



**PINK DISEASE MENU**

most of these articles were gathered by

**Heather Thiele.**

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● [MERCURY & PINK DISEASE-Lancet 1951](#)

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● [THE MEDICAL JOURNAL OF AUSTRALIA \(June 11-1960\)](#)

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● [MORTALITY FROM PINK DISEASE in 1923-1947](#)

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● [DISEASES KNOWN TO BE CAUSED BY THE DIET](#)

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● [Dr. CHEEK...discoverer of possible CAUSE/linkage with Hg & Enzyme.](#)

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● [PINK DISEASE-10 YEARS AFTER \(The Epilogue\)](#)

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**Acrodynia. Pink Disease, Swift  
Disease,  
Feer Disease, Erythodema,  
Dermatopolyneuritus**

**Nelson's Textbook Chemical and Drug Poisoning**

Acrodynia (the term derived from the Greek, denotes painful extremities) is principally a syndrome of chronic mercury poisoning in infants and young children consisting of many unusual symptoms which, in the well established cases, are so distinctive that there is practically no difficult diagnosis. In few other conditions is extreme and persistent misery such prominent part of the clinical picture. The condition was recognised in Australia as early as 1890 and established as a clinical entity in the British and American literature by Byfield and Bilderback in 1920.

### Etiology.

Most and perhaps all cases of acrodynia represent the clinical response to repeated contact with or ingestion of mercury in products such as house paints, wallpapers, teething powders, vermifuges and diaper rinses. The interval between mercury exposure and onset of symptoms may vary from 1 week to several months. The condition is probably the manifestation of a sensitisation to mercury in the hypersensitive child.

### Pathology.

Pathological findings are mainly present in the central nervous system. Degeneration and chromatolysis of the cerebral and cerebellar cortex are prominent.

### Clinical Manifestations.

The natural course of acrodynia is prolonged, extending from several months to years. There are all grades of severity. The child becomes listless, no longer interested in play, restless and irritable. Generalised inconsistent rashes, which are protean, recur from time to time. Early, the tips of the fingers, toes, and nose acquire a pinkish colour and later the hands and feet become a dusky pink, with patchy areas of ischemia and cyanotic congestion. The colouring shades off at the wrists and ankles. These changes in the extremities are the most distinctive features of the syndrome and are responsible for the term pink disease. Frequently the cheeks and the tip of the nose acquire a scarlet colour.

As the disease becomes established, the sweat glands are enormously dilated and enlarged and perspiration is profuse. Secondary infection may lead to a severe pyoderma. There is desquamation of the soles and palms, which, though usually superficial, may be severe and recur during the course of the disease. The fingers and toes appear oedematous; the swelling is due to hyperplasia and hyperkeratosis of the skin. An outstanding symptom is constant pruritus with excruciating pain in the hands and feet. Children will rub their hands together for hours, and older children will complain of a severe burning sensation.

The nails become dark and frequently drop off. Occasionally, gangrene of the toes and fingers develop and trophic ulcers may result from the constant rubbing of the hands and feet. The hair tends to fall out and is often pulled out by the child.

There is photophobia without evidence of local inflammation of the eyes. The children shield their eyes or bury their faces in their pillows. The lax ligaments and hypotonia permit the children to assume unusual positions.

In extreme cases the teeth may be lost; necrosis of the jaw bones frequently follows. Initially, the gums appear normal except for a slightly deeper red colour, later they become inflamed and swollen. Salivation then becomes pronounced, and the saliva often flows from the mouth in a constant stream. Anorexia is prominent, but because of the excessive perspiration large quantities of water are consumed. There may be diarrhoea and prolapse of the rectum is a frequent complication. The blood pressure and pulse rate may be increased significantly. Fever is usually not present unless there is some complication such as urinary tract infection or bronchopneumonia.

Neurological symptoms are an important part of the syndrome and include neuritis, mental apathy, and irritability. Early in the disease the tendon reflexes may be normal or increased, but later they disappear. There is not a true motor paralysis, but because of the soft, flabby musculature the child has no desire to walk and is hypotonic, listless and hypomotile. The severe pain prevents normal sleep. There is no time when a child with acrodynia appears happy or comfortable; the child does not play or smile, but appears dejected and melancholic, a picture of abject misery.

### Laboratory Data.

There are no characteristic changes in the blood or cerebrospinal fluid. Proteinuria may occur, and a nephrotic syndrome may develop. Slit lamp examination may show a lenticular gray or red brown reflex.

### Prevention.

The withdrawal of mercury from various household products has led to a marked decrease in the incidence of acrodynia. However, mercurial drugs should be avoided in pediatric practice whenever possible, and the physician should be alert to other sources of mercury, especially contamination of food sources from agricultural processes and industrial waste.

### Treatment.

The treatment of acrodynia includes the removal of mercury, the administration of antidotes, and careful supportive measures.

BAL is effective, especially when given early in the disease and the dose and side effects are the same as for acute poisonings. L-Penicillimine (N-acetyl-D,L-penicillimine) has been used successfully to treat acrodynia and has an advantage over BAL in that it can be given orally. The effective dose is

**30mg/kg daily in 2-3 divided doses for 4 weeks or until the symptoms improve. Side effects include fever, rashes, proteinuria, leukopenia and thrombocytopenia.**

**Barbituates, paraldehyde, hydroxyzine or chlorpromazine may be used for irritability and pain. Nourishing foods containing proteins, minerals and vitamins should be given. Frequently, nasogastric tube feeding is necessary for severe anorexia. Intravenous replacement of fluid and electrolytes may be required for severe dehydration. Appropriate antibiotics should be given for secondary pyogenic cutaneous and urinary infections.**

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**RETURN to MAIN MENU** 



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Duchess of York Hospital  
for Babies, Manchester.  
The Lancet March 1952**

## MERCURY & PINK DISEASE

An association between mercury and pink disease (infantile acrodynia) was suggested by the work of Warkany and Hubbard (1948, 1951), Fanconi et al (1947) and Fanconi and Botsztejn (1948). In 38 of 41 investigated cases Warkany and Hubbard found an abnormal quantity of mercury excreted in the urine.

Other workers (Bivings and Lewis, 1948, Elmore 1948, van Crefeld and Paulssen 1949, Lefebvre 1949, Loebenstein 1949. Watkins 1950, Kromann 1950) have supported Warkany's and Fanconi's claims.

In Manchester pink disease is relatively common. In the 3 Manchester children's hospitals during 1950 the numbers of cases given the diagnosis were:

Royal Manchester Children's Hospital	---37
Booth Hall Hospital	-----7
Duchess of York Hospital for Babies	-----17
Total	-----61

These figures probably give a reliable picture of the incidence of pink disease, because it is fair to assume that most of the affected infants come to hospital at some stage of their illness.

The use of powders to prevent or to cure teething difficulties is widespread. such powders are variously labelled as "teething" or "cooling" powders and some of them contain mercury in relatively large quantities. The content of calomel varies from 16% to 33%.

## INVESTIGATIONS & RESULTS

We have approached the problem of mercury in pink disease from various angles.

1/ We followed up many cases in the hope of finding some other form of clinical hypersensitivity to mercury or an association with other allergic disorders in the patients or their families.

