However, now it is usually known as Pink Disease in British countries and acrodynia in America.

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ETIOLOGICAL FACTORS

In considering the etiology of Pink Disease, there are numerous outstanding factors which have occurred in my examination of cases.

Geographical Distribution.

In ninety-seven cases seen at the Babies' Hospital, Newcastle-on-Tyne, thirty-six of those lived in the industrial Tyneside, that is in the towns actually on the banks of the river Tyne, while sixty-one came from the country areas of Northumberland and Durham. These figures are very striking when one bears in mind the very dense population of Tyneside compared with the neighbouring country.

In France, it is held, that the majority of cases occur in riverside districts.

Age Incidence.

The age incidence is very striking. From notes of one hundred and forty-seven cases of Pink Disease gathered in Newcastle the graph on Page 10 was compiled.

It will be seen from this graph that the majority of cases commence between the ages of five and seven months, after which there is a fairly gradual drop until just over one year.

Most authors give the maximum age incidence as nine months. Wood (1921) in eighty-eight cases found
the ages ranged from four months to three and a half years with fifty-seven of them between nine and eighteen months.

Neale and Hucknall (1934) give the age incidence as six months to one year.

Braithwaite (1933) states the age incidence to be four months to twenty-two months with an average of nine months.
Sex Incidence.

In ninety-seven cases of Pink Disease, I found that fifty-two were male and forty-five were female. Other observers do not appear to have found any difference in the sex incidence.

Seasonal Incidence.

The following table shows the monthly incidence:

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<thead>
<tr>
<th>Month</th>
<th>Incidence</th>
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<tbody>
<tr>
<td>January</td>
<td>11</td>
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<td>February</td>
<td>13</td>
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<td>March</td>
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<td>November</td>
<td>7</td>
</tr>
<tr>
<td>December</td>
<td>14</td>
</tr>
</tbody>
</table>

This shows very little alteration during each month. There is a slight although not significant increase during the first few months of the year.

In a thesis, de Cosine gives the following table:

<table>
<thead>
<tr>
<th>Month</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>January</td>
<td>15</td>
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<td>February</td>
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<td>August</td>
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<td>November</td>
<td>4</td>
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<tr>
<td>December</td>
<td>4</td>
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</tbody>
</table>

Here we have a more appreciable increase during the first few months of the year.
Braithwaite (1933) gives the following table:-

<table>
<thead>
<tr>
<th>Month</th>
<th>Cases</th>
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<tbody>
<tr>
<td>January</td>
<td>2</td>
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<tr>
<td>February</td>
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<td>November</td>
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<td>December</td>
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</tbody>
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This also gives us very little information.

**Duration of Disease.**

We have found at the Babies' Hospital, Newcastle, that the duration of the disease varies to some extent, but in the great majority of cases the disease lasts between three and six months although in a few cases it lasted nearly a year. In my series of cases, I found that in 23% of the cases it lasted under four months, in 54% between four and six months and the remainder over six months and up to one year.

In no case have I found it possible to trace any contact with another child suffering from Pink Disease.

Wood, A.H. and I. (1935) have also been impressed by the absence of any contact in cases of Pink Disease. They explain it by the fact that the organism is a widely spread virus which only occasionally assumes a pathogenic role in a susceptible individual.

There has never been any suggestion of an epidemic of Pink Disease in Newcastle. The figures for
five consecutive years at the Babies' Hospital are: 13, 10, 12, 16 and 13. This shows a remarkable consistency.

In France, especially, numerous small epidemics have been recorded. It is just possible however that doctors in certain parts, having seen cases, are recognising other milder degrees of the disease. Certainly there is no evidence in the literature of any epidemics in Britain.

In only one instance have I seen two cases of Pink Disease in one family. The two cases (L.P. and D.P.) are fully recorded in Appendix I. As can be seen there is no evidence of any contact as D.P. died over three years before L.P. was born.

**Home and Social Conditions.**

What has been probably the most striking fact on enquiry into these cases of Pink Disease are the home conditions. The mothers have practically all been good, sensible women with other healthy children. A great number have been miner's wives coming from the country districts of Northumberland and Durham.

Most of the babies have been breast fed and, if bottle fed, have received cod liver oil or orange juice or vitamins in some other form.

We found that very few came from the unemployed classes or lower working classes but the great
majority from the middle or upper working classes.

**Effect of Vitamin B Treatment.**

I have described in Appendix I two cases of Pink Disease treated with a highly concentrated extract of vitamin B prepared by Professor Peters of the Department of Brochemistry at Oxford.