2/ We tried to find the incidence of the ingestion of mercurial teething powders among a healthy infant population and its regional and numerical correlation with pink disease.

3/ The urinary excretion of mercury was studied.



#### **4/ The response to BAL was investigated. Follow up**

**The children followed up were those in whom pink disease had been diagnosed at the Duchess of York Hospital for Babies in 1930-50. The case notes of 213 patients were available. Of these 37 had died, the cause of death, so far as could be ascertained, being as follows:**

Mortality in 213 cases
Pink disease 16
Bronchopneumonia 12
Sudden death 4
Empyema-fibrinous pericarditis 1
Gastroenteritis 1
Bronchiolitis 1
Bronchiectasis 1
Septicemia 1
Total-----37 (17%)

**The main single complication leading to a fatal outcome was bronchopneumonia. In 4 cases death took place suddenly. In 16 cases no definite cause of death was found and death was “attributed” to the primary illness.**

**Of the remaining 176 patients 110 were re-examined and a detailed history was obtained from the parents, particularly with regard to exposure to mercury, sequela of the disease and allergic disorders. In 80 (73%) development had been normal, mentally and physically; the other 30 (27%) were described as nervous or highly strung, some of them having temper tantrums, nocturnal enuresis, nail biting, exaggerated fears and stammer. One girl still keeps rubbing her hands and the mother maintains that this dates back to her acrodynia.**

**In only 10 patients could a history of allergic disorders be elicited. In most of them these were urticarial rashes and only 1 had asthma. In 7 other cases a family history of allergy was obtained. Thus 15% of the patients had some relationship to the allergic diathesis. This figure comes well within the suggested range of allergic disorders among the general population.**

**No instance of recrudescence or second illness was reported.**

**Five children with severe pink disease showed simultaneous recovery from an intercurrent infection and the acrodynia. The intervening illnesses were measles in 3 cases, chickenpox and tonsillitis.**

### **Mercurial Teething Powders**

**In 97 cases a clear answer was given to the question of exposure to mercury: 49 children (50%) had received mercurial teething powders. In 29**

cases these had been given before the onset of their illness, while in the other 20 they had been given to alleviate its manifestations.

Thus almost 30% had certainly ingested mercury, often for many months before the beginning of the pink disease. In 5 cases the child had had mercurial teething powders throughout the illness and for years afterwards without ill effect.

A relatively high incidence of ingestion of mercury by affected infants having been found, it seemed of desirable import to ascertain how frequently teething powders are given to the healthy infant population. The subjects of this inquiry were 1561 infants, from 4 months to 2 years age, attending the welfare centres of Manchester and Salford public-health authorities. Of these, 619 (39.6%) had received teething or cooling powders of various kinds and in 109 (6.9%) these were mercurial.

As the Habit of giving babies teething powders may vary considerably from region to region, we then chose another area where we knew that the incidence of pink disease was low-ie. the county of Warwick, where there are 5-10 cases a year in a population about half that of Manchester and Salford. The parents of 1588 Warwickshire children of the same age group were questioned and it was found that 679 children were habitually given teething powders, which in 584 cases (37%) contained mercury.

In the Manchester and Salford areas the incidence of pink disease did not seem to be higher in the districts where mercurial teething powders were commonly given to infants.

## Urinary Excretion of Mercury

The urine of children who had had active pink disease during the past two and half years was examined for mercury. The analysis was made by 2 different laboratories using the same method, but varying in the form of collection, one using heavy metal free glass containers, the other ordinary glass bottles. Each laboratory established a normal range of mercury excretion, which was slightly higher in that using ordinary bottles.

Of 94 cases examined no abnormal excretion of mercury was detected in 33 (35%) and 61 (65%) had increased amounts ranging from 20 to 250 ug per 100ml. The 65% with an abnormally large quantity of mercury in the urine compares well with the 50% in the follow up group who had been given mercury either before or after the onset of pink disease.

## Patch Tests

Patch tests with calomel, calomel ointment and blue ointment were made on 10 patients with florid acrodynia and a positive result was obtained in 1. This child, whose skin reacted strongly to the blue ointment, showed a weaker response to calomel powder. Among 30 healthy infants and children, one, who had never (so far as could be ascertained) ingested mercury previously, gave a mild reaction to calomel.

## **Response to Dimercaprol**

**Dimercaprol was given to 15 infants who were said to have ingested mercury for many months before the onset of pink disease and in whom a high urinary excretion of mercury was found. The treatment was given in hospital and the patients were carefully observed. The dose used was 1 mg per lb of body weight according to the schedule suggested by Bivings and Lewis (1948). Maximal excretion of mercury in the urine was noticed within 24 hours of the start of treatment and gradually decreased in the course of the treatment.**

**In all the cases there was a definite change in emotional behaviour. The patients became less irritable, smiled again and took their feeds more readily; 4 gained weight during treatment; 3 lost their skin rash and in 2 the perspiration decreased. All the other clinical manifestations such as pinkness of hands and feet, hypotonia, tachycardia, pain in the extremities and (in the majority) perspiration persisted.**

**In 3 infants, however, who did not present the characteristic clinical picture of acrodynia, but only certain manifestations which are commonly associated with it, dimercaprol produced definite improvement and laboratory findings supported the opinion that this was due to the elimination of mercury in the urine.**

**An account of these is given because they are regarded as evidence that chronic ingestion of mercury produces changes in the serum-cholesterol, probably due to renal damage, simultaneously with symptoms like those of acrodynia. They thus establish a link between the accepted forms of mercury poisoning and acrodynia.**

## **CASE RECORDS**

### **Case 1**

**A boy aged 21 months was brought to the outpatients dep' because of a change in his behaviour. For the past month he had become fretful, crying frequently, refusing to play with his toys, disinclined to walk and preferring to lie on the floor. He had little appetite. He had been given mercurial teething powder from the age of 4 months, 3 to 4 times weekly, for nearly a year, until 6 months ago, when the dosage was gradually reduced and during the past 4 weeks he had had only 1 powder.**

**On examination he appeared well nourished, but rather pale and there was no pinkness of hands or feet, but only slight hypotonia and a pulse rate of 120. A non pitting edema over the dorsum of both feet and a chronic nasal infection were the most noticeable findings. He had much albuminuria and because of this was admitted to hospital.**

**The concentration of albumin in the urine was 1%, A one way chromatogram in phenol revealed bands similar to those seen in nephrosis. The amount of mercury in the urine was 102 ug per 100ml. Examination of the blood showed:**

Serum cholesterol-----	585 mg per 100ml
Serum chlorides-----	685 “
Serum proteins-----	6.64 g “
Albumin-----	2.6 g “
Globulin-----	4.04 g ‘

Because of the heavy mercury ingestion and excretion, dimercaprol was given for 8 days. The albuminuria decreased daily and ceased entirely a fortnight after the end of treatment. The child's behaviour improved and serum cholesterol and serum protein levels reverted to normal.

### Case 2

A girl aged 7 months was brought to hospital with intractable conjunctivitis. She had had diarrhea and vomiting for 5 days preceding the eye trouble and consequently had lost weight. For the past 2 months she had a mercurial teething powder nightly.

On examination severe photophobia was the only pathological finding. Nothing was found on routine laboratory examination of the urine and the amount of mercury in the urine was 150ug per 100ml.

The teething powder was discontinued and after 10 days the urinary excretion of mercury had decreased to 32ug per 100ml. The photophobia had somewhat improved, but was still disturbing. The serum cholesterol was 396mg per 100ml; serum protein was normal. After treatment with dimercaprol the photophobia cleared completely and the serum cholesterol returned to normal.

### Case 3

A boy aged 15 months was admitted to hospital with typical acrodynia. He had mercurial teething powders twice weekly for the past 9 months, the last one a few days before his arrival in hospital. His urine contained mercury 52ug per 100ml. The serum cholesterol was 525mg per 100ml, serum protein was normal. After treatment with dimercaprol the urinary excretion of mercury ceased, the serum cholesterol was 230mg per 100ml, the infant began to gain weight and was more cheerful, but all the other manifestations persisted for many weeks.

## DISCUSSION

Warkany and Hubbard (1951) have marshalled weighty evidence that mercury can cause pink disease. Particularly, the finding of an abnormal amount of mercury in the urine in some 93% of their cases is of great importance. However, the criticism may be made that the cases examined may have been subjected to unintentional selection because they were referred to Warkany and Hubbard by pediatricians of other cities especially for the

### **estimation of urinary mercury.**

**In our series about 72% of patients had mercury in their urine and as only 6.9% of the local child population were in the habit of taking mercurial teething powders this finding strongly points to this metal as an important etiological factor in pink disease. But, there may well be other factors which, either in conjunction with mercury or independently, can produce the clinical picture of acrodynia. This is suggested by the fact that in Warwickshire, where 37% of the children were found to have had mercury teething powders, the incidence of acrodynia was much lower.**

**A further point deserving consideration is the age distribution. Most of the cases in this as well as in other series published in this country (Fisher 1947) occur in the 1st and 2nd years of life. In Switzerland (Fanconi et al 1947) and in France (Cosmi 1930) most cases occur in the 2nd, 3rd and 4th year of life. This could be related to different habits of using mercury indiscriminately. In this country mercurial teething or cooling powders are given to infants, while in France and Switzerland, santonin and calomel are given to older children as anthelmintics. The allergic response to the ingestion of mercury known as calomel disease (Jenny 1930), Fanconi et al (1947), Baumann (1949), is hardly ever seen in infants aged less than 1 year old.**

**The seasonal incidence in our series favours the months of spring. In view of the insidious onset of pink disease this might be due to the higher incidence of upper respiratory infections during the winter months and with it a large number of fretful and irritable infants providing their parents with an opportunity to treat supposed teething troubles with teething powders.**

**Fanconi and his workers support their concept of pink disease as a neuro-allergic manifestation with the observations that has followed single administrations of santonin and calomel; that the age distribution is similar to that of calomel useage, which undoubtedly can be regarded as an antigen-antibody response, and that Landolt and Egli (1948) in Switzerland, found allergic disorders in 32% of former acrodynia patients. The Swiss workers also include polyradiculitis and lipoid nephrosis among the hypersensitivity reactions to mercury.**

**Warkany and Hubbard prefer the term "idiosyncrasy", using it as a connotation for a temporary individual susceptibility to mercury intoxication, implying a lowered tolerance. They emphasise the many features of acrodynia common to subacute and chronic mercurial poisoning.**

**This theory of a temporary decrease in tolerance for mercury due to unknown factors established a useful working hypothesis, but is unfortunately clouded by reference to it as an idiosyncrasy.**

**We found no evidence that acrodynia is an allergic response to mercury. The incidence of allergic disorders in acrodynia patients was about the same as in the general child population. There was no record of a germ attack and no instance of eosinophilia in 97 investigated cases; there were only 1 positive patch test among 10 active cases and 1 among 30 controls.**



**The regular ingestion of mercury as teething powders over many months before signs of pink disease develop is hardly compatible with its proposed role as an antigen. A person can scarcely be credited with antigenic properties, because toxic reactions to it seem to vary with individual degrees of tolerance.**

**The disappointing results of treatment with dimercaprol observed also by Warkany and Hubbard again do not lend support to the idea that pink disease is an allergic phenomenon.**

**The 3 infants, however, who presented only some manifestations of pink disease after protracted ingestion of mercury and whose raised serum cholesterol level fell after the elimination of mercury, might be regarded as evidence of a toxic action on the kidneys preceding the more severe poisoning leading to nephrosis.**

**Cheek (1950, 1951) found lowered serum sodium levels in patients with acrodynia and suggested an underlying disturbance of adrenal function as causing pink disease. Williams et al (1951) were unable to confirm Cheek's findings. The serum sodium levels of 18 patients in the present series were examined and only in 1 of them was the serum sodium level abnormally low. None of these patients improved on treatment with salt, although some of the mothers thought the babies' emotional condition had improved.**

## **SUMMARY**

**An attempt was made to study the relationship of mercury to pink disease on the basis of (1) a follow up study of 213 patients; (2) an inquiry into the habitual ingestion of mercurial teething powders among a cross section of the healthy infant population of 2 regions varying in the incidence of pink disease; (3) the urinary excretion of mercury in acrodynia patients; (4) the response to treatment with dimercaprol.**

**Of the 213 acrodynia patients seen during a 20 year period 37 had died. Of the remaining 176 patients 110 were re-examined. 73% had developed normally; 27% were described as having minor psychosomatic disorders and 50% gave a history of the ingestion of mercury.**

**The inquiry into the administration of teething powders to healthy infants in Salford and Manchester included 1561 babies, 109 (6.9%) of whom were habitually given mercurial teething powders. In the county of Warwick, of 1588 infants 584 (37%) ingested more or less regularly mercurial teething powders.**

**The urinary excretion of mercury in 94 florid cases of acrodynia studied during a 3 year period was abnormally high in 61 (65%).**

**The treatment of 15 cases with dimercaprol did not lead to any great improvement except in 3 cases which are reported.**

**The high incidence of pathological excretion of mercury in active cases of pink disease compared with the relatively low exposure rate among healthy infants in the same region is regarded as evidence that mercury is an**

**etiological factor in acrodynia, leading to chronic or subacute poisoning in infants with a low tolerance, probably in combination with other factors. The importance of other causal agents still unknown is not denied.**

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**RETURN to MAIN MENU** 



**THE MEDICAL JOURNAL OF AUSTRALIA**  
**June 11-1960**  
**THE RISE AND DECLINE OF PINK DISEASE By F W Clements,**  
**M.D. Institute of Child Health, Sydney.**

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## Summary.

- 1/** A brief outline is given of the main reports published in Australia on pink disease.
- 2/** It is pointed out that, in both the UK and Australia, death rates rose from a low level when the condition was first recorded to a peak in the late 1940's and now the disease has almost disappeared.
- 3/** The number of hospital admissions for this condition in the 4 major children's hospitals in Australia has roughly paralleled the mortality rates.
- 4/** The dates of the introduction of the legislation in 5 Australian states to control the dispensing of mercury in teething powders and syrups are recorded. It is pointed out that the sharp decline in both morbidity and mortality preceded the introduction of legislation.
- 5/** Although Calomel may be a main aetiological factor in pink disease, the demographical information neither substantiates nor denies this hypothesis.