Although one cannot be too dogmatic after using this concentrate in only two cases, the results appear to point to the fact that Pink Disease is not due to any lack of Vitamin B. In the second case the disease lasted four and a half months which is in my experience the average duration of Pink Disease. The gain in weight in hospital was more before the concentrate was given than afterwards. There was no effect on the tachycardia, which is one of the chief signs of the disease. One might say that we had not given enough of the vitamin, but any other vitamin deficiency disease responds very quickly to the vitamin when given.

The first case, which had much more of the concentrate, died of heart failure, typical of Pink Disease. Why we should have this heart failure has not been explained by those who adhere to a theory of vitamin deficiency except by saying that it resembles the heart failure of beri beri. This does not appear to be correct as the heart failure in beri beri is,
as a rule, congestive. The heart failure in Pink Disease more closely resembles that in diphtheria.

We may summarise those etiological factors as follows:
1. Most cases come from the country.
2. Striking age incidence. Usually five to seven months, probably higher abroad.
3. No difference in sex incidence.
4. No definite seasonal incidence although some observers declare there are more cases during the first few months of the year.
5. Duration is usually four to six months.
6. No contacts between cases.
7. No epidemics.
8. Good home and social conditions.
9. No deficiency in diet.
10. No help from concentrated Vitamin B in two cases of Pink Disease.

DISCUSSION ON ETIOLOGY

I have discussed some of the important factors dealing with etiology as they have appeared to me from an examination of my series of cases of Pink Disease. I have also extracted from the literature on Pink Disease some of the important points having a bearing...
on etiology.

From these facts, I shall discuss the various theories on the etiology of Pink Disease:

One of the commonest and most widely held theory is that Pink Disease is due to vitamin deficiency, probably Vitamin B. A vitamin deficiency disease may be due either to a deficiency of vitamins in the diet or to deficient absorption of these vitamins. This disease does not, in my opinion, fall into either of these two classes. As already mentioned, one is struck by the feeding of children suffering from Pink Disease. The great majority have been breast fed or, if bottle fed, the diet has been supplemented with some vitamin containing substance. I have never seen a case of Pink Disease suffering from any other vitamin deficiency disease, such as rickets. Also I have never seen a child, having recovered from Pink Disease, showing any other signs of vitamin deficiency. This is very interesting when one considers how quite frequently one finds the two classical vitamin deficiency diseases, scurvy and rickets, in the same person.

As regards deficient absorption of vitamins, in no case has there been any evidence of intestinal indigestion, such as coeliac disease.

Pink disease runs a typical course, lasting about
four months, and one cannot imagine any condition in which there would be a deficient absorption of vitamins for say four months and then complete recovery.

The other etiological factors which are against any vitamin deficiency are the peculiar age incidence and the fact that it does not affect adults. The duration of the disease is much too constant for a vitamin deficiency disease. One cannot imagine a vitamin deficiency disease lasting say four months, uninfluenced by treatment and then clearing up without any permanent damage. I have only seen two cases in one family (Appendix I) and in this case there were nine children.

The geographical distribution is also very enlightening. As already stated the majority of my cases have come from the country and not the towns. In a vitamin deficiency disease, one would surely expect to find quite the opposite.

The home conditions have, in most cases, been satisfactory and, as already stated, very few cases came from the very poor and unemployed classes.

I have described two cases of Pink Disease treated with a concentrated Vitamin B preparation.
One case died of heart failure, which is so typical of Pink Disease. The high pulse rate in Pink Disease is very typical of the disease and one would expect that if it is due to Vitamin B deficiency, the administration of the concentrated vitamin would have a definite effect on the pulse rate. In these two cases however one died of heart failure and in the other case, there was no alteration in the pulse rate with treatment and the disease lasted four and a half months, which is about the normal duration.

Findlay and Stern (1929) have fed rats on a diet with all vitamins, the only protein given being white of egg. The claim to have got changes in the central nervous system resembling those of Pink Disease in children. They also claim to be able to cure this with yeast and suggest that it is due to some diet deficiency, but not of the known vitamins. We must remember however, that although Pink Disease is now a definite clinical entity, it has not yet been described as a definite pathological entity, so that we cannot accept this theory.

Helmick (1927) suggests that Pink Disease is an allergic state manifested by successive attacks of varied clinical symptoms occurring in combination. The basis of Helmick's argument appears to be that the
most important conditions which have been ascribed to allergy are cyclic vomiting, urticaria, eczema, rhinitis, asthma and angio-neurotic oedema, and a combination of these, he says, constitutes Pink Disease. In the cases of Pink Disease which I have seen, cyclic vomiting is an extremely rare symptom, the skin rash is more like a pure sweat rash and does not resemble urticaria or eczema and the rhinitis does not resemble hay fever.