1/ The recognition, description and now the almost complete disappearance of pink disease present a number of interesting features. Swift, of Adelaide, is usually credited with the first full description of the disease, which he gave to the Australasian Medical Congress in Auckland in 1914 (Swift 1914).

However, it would appear that a number of earlier writers made reference to the condition. Professor Sir Edward Ford has drawn my attention to a report by Dr. Bancroft, of Brisbane, to the local board of Health in 1881, that he "sees many children brought to death's door from their parents dosing them with a powerful powder of mercury..." Selter, of Solingen in the Ruhr (Wood and Wood, 1935), published a good description of the disease in 1903. Swift's description was apparently based on 14 cases in his practice in the preceding 2 years, although he had been shown an occasional child with this condition by Dr. Still in London some years earlier.

In 1920, A J Wood presented a paper to the 11th Australasian Medical Congress

in Brisbane, basing his clinical description on the records of some 51 cases in his practice in the preceding 6 years or so (Wood 1920). In 1935 A J Wood and his son, Ian, in a report to the annual meeting of the British Medical Association in Melbourne, indicated that their series totalled 150, of which 60 had been added between 1920-1935 (Wood & Wood, 1935).

The next major contribution to the Australian literature on this disease was made by Southby in 1949, when he was able to draw upon the records of 502 children diagnosed as having had this condition. This total was made up partly from his experiences in his private and hospital practices, and partly from the practices of some of his colleagues (Southby, 1949).

This brief revue of the source material for the major Australian contribution suggests either a wider recognition or a mounting incidence from the 1st recognition through to the late 1940's. This would seem to parallel events in England & Wales. Logan (1949) has shown that the death rates from pink disease of children aged under 5 years rapidly mounted from 0.3 per million in 1923 to a peak of 31.4 per million in 1936. For a few years the numbers fluctuated and they dropped to a lower plateau, which continued at around 17.0 per million until 1946.

In 1947 there was a sharp rise to 29.0 per million. Logan suggested that the widening recognition of the disease was probably responsible for the steady rise in death rates to the plateau which commenced in the early 1940's. Since 1948 there has been a sharp decline to almost disappearance. This will be discussed later.

Control of a disease is dependent upon the definition of the aetiology. For many years the aetiology of pink disease has been the subject of much speculation and some experimentation. Earlier theories covered a wide range of possibilities, including an allergic response, endocrine dysfunction, poisoning by arsenic and ergot, an infective agent. Some of these, like the arsenic and ergot theories, were disposed of; but the difficulties of testing other hypotheses left some of them still possibilities when Franconi and his co-workers (1947) suggested that mercury poisoning and/or sensitivity was the main or perhaps the only aetiological factor.

This hypotheses, which was supported by the work of Warkany and Hubbard, a year or so later, offered for the first time a possible tangible objective for the control of pink disease-namely, the removal of mercury from teething powders and syrups, the commonest source for infants and young children, and perhaps the restricted use of mercurial ointments on young children.

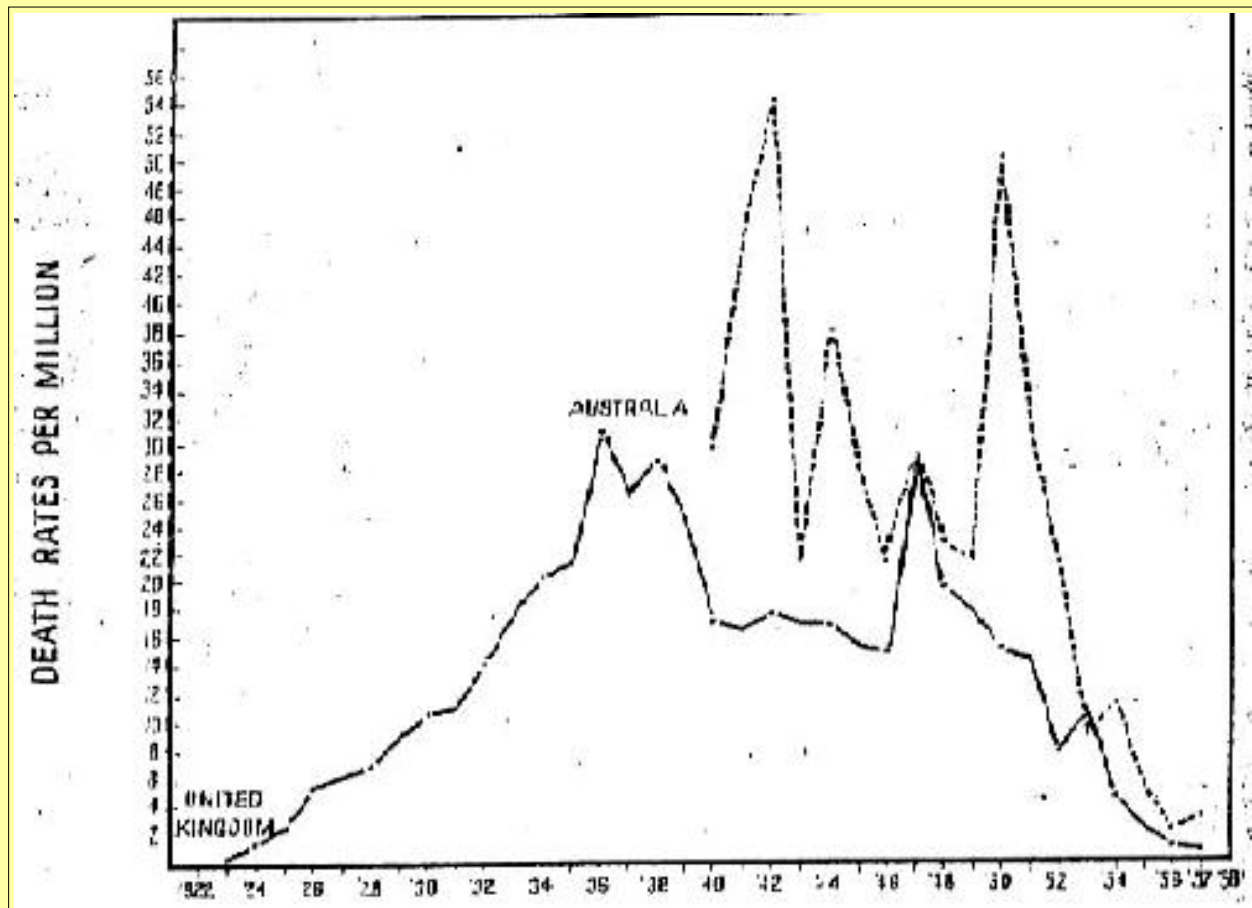
Action to this end occurred in England before it did in Australia. Colver (1956) points out that the warnings by prominent paediatricians and public-health workers in the early 1950's (Gaisford, 1949; James, 1951) considerably REDUCED the number of prescriptions written by doctors, and ultimately led to the withdrawal by a principal manufacturer of mercury from teething powders.

This was effective in December 1953, although some small manufacturers and pharmacists still appeared to be including the metal in locally dispensed powders (Dathan and Macaulay, 1955). It has apparently not been thought necessary to introduce legislation in England to control the use of mercury in teething powders. Colver (1956) has shown that between 1947-1955 there was a reduction of about 75% in the number of patients with pink disease treated at the Sheffield Children's

## Hospital and the City General Hospital.

The analysis of death rates in England & Wales commenced by Logan has been extended from subsequent annual reports by the Registrar-General, and the figures are incorporated in

Figure No.1



### Death rates for pink disease in children aged under 5 years in UK & Australia 1922-1958

It will be seen that, from a plateau of around 30 per million (based on the population aged under 5 years) in the late 1940's, the rate has fallen to an insignificant point in 1957.

**The sequence of events in Australia will now be reviewed.**

**Legislation in Australia to Control the Use of Mercury in Teething Powders.**

On August 20, 1953, The South Australian Government promulgated a regulation prohibiting the use of mercury in teething powders unless prescribed by a medical practitioner.

On June 15, 1954, the following regulation (75A) was gazetted in Queensland: No person other than upon the written prescription of a medical practitioner, shall sell any teething powder, soothing powder, infant powder or similar preparation containing mercurous chloride for internal use by children under 5 years of age.

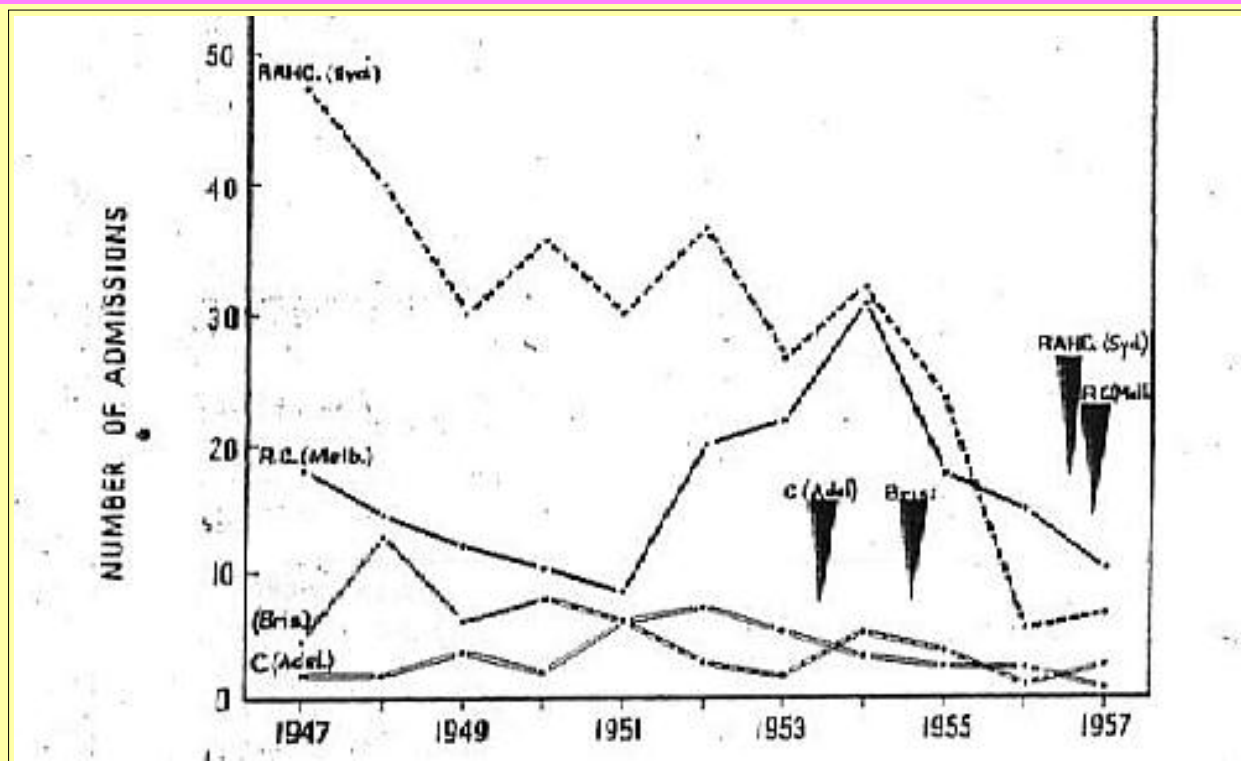
Similar regulations were gazetted in Tasmania on April 27, 1955, in NSW on August 10, 1956 and in Victoria on October 22, 1956. Although specific legislation on this matter has not been introduced in WA, the Commissioner of Public Health has advised that the problem is adequately controlled by existing legislation (Tenzell, 1957).

**Almost complete Australia wide legislation is due in no small measure to the efforts of the Australian Paediatric Association, both as a corporate organisation and through the personal efforts of individual members in each state. It is of interest to record that, although the regulation was promulgated in NSW on August 10, 1956, teething powders containing mercury were purchased from a large number of pharmacists as late as the first quarter of 1958. It was suggested that this was due to the lack of publicity given to the new regulation. The position has since been rectified. This point is stressed because of its relationship to trends in morbidity and mortality.**

### **The Incidence of Pink Disease.**

The exact incidence of this condition cannot be estimated accurately. It is not a notifiable disease and minor forms are probably not recognised. A hospital tends to attract patients with specific diseases if special facilities are provided for their diagnosis and treatment. For a number of years a pink disease clinic was conducted at the Royal Alexandra Hospital for Children. In the middle 1950's special facilities existed at the Royal Children's Hospital, Melbourne. These services may have had some influence on the figures given for the numbers of children treated at the various hospitals. **The numbers of children treated at the R.A.H. Sydney, the R.C.H. Melbourne and the Adelaide Children's Hospital (Incorporated) and the Mater Children's Hospital Brisbane, over the 11 year period 1947-1957, are shown in**

#### Figure No.2



### Numbers of children with pink disease admitted to 4 major hospitals.

The arrows on this chart indicate the approximate dates of introduction of legislation in each state to control the use of mercury.