Furthermore, Pink Disease is a definite entity which lasts about four months with complete recovery in most cases and this cannot be said of any allergic condition. As already stated, Pink Disease has a definite age incidence and there is no hereditary tendency as is seen in most allergic conditions. Fortunately this suggestion has not been upheld.

As has already been mentioned, Braithwaite (1933) has put forward the theory that Pink Disease is caused by an abnormal reaction of the child to sunlight. His argument appears to be based on the month of onset of the disease in twenty-seven cases. The following graph shows the charts of three series of cases, namely of Braithwaite, Rocaz and my own:
As can be seen from this graph, there is no increase in the number of cases in the summer months, as one would expect with an abnormal reaction to sunlight. There are slightly more cases during the winter months.
An interesting point in this theory is that two men claim good results in treatment from exactly opposite methods. Braithwaite treats all his cases with red windows and claims good results by the exclusion of ultra violet rays present in the sunlight by those windows. Bruton Sweet (1936) claims good results in treatment with a mercury vapour lamp which is rich in these rays.

Braithwaite may be getting good results by isolating his cases in hospital and so preventing ward infection which seems definitely to increase the length of the disease and the mortality rate.

The last important theory is that Pink Disease is due to an infection. As might be expected, focal sepsis has been blamed and Rodda (1925) advised eradication of septic foci, such as diseased tonsils. This theory has not been proved and has been dropped. Vipond (1922) published an article claiming to have isolated a diplocoecus from enlarged glands and reported excellent results with a vaccine made from this organism. In 1926, he published another article, strongly advocating this treatment. This is probably a secondary infection as Vipond has not been able to produce the disease in animals by its injection. This would be necessary to prove his theory.

Thus we are rather driven to the theory of a
filterable virus. When one pauses to think of other
diseases, such as acute poliomyelitis and measles,
which are now definitely established as virus disease,
one is struck by the similarity of some aspects of Pink
Disease with them.

On examining the symptomatology of Pink Disease,
one finds that in a great number of cases there are
symptoms similar to those of acute coryza at the onset
of the disease. This points to an infection through
the naso pharynx. The varied symptoms and signs of
Pink Disease suggest some affections of the nervous
system and Feer, in 1922, described the condition as a
"neuritis of the vegetative nervous system". French
observers all seem to support the view that it is a
virus infection of the nervous system, usually attacking
the sympathetic and parasympathetic systems.

As I shall describe later in this thesis, the only
complications or after effects which I have seen
following Pink Disease, are recurrent bronchitis and
bronchiectasis. Here again, we can compare Pink
Disease with measles in which one often finds chest
complications following the disease. Also during Pink
Disease it is very common to find some bronchitis
as with measles.

Examination of the etiological factors which I
have already investigated show that some factors point
very strongly to virus infection while some others
will require some explanation.

The fact that there is a more or less constant course in Pink Disease, the effects on the heart, the good home and social conditions, the good diets and the absence of any help from treatment with concentrated vitamin, all support a virus theory.

We must however explain the absence of epidemics, the striking age incidence and the absence of contact between cases.

Wood, A.J. and I. (1935) explain those facts by saying that the virus is widely spread throughout the community in a non-pathogenic state, sometimes reacting to produce immune bodies and rarely becoming pathogenic to produce Pink Disease in a susceptible individual. This would explain the peculiar age limits of the disease and also that fact that, in my experience, country children contract Pink Disease more commonly than town children. The town children would derive more immunity from the virus in its non-pathogenic state as they would be much more likely to come in contact with it. This would also explain the rarity of Pink Disease in the very poor classes, in which there is very little segregation. The endemic nature of Pink Disease and the absence of epidemics is also explained by this theory.

Although it is impossible to go any further than
theory until the disease has been transmitted experimentally to animals, the virus theory seems at present to be the most satisfactory.

Also as regards pathology, no clear description has been given, although peculiar changes have been found in the basal nuclei, somewhat resembling an encephalitis. Thus Pink Disease will probably have to be described clearly as a pathological entity before it can be conclusively proved to be due to a filterable virus.
OBSERVATIONS ON AFTER HISTORY.

I have taken a series of sixteen cases which have recovered from Pink Disease and examined them at intervals of a few weeks to a few years after recovery. Thirteen of the cases have been picked at random and the other three specially selected because of their known after history. The cases are all described in Appendix I.

As can be seen from the cases, all the thirteen children have been healthy since recovery apart from chest complications in some. The nutrition of these children was on the whole good. Most had good teeth and there was no evidence of rickets.

Case 1 shows a child with Pink Disease which lasted only ten weeks but who was still having recurrent bronchitis six months after. Cases 2, 3, 4 and 11 have been healthy since recovery. Cases 5, 6, 12 and 13 have had recurrent bronchitis or "troubled with chest". Cases 7, 8, 9 and 10 have had pneumonia and in the cases of 7 and 9 twice.