### Trends in Mortality.

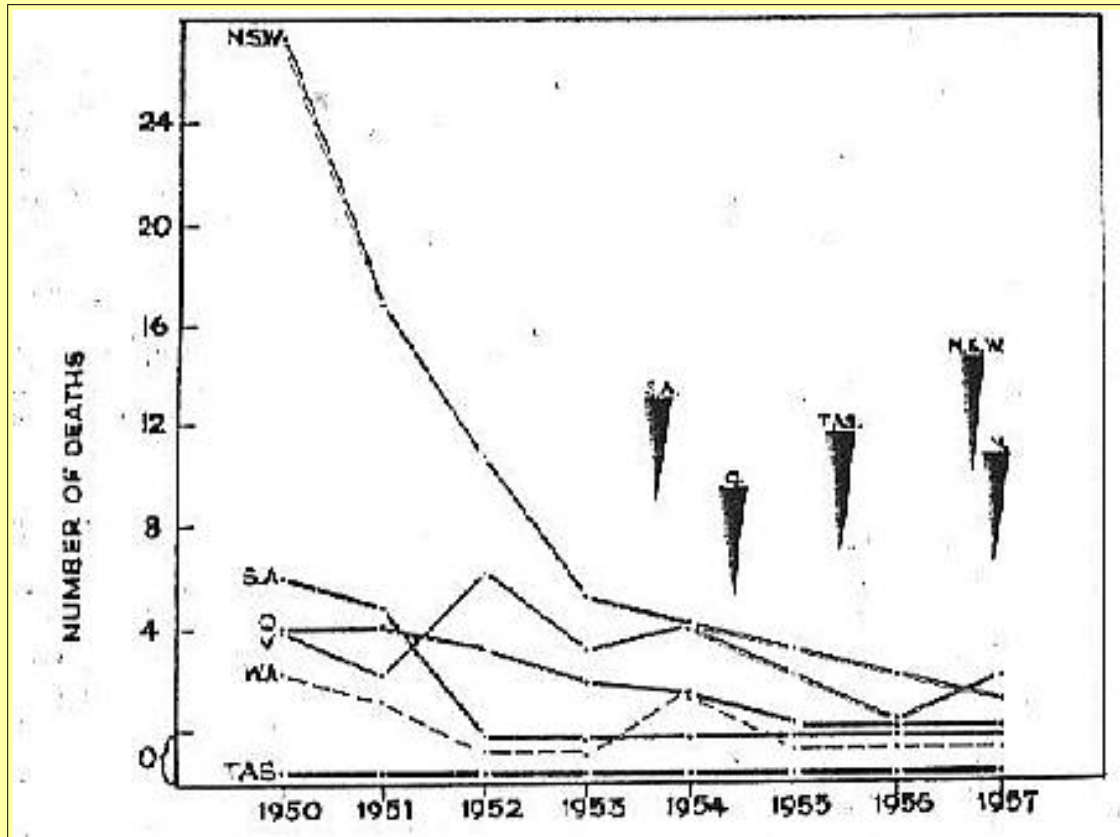
The numbers of children who died with the diagnosis “pink disease” were first recorded in official Australian statistics in 1940. In 1948 the 6th Revision of the International Classification of Diseases and Causes of Death was introduced, but it was not adopted for Australian official statistics until 1950. However, these changes did not affect the recording.

The trend in mortality in Australia is shown in figure 1, along with the trend in England & Wales. For comparison, the Australian rates are expressed in the same terms as those for England & Wales-viz.-deaths per million children aged under 5 years. Since few deaths occur above the age of 2 years, a better rate would have been for children aged under 2 years.

A feature of the Australian data is the wide fluctuations from year to year, for which there does not appear to be any explanation. With the exception of the year 1950, the trend has been progressively downward, until the current rates are but a fraction of what they were in the 1940's. It is nevertheless disconcerting to note that, throughout the years for which both English and Australian figures are available, the Australian rates have been appreciably higher.

Some interesting facts emerged when the numbers of deaths and the death rates for the various states were compared. These figures are shown in fig's

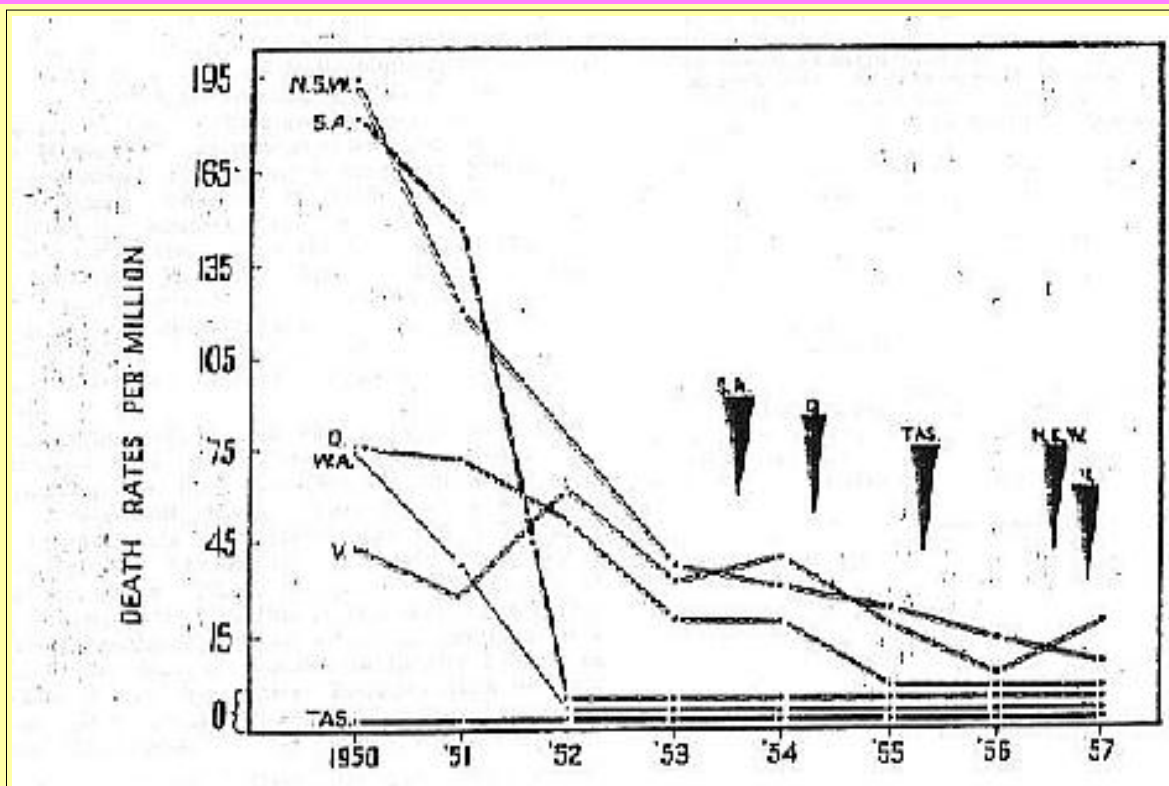
**Figure No.3**



**Number of deaths in Aust' states.  
Arrows-date of Calomel legislation.**

**Figure No.4**





### Death rates for under 2 years age.

It will be noted that initially high rates existed in NSW and SA with almost insignificant figures for TAS. **The differences between the states may well be a reflection of interest and enthusiasm in diagnosis.** Attention is drawn to the arrows in figure 2 AND figure 3 which indicate the approximate date when the legislation was introduced in each state to control the sale of teething powders containing mercury. The position of each of these arrows in relation to the shape of the curves in figure 4 is of particular interest.

### Discussion.

Pink disease is fast disappearing, and will, no doubt, shortly join the long list of diseases of childhood which in the last 2 or 3 decades have become rarities, to be displayed at a clinical evening. The cause of the disappearance is not clear. The conclusions to be drawn from figure 2 and figure 4 do not support the implication that legislative control of the use of mercury in teething powders is the cause.

The fall in both the numbers of children admitted to hospital and mortality rates had occurred before the legislation could have been effective. **Analysis of teething powders showed that voluntary exclusion by manufacturers or pharmacists had not preceded the legislation.** It is interesting to note that the trend of mortality in England is similar to that in Australia and, there, the removal of mercury was on a voluntary basis.

It could be argued that over the past decade fewer teething powders were given to young children, the mothers responding to the educational efforts of baby health centre

nurses and others. Unfortunately we have no evidence to test this suggestion and we have been unable to obtain any figures for the sale of teething powders over the years. The apparent ineffectiveness of legislation is disappointing to those who worked for this action; **but it is important to record these changes in a disease pattern now, lest at some time in the future an attempt is made to use the virtual disappearance of pink disease so soon after the introduction of legislation as an example of the effectiveness of this form of disease control.** ( ??????)

Although the late Frank Barrett (Barrett, 1957) at one time strongly held, as a result of his extensive experimental work, that pink disease was due to mercury poisoning, and although several English writers have claimed that the disappearance of the condition in England is proof of the implication of mercury in the aetiology, the Australian statistical information certainly does not support this point. Neither does it deny the hypothesis. For the sake of the theory, it is **unfortunate that the spectacular fall in death rates should have preceded the introduction of the legislation.**

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**William P D Logan MD, B Sc. Glasgow. DPH  
From the General Register Office  
The Lancet APRIL 1949**

Interest in this relatively rare and etiologically obscure disease of childhood has been stimulated by the suggestion of Warkeny and Hubbard that mercury administered in teething powders or in ointments may be the causal agent; out of 20 cases of pink disease mercury was found in the urine of 18. It may be opportune, therefore, to review the mortality of pink disease in England and Wales during the past 25 years.

The synonyms for pink disease include erthroderma, polyneuritica, dermato-polyneuritis and acrodynia, but their use on death certificates is being steadily given up in favour of the simpler name.

Table 1 gives the number of deaths and the death-rate from pink disease in each year from 1923 to 1947 and fig 1 illustrates the trend of the death rate over those years.

**TABLE 1**

Y E A R S	Annual Deaths									Annual death rate*		
	Male				Female				Both sexes all ages	All ages		
	Age (yrs)			All ages	Age (yrs)			All ages		Male	Female	Both sexes
	0-	1-	5-		0-	1-	5-					
1923	-	-	-	-	-	1	-	1	1	-	0.6	0.3
1924	-	1	-	1	-	3	-	3	4	0.5	1.6	1.1
1925	3	-	-	3	1	4	-	5	8	1.7	2.9	2.3
1926	6	4	1	11	5	4	-	9	20	6.4	5.4	5.9
1927	3	3	-	6	8	6	-	14	20	3.6	8.6	6.1
1928	5	8	-	13	4	4	-	8	21	8.1	5.1	6.6
1929	11	5	-	16	8	4	-	12	28	10.2	7.8	9
1930	14	5	-	19	8	6	-	14	33	12.3	9.3	10.8
1931	7	6	1	14	13	6	-	19	33	9.2	12.8	11
1932	15	10	2	27	5	11	-	16	43	18	10.9	14.5
1933	18	11	-	29	14	11	-	25	54	19.5	17.3	18.4
1934	23	10	-	33	18	8	-	26	59	22.6	18.3	20.5

1935	21	13	-	34	18	7	1	26	60	23.6	18.6	21.2
1936	23	14	-	37	24	26	1	51	88	26	37.9	31.4
1937	15	11	-	26	28	19	-	47	73	18.3	34.3	26.1
1938	24	18	-	42	24	15	-	39	81	29.3	28.2	28.7
1939	18	9	-	27	24	16	2	42	69	18.5	29.9	24.1
1940	12	11	-	23	13	13	-	26	49	15.7	18.4	17
1941	16	6	-	22	12	13	-	25	47	15.2	17.9	16.5
1942	18	10	-	28	12	10	-	22	50	19.2	15.7	17.5
1943	17	3	-	20	18	11	-	29	49	13.4	20.3	16.8
1944	17	11	-	28	15	7	-	22	50	18.2	14.9	16.5
1945	15	8	1	24	16	8	-	24	48	15	15.7	15.3
1946	13	6	-	19	22	7	-	29	48	11.4	18.3	14.7
1947	43	15	-	58	32	13	-	45	103	32	26.1	29.1

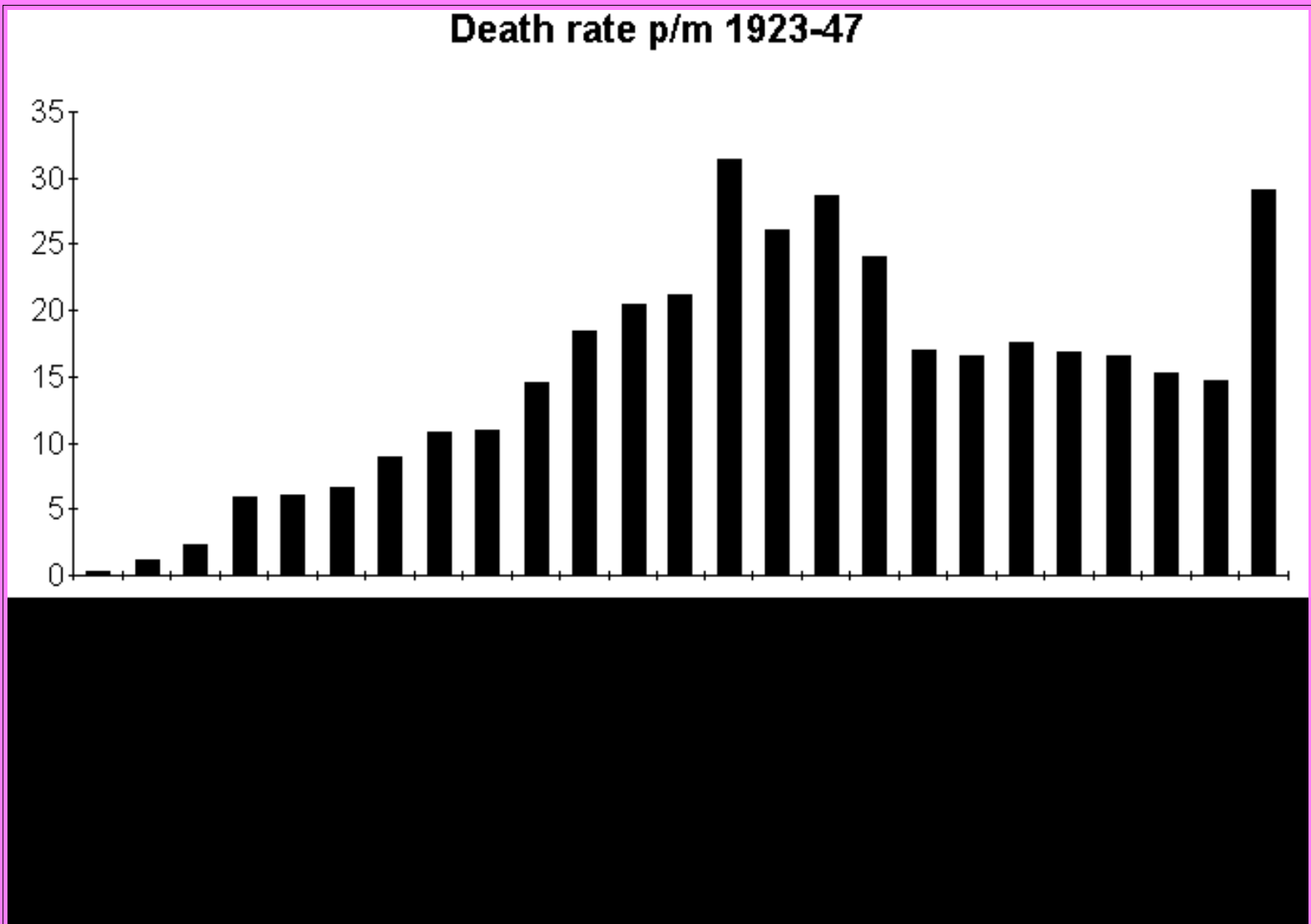
Starting with 1 death in 1923 ( a rate of 0.3 per million) the recorded deaths and the death rate progressively increased as the disease became more widely recognised up to 1939, when there were 88 deaths (31.4 per million). For the next 3 years the numbers fluctuated, dropped to a much lower level in 1940 (49 deaths, 17 per million) and remained practically constant at this lower level during the next 6 years.