Thus, out of those thirteen cases, nine have had chest trouble since recovery from Pink Disease. None of these children have suffered from any other diseases such as pyelitis, cystitis or otitis media which are usually significant of a generalised infection in children.
Three other cases are described, both showing bronchiectasis following Pink Disease, one by X-ray and lipiodol and the other two by operation and removal of the affected lobe.

These three cases of bronchiectasis were treated at the Babies' Hospital, Newcastle, when they originally suffered from Pink Disease and are included in my series of cases in the discussion on etiology. Thus we have an incidence of at least 3% of cases of Pink Disease developing bronchiectasis. As it has been impossible to follow up all the cases, it is not known whether there have been any further cases of bronchiectasis.

DISCUSSION ON AFTER HISTORY

In the literature on Pink Disease, I have found no mention of any complications following the disease. Some authors have noted a slight change in the mentality of the child. Only one of the cases examined showed any change. It was one of the cases of bronchiectasis and this was quite enough to cause temper and misery.

The nutrition and teeth were, on the whole, good, which is interesting in view of the theory of vitamin deficiency being the cause of Pink Disease.

The most striking point in this survey of cases
following the disease is the definite incidence of chest complications. The figures already quoted showing nine out of thirteen cases picked at random, have suffered from either recurrent bronchitis or pneumonia.

One could account for this following Pink Disease in two ways. Either it is a definite affection of the respiratory tract due to Pink Disease or due to a recurrence of the intercurrent infection which so often manifests itself during the course of the disease. It is a well recognised fact that enteritis, pyelitis and otitis media are very common in Pink Disease.

Neo natal sepsis recurs in many infants during the first six to nine months and manifests itself in the form of bronchitis, pyelitis, enteritis, otitis media or skin sepsis. Thus it may be that an intercurrent infection during Pink Disease may in the same way lie dormant after recovery and occasionally flare up with attacks of pneumonia or bronchitis. This is however rather unlikely since, as already mentioned, no case showed any signs of a generalised infection such as otitis media or pyelitis. Here we have a specific inflammation of the respiratory tract.

Moreover all those cases which have suffered from Pink Disease had a high vitamin diet during and after the illness and should be more immune from affections of the respiratory tract.
When we consider the additional evidence of the three cases of bronchiectasis, one might argue that bronchiectasis follows upon a congenital abnormality in the lungs but a three per cent incidence is so much greater than the normal incidence of bronchiectasis in children.

The other suggestion that we have a definite affection of the respiratory tract during Pink Disease seems to be much more rational than the possibility of a secondary infection. Most cases of Pink Disease show some catarrh of the respiratory tract at the beginning or during the course of the illness. This manifests itself in the form of naso-pharyngeal catarrh, tracheitis or bronchitis or a combination of these. Some authorities say that the naso-pharyngeal catarrh at the onset is due to the primary invasion of the virus causing Pink Disease. If we assume this to be the case, it is quite possible that this virus may permanently damage the mucous membrane of the respiratory tract in some cases. This would account for the recurrent bronchitis, pneumonia and bronchiectasis.
APPENDIX I

TWO CASES OF PINK DISEASE OCCURRING IN ONE FAMILY.

1. L.P. aet 7 months. First seen 15.3.35.

History: Was very well until 5 weeks ago, and, according to the mother, "a big happy baby". At 5 months weighed 15½ lbs. Commenced with restlessness at nights and extreme misery 5 months ago, followed 2 weeks ago by marked photophobia which soon improved. On examination the baby was very miserable, scratching, plucking fingers and toes, with a pulse rate of 150. The feeding had been breast with one supplementary feed of Nestle’s milk and cod liver oil daily.

Family History:

Mother aet 39: In good health, a very capable woman and a good witness.

Father aet 41: A miner who has also enjoyed good health until recently when he had pleurisy (?) and was off work for ten weeks.

The house had three rooms.

The other children were:

1. Girl aet 20, married and well.
2. Girl aet 17, well.
3. Girl aet 15, well.
4. Girl aet 14, well.
5. Boy died at 8½ months, bronchitis.
6. Boy aet 6, well.
7. Girl died of Pink Disease in the Newcastle Babies' Hospital.
9. The child in question.

The mother states that (according to her mother) she had the same trouble when a baby. Whether this was Pink Disease or not is of course uncertain.

The baby was treated at home and given marmite and small doses of luminal every evening. After five months he was free from symptoms of Pink Disease. Six months after recovery the child was examined (aet 1½ years). He then weighed 23½ lbs; the anterior fontanelle was closed; he had 16 teeth with no evidence of caries and the chest was clear.