It is difficult to believe that this was a chance sequence and it cannot be explained by changes in the birth rate which behaved dissimilarly. In 1947, however, deaths rose sharply; the number (103, was the highest yet recorded and the death rate (29.2 per million) was almost as high as in 1936.

The figures, it should be noted, have not been corrected for the changes in classification that came into force in 1940 and would not materially alter the picture.

The association here revealed between the mortality of pink disease and the war may or may not indicate a real temporary change in the behaviour of the disease. The circumstances of war may have altered the standard of death certification of pink disease; or may have reduced its prevalence or fatality.

Figure 1



As table 1 shows, variations in the predominating sex occurred randomly from year to year. In numbers of deaths each sex predominated in 12 of the 25 years, whereas in 1945 the deaths were divided equally between the sexes. The female death rate exceeded the male in 13 years.

Table 2 shows that, aggregating years 1923-47, there was no significant difference between the sexes: 49.2% of deaths in males and 50.8% in females. The percentage for each sex differs from expectation (the 25 year average proportion) of each sex in the child population: (males 50.8% and females 49.2%) by 1.6% with a standard error of 1.5%.

Most deaths occurred under the age of 1 year and none over the age of 9 years. In four of the earlier years ( 1923-24-28-32) deaths at ages over 1 year were more numerous than those under 1 year; but after 1932 the lowest age group has persistently shown an excess ranging from 7 to 32, except in 1940, when the excess

was only 1 death.

Table 2 shows that, of all the deaths in 1923-47, about 61% were in children under 1 year. 38% in ages 1-4 years and less than 1% at 5 years of age or over. There was no significant difference in age distribution between the sexes.

**TABLE 2**

Age	Male	Female	Both sexes
0-	357	342	699 (61.4%)
1-	198	233	431 (37.8%)
5-	5	4	9 (0.8%)
All ages	560 49.2%	579 50.8%	1139 (100%)

**TABLE 3**

under 1 year						
Age	under 4 weeks	4 weeks to 3 months	3-6 months	6-12 months	Total under 1 year	
# of deaths	2	4	26	184	216	
% of total	0.9	1.9	12	85.2	100	
under 5 years						
# of deaths	216	113	3	3	0	340
% of total	63.5	33.2	2.4	0.9	0	100

For the years 1940-46 table 3 provides a further analysis of deaths by age: 63.5% of all deaths under 5 years were in children aged under 1 year and 33.2% between 1 and 2 years. Among deaths under 1 year over 85% took place in the second 6 months of life. There were few deaths under 6 months or over 2 years of age.

Discussing the age distribution of morbidity in pink disease, Fisher, who had formed the impression that with the passage of time the "age of attack" was becoming lower, found, on analysis of his figures, no evidence of any significant age shift. In our present series of deaths, on the other hand, there is evidence of a significant age shift between 1923 and 1947 from the higher to the lowest age group.

The deaths, aggregated for the years 1940-46, in each of the 12 main regions of England and Wales are contained in table 4. In the absence of information about regional populations at ages during the war years, total live births in each region, aggregated for the same years, have been used as a base for the calculation of "death rates". Such rates, it should be noted, do not take account of migrational movements of the child population during the war.

**TABLE 4**

Region	# of deaths 1940-1946						Both sexes all ages	Death rate per million 1940-46 both sexes, all ages	# of deaths both sexes, all ages 1947
	Male			Female					
	age in years								
	0-	1-	5-	0-	1-	5-			
Greater London	7	7	-	9	11	-	34	40.9=7	5
Rest of S/east	4	11	-	8	5	-	26	38.3=7.5	8
North 1	20	4	-	18	12	-	54	201.4=27.4	10
North 2	3	-	-	2	3	-	8	51.2=18.1	4
North 3	15	8	-	18	5	-	46	114.3=16.9	14
North 4	18	12	1	16	9	-	56	78.8=10.5	22
Midland 1	19	4	-	8	11	-	42	65.8=10.2	17
Midland 2	10	5	-	14	1	-	30	95.5=17.4	17

East	7	1	-	6	2	-	16	71.4=17.9	3
South west	-	-	-	2	4	-	6	24.1=9.8	7
Wales 1	2	1	-	6	1	-	10	45.6=14.4	3
Wales 2	3	2	-	3	5	-	13	158.7=44	1
England and Wales	108	55	1	108	69	-	341	71.4=3.9	103

There are highly significant differences between the rates in the 12 regions. The highest rate was recorded in North 1 (201.4 per million), followed by Wales 2 (158.7) and North 3 (114.3). The lowest rate occurred in the South-west region (24.1), followed by the South-east (38.3), and then by Greater London (40.9). These regional differences are illustrated and may be compared region with region in fig 2.

The regional distribution of deaths in 1947 is shown in the last column of Table 3. It will be seen that the large increase in deaths during that year was not concentrated in any one part of the country, but was shared among the regions in about the same proportion as in previous years.

It is conjectural whether these differences in death rate between the regions are due to differences in morbidity, in fatality or in standards of diagnosis. It would be interesting to know whether there exist regional differences of habit in the administration of mercurial medicaments to young children.

## SUMMARY

The death rate of pink disease fell to a constant low level during the late war, but rose sharply in 1947.

There was no significant difference in sex mortality over the years 1923-47.

About two thirds of the deaths were in children aged under 1 year, especially at ages 6-12 months. Of the other third practically all were between the age of 1 and 2 years.

During 1940-46 there were highly significant differences between regional death rates.

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**DISEASES KNOWN TO BE CAUSED BY THE DIET**

**PINK DISEASE - ACRODYNIA**

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**Although the culprit agent of pink disease was not strictly a food, the story of it's discovery and eradication is nicely illustrative of this kind of detective work.**

**Pink disease was a chronic and unpleasant, occasionally fatal, illness of babies and young children that first became apparent in the late 19th century in Australia