History: The baby had been entirely breast fed. Healthy until three months ago when mother noticed baby becoming very irritable and sleeping badly. Had been losing weight and not taking feeds and always lay with face buried in pillows. Hands and feet had been rather red for the past two months. At the same time a rash was noticed.

Examination: Extremely miserable baby with soft
wrinkled skin, showing marked recent wasting especially evident on the thighs. Feet and hands were very pink and puffy and felt quite cold. There was a sudaminaious rash over the body. Eyes were sunken but there was no evidence of photophobia. Throat was clear. Baby had six teeth. Pulse rate was 130. The lungs were quite clear. Knee jerks were present.

Progress:

23.6.31: Desquamation between fingers of both hands and septic ulceration.

27.6.31: Photophobia was present for the first time and baby passed a little blood per rectum in the morning. Condition of hands remained much the same. Temperature was raised to 100 and the pulse rate was 140.

2.7.31: Baby very weak with temperature of 104 and heart rate 170. Stools were very loose and the septic lesions on the fingers very marked. The knee jerks were still active.

4.7.31: Baby died due to toxaemia from trophic septic lesions on fingers and gastro enteritis.

**TWO CASES OF PINK DISEASE TREATED WITH CONCENTRATED VITAMIN B.**

1. M.D. aet 6 months.

Admitted to Babies' Hospital, Newcastle 14.1.36.

Died 31.1.36.
Family History: Only child of intelligent young mother. Father working as a warehouseman. Both parents are in good health.

History: Baby was in good health until seven weeks ago when she commenced to scratch herself and was very irritable. Since then she had slept very badly and had not gained weight. Three weeks ago the eyes began to water and she could not stand the light against them. She had lain with her face buried in the pillows.

Feeding: Breast fed for two months when mother's milk left her. Ambrosia, 2 months. Lacta, 2 months. During the past month she had had Numol and orange juice.

Examination: A very miserable baby lying curled up in her cot with her face to the wall and her eyes closed. She clutched at the bars of the cot and was continually scratching herself and rubbing her feet together. She was fairly happy when being nursed and did not seem to object to the firelight but always turned away from the daylight. There was a fairly marked desquamation of the skin between the fingers and toes and both feet and hands were pink and rather cold.

Sleeping pulse: 180 per minute.

Lungs showed no abnormality.

Urine was acid and contained nothing abnormal.

Knee jerks were both rather brisk.
Baby had no teeth present.

Blood: R.B.Cs. . . 5,750,000
W.B.Cs. . . 10,150
Haemoglobin 70%

Weight: 13 lbs 5 ozs.

Temperature: 98°F.

Bowels: normal.

15.1.36: Vitamin B was commenced by mouth and it was decided to give 10cc daily for the first five days and then 5cc daily for ten days.

16.1.36: Temperature rose to 102°F. that morning but baby had gained 5 ozs. since admission. Sleeping pulse: 178.

17.1.36: Temperature had come down to normal. Baby took feeds by spoon fairly well but would not suck from the bottle. There did not appear to be any change in the photophobia or irritability. Sleeping pulse during day: 176 per minute, during night: 160 per minute. Urine clear.

18.1.36: Photophobia was if anything more marked. Sleeping pulse during day: 176 per minute, during night: 166 per minute.

19.1.36: Temperature had risen to 102°F. Sleeping pulse: 170. Urine: trace of albumin and a heavy deposit of phosphates. Microscopically there were a few pus cells. During the past four days the weight had remained stationary. She had been coughing
occasionally.

20.1.36: There appeared to be a little improvement in
the irritability but the wasting of the thighs was
more marked. Chest: bilateral rhonchi but no
evidence of consolidation.

23.1.36: Condition was much the same.

25.1.36: Photophobia was absent that morning but the
baby was lying very quietly and had vomited three times
in 24 hours. Heart: rate 168 but rhythm was becoming
rather tic-tac. Now she had commenced to lose weight.
Urine: albumin, negative. Pus: negative.

25.1.36 - 30.1.36: Baby gradually became more ill with
heart failure, vomiting and marked loss of weight.
There was a gradually rising temperature and hands and
feet were very cold, typical of heart failure of Pink
Disease.

31.1.36: Baby died and unfortunately permission for
an autopsy was refused.


Discharged 20.7.35

Family History: House had five rooms and kitchen.
Fourth child, three other children aged 6 years,
4 years and 2½ years, were well. Husband working as
a miner.

History: Baby was well until three weeks ago when he
commenced to be very miserable and irritable. He had been sweating a lot, had had no appetite, was scratching himself and was vomiting. For the past week he had been unable to stand the light against his eyes. **Feeding:** Breast fed for first four months followed by fresh cow's milk with orange juice and lately a little potato and gravy.  

**Examination:** The baby showed the typical appearance of a case of Pink Disease with mild photophobia, extreme restlessness, scratching body, rubbing feet and hands, feet pinkish and rather cold. The sleeping pulse rate varied between 144 and 172 per minute. The knee jerks were both present despite very marked hypotonia. Weight was 17 lbs.  

During the first ten days in hospital the baby gained ½ lb. in weight and generally was much better than on admission. The vitamin B concentrate was commenced on 3rd July and given in the following amounts:  

<table>
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<tr>
<th>Date</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>July 3rd</td>
<td>5cc.</td>
</tr>
<tr>
<td>July 5th</td>
<td>21cc.</td>
</tr>
<tr>
<td>July 6th</td>
<td>12cc.</td>
</tr>
</tbody>
</table>

Thus in four days he received 38cc. of vitamin B concentrate. Careful observations were kept daily until July 20th and no appreciable change could be seen. The sleeping pulse rate remained at a level between 140 and 170 per minute. He was then discharged from Hospital.
Sixteen days after commencing the vitamin, his weight had increased by \( \frac{1}{2} \) lb. The concentrate was taken readily and did not appear to cause any ill effects. The baby was seen again on August 2nd when there did not appear to be any change in the symptoms or condition. With this baby the Pink Disease lasted for 4\( \frac{1}{2} \) months.

The child was seen again when eighteen months old and was in excellent condition. He had sixteen teeth, the anterior fontanelle was closed, there was no evidence of rickets and he weighed 23 lbs. 8 ozs.

THIRTEEN CASES EXAMINED AT VARYING INTERVALS AFTER RECOVERY FROM PINK DISEASE.

1. J.R. (female) aet 15 months.
Pink Disease commenced at 9 months.
Feeding: breast and orange juice daily.
Family history: 5th child. Good mother. One child died of pneumonia.
Duration of illness: 2\( \frac{1}{2} \) months.
Progress: since recovering from Pink Disease has had recurrent bronchitis.
Present state: fairly well nourished child with closed anterior fontanelle, has 10 teeth and weighs 19 lbs. 12 ozs. There is no evidence of rickets and chest at present is clear.
2. J.F.B. aet 18 months.
Pink Disease commenced at 11 months.
Feeding: Fresh cow's milk.
Family history: Four children, all alive and well.
   Very good mother.
Duration of illness: 4½ months.
Progress: Since recovering has been very well.
Present state: Well nourished baby with 16 teeth, anterior fontanelle closed, weight 23 lbs. 8 ozs.

3. L.P. aet 18 months.
Pink Disease commenced at 7 months.
Feeding: Breast, supplemented by two feeds of Nestle's daily and cod liver oil.
Family history: Nine children but two have died, one of pink disease; a very capable mother.
Duration of illness: 5 months.
Progress: Very well since recovery. Walked at 15 months.
Present state: A well nourished baby with 16 teeth, anterior fontanelle closed, chest clear, weight 23 lbs. 3½ ozs.

4. J.W. aet 19 months.
Pink disease commenced at 7 months.
Feeding: Breast for 1 month, then Ambrosia with orange juice and cod liver oil.
Family History: 3 children all well; father suffers from epilepsy.

Duration of illness: 6 months.

Progress: Has had whooping cough and marked skin sepsis. Walked at one year.

Present state: Has 16 teeth, anterior fontanelle closed, weight 24 lbs. 15 ozs. Baby still does not sleep well. Chest is clear.

5. R.G. aet 3 years.

Pink Disease commenced at 10 months.
Feeding: Breast for 6 weeks, followed by Ostermilk with orange juice every other day.
Family history: Two children; good mother.
Duration of illness: 5 months.
Progress: Since recovery has been very "troubled with his chest", numerous attacks of bronchitis and diarrhoea.

Present state: Now a well nourished boy with good teeth; chest is clear.

6. J.C. (female) aet 2 years.

Pink Disease commenced at 6 months.
Feeding: Ambrosia for 3 months followed by fresh cow's milk.

Family History: Two children both well; good mother.
Duration of illness: 6 months.
Progress: Since recovery has had recurrent bronchitis.

Present state: Child is not well nourished. She has all her teeth but they are badly decayed. Weight is 21 lbs. 2\(\frac{1}{2}\) ozs.

7. J.J. aet 3 years.
Pink Disease commenced at 9 months.
Feeding: Breast with orange juice daily.
Family history: Two children both healthy.
Duration of illness: 1 year.
Progress: Since Pink Disease, has had pneumonia twice and bronchitis twice.
Present state: Weight 28 lbs. 8 ozs., teeth are good but poorly developed. Becomes rather blue and breathless on exertion.

8. A.H. aet 3 years.
Pink Disease commenced at 8 months.
Feeding: Breast with orange juice and cod liver oil.
Family history: Two children, both healthy.
Duration of illness: 6 months.
Progress: Has had pneumonia, whooping cough, and chicken pox and has a constant cough. Commenced to walk at 1 year 7 months.
Present state: Now appears to be in excellent condition. No evidence of rickets.

9. J.M. aet 4 years.
Pink Disease commenced at 4 months.
Feeding: Breast.

Family history: Two children, both healthy.

Duration of illness: 1 year.

Progress: Since illness, has had pneumonia twice, whooping cough and chicken pox. First walked at 2 years.

Present condition: Appears to be in excellent condition. No evidence of rickets.

10. M.S. (female) aet 2 1/2 years.

Pink Disease commenced at 11 months.

Feeding: Breast with cod liver oil.

Duration of illness: 6 months.

Progress: Since Pink Disease has had bronchopneumonia, whooping cough and measles. She always has a loose cough.

Present state: A well cared for child with very little subcutaneous fat. Chest shows marked subdiaphragmatic recession and on auscultation is full of moist sounds. There is no clubbing of the fingers but the general condition gives the impression that this may go on to a bronchiectasis.

11. C.W. aet 3 years.

Pink Disease commenced at 9 months.

Feeding: Breast.
Duration of illness: 12 months.

Progress: Has made good progress but still has some trouble with his eyes against the light.

Present state: Not in excellent condition.

12. J.Y. aet 3 years 9 months.

Pink Disease commenced at 5 months.

Feeding: Breast.

Family history: Two children, both well; good mother.

Duration of illness: 4 months.

Progress: Has made good progress but a little "chesty" in the winter and has had chicken pox.

Present state: Child in excellent condition.

13. M.I. (female) aet 1 year.

Pink Disease commenced at 4½ months.

Feeding: Breast for 3 months followed by Ambrosia and orange juice since 1 month.

Duration of illness: 5 months.

Progress: Has been gaining weight satisfactorily but still has a very bad cough.

Present state: Now weighs 18 lbs. and is quite well generally, but has a very marked loose cough. Chest is full of moist sounds due to marked bronchitis. There is no evidence of rickets.
THREE CASES OF BRONCHIECTASIS
FOLLOWING PINK DISEASE.

1. D.H. aged 6 years.

**Family History:** Two other children aged 12 and 10 years; both healthy. Parents are both healthy. Living in a good house with three rooms in a healthy district.

**History:** Full term baby and natural labour. Feeding: Breast fed for 10 months followed by cow's milk, eggs, fruit, milk puddings, fish, gravy and vegetables. Cut first tooth at 6 months and was walking at 10 months. No illnesses until 13 months old when she commenced to be fretful and mother noticed a rash on back of baby's hands and between fingers. Two weeks late, similar condition of the feet commenced and she was always rubbing her hands and feet. Did not sleep at nights and would not smile. She always slept with face buried in pillows. A week later a rash developed over the body.

**Examination at 14 months:**
Baby looked fairly well nourished and was a good colour. She was very fretful, looked miserable and wriggled about when handled.

- **Ears:** No discharge.
- **Eyes:** There was no apparent photophobia but baby lay with face buried in the bed clothes. There
was slight redness of right eye but no discharge.

Mouth: Teeth were good and firm.

Throat: Normal.

Skin: The feet, especially the soles and edges of the dorsum were very pink and looked puffy. They also had a cold feeling and the skin between the toes was desquamating. There was a petechial rash on the feet extending up the legs to the knees. The hands presented a similar appearance to the feet. There was a rash on the chest extending up to the neck.

Heart: Rate 160

Chest: Nothing abnormal on percussion and no adventitious sounds heard.

Abdomen: Soft with loss of subcutaneous fat.

Spleen: Not palpable.

Knee jerks: Both active.

Tuberculin reaction: Negative.

Baby remained in hospital for three weeks and made some improvement but lost nearly 1 lb. in weight. During this time, she had a slight cough.

When 1 year 11 months, she attended as an out patient and mother complained of child having a chronic cough, with phlegm. She was Xrayed as shown and the radiologist's report was:— "Large opacity of right lung root, interlobar pleura thickened and
upper lobe hazy. There is evidence of enlargement of lymph nodes in the left lung. Suggests tubercle."

The history and examination at the time was:-
Child was not making satisfactory progress and had had
Chest: Very poorly developed.

Percussion: No dullness.

Auscultation: Breath sounds were vesicular over both lungs but there were occasional moist sounds at the left base.

Fingers showed mild clubbing.

Lipiodol examination gave the following pictures:
Although it is not clearly shown on the reproduction on the preceding page, the negative shows dilatation of the bronchial tubes in the left lower lobe.
2. H.T. 

Admitted to Babies' Hospital, Newcastle
17.8.31

Discharged from Babies' Hospital, Newcastle
19.9.31

History: Was a healthy baby until 10 months old when he commenced to be very irritable, sleepless and always rubbing hands and feet. There was marked dribbling of saliva. He was always lying on his face.

Examination: A very irritable and miserable child, showing red and puffy cold hands and feet.

Mouth: Tongue was filthy and appeared as if the tip had sloughed away.

Heart rate: 152 per minute.

Knee jerks: Present.

Chest: Showed no abnormality.

Progress: Child was treated with a concentrated extract of Vitamin B from Professor Peters of Oxford. He appeared to become worse and the Vitamin B was stopped after four days. Two days after the vitamin was stopped a large piece of the tongue sloughed off. After that, there was a slow steady progress and he was discharged, though still showing signs of Pink Disease.

16.2.39: Patient was admitted to Newcastle General Hospital.

History: Cough and sputum since being a baby. The sputum was green and most of it came up first thing in
the morning or if the child had been lying on his left side.

Previous History: Scarlet fever three years ago.

Radiologist's Report: Bronchiectasis at left base.
Examination:
General condition was fair.
Teeth were good.
Tongue had no tip and was very scarred.
Fingers showed definite clubbing.

Chest: Diminished movement on the left side.
Percussion: Slight dullness at left base.
Auscultation: Numerous rhonchi at the left base.
Xray of chest: See previous page.

Progress: Operation by Mr George Mason (25.4.39).
The left lower lobe was removed and the specimen showed typical bronchiectasis. After operation, the patient made good progress.


Admitted to Newcastle General Hospital 7.7.39.

Previous History: Was a healthy baby until 6 months old when she developed Pink Disease. Was admitted to Babies' Hospital, Newcastle in October, 1926, with typical symptoms of Pink Disease. The child was discharged from Hospital after a month. The disease lasted six months.

On discharge from hospital, the child had a cough which has been present ever since.

In 1927, developed pneumonia.
In 1928: Whooping cough.
In 1929: Measles and mumps.
In 1933, her chest was Xrayed at the Royal Victoria Infirmary, Newcastle, and since then there has been copious sputum, especially in the mornings. There has never been any haemoptysis.

Family History: One boy aged 18 years. Good mother living in a country district in ideal surroundings.

Examination on Admission:
- General condition: Fair.
- Teeth: good.
- Mouth: clean.
- Fingers: No clubbing.

Examination of Chest: Diminished movement on left side with dullness on percussion at the left base.

Auscultation:
- Breath sounds: Diminished at left base.
- Vocal resonance: Diminished at left base.
- Numerous rhonchi over the whole chest, especially on the left side.

Progress: 25.7.39: Bronchoscopy showed pus on both sides mainly on the left.

Examination of pus: No tubercle bacilli. No Vincent's Spirochaetes. Growth was mainly haemolytic streptococci.

Lipiodol gave the following Xray pictures showing definite bronchiectasis in the left lower lobe.
Progress: 11.8.39: Operation by Mr Mason. The left lower lobe was removed and showed typical bronchiectasis.

23.8.39: Patient was making satisfactory progress.
## APPENDIX II

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year(s)</th>
<th>Journal/Volume/Issue/Number</th>
</tr>
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<tbody>
<tr>
<td>Bilderback J.B.</td>
<td>1920</td>
<td>Northwest Med. XIX, 263</td>
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<td>Journ. Amer. Med. Ass., LXXXIV, 495</td>
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<tr>
<td>Praithwaite J.V.C.</td>
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<td>Findlay G.M. and Stern R.O.</td>
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<td>Selter F.</td>
<td>1903</td>
<td>Arch. f. Kindern., XXXVII, 468</td>
</tr>
<tr>
<td>Vipond A.E.</td>
<td>1922</td>
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</tr>
</tbody>
</table>
CONCLUSION

Pink Disease appears to be due to a filterable virus and not to any vitamin deficiency in the diet. This conclusion is based upon the following observations:

1. Peculiar age incidence.
2. The good home and social conditions of the patients and striking absence of Pink Disease in the very poor classes.
3. The absence of any other signs of vitamin deficiency in those cases of Pink Disease.
4. The typical course and duration of the disease.
5. The absence of response to treatment with high vitamin diets.

The only complications following Pink Disease are affectations of the respiratory tract. Cases recovered from Pink Disease appear prone to bronchitis and pneumonia and bronchiectasis following Pink Disease seems to be a definite clinical entity.

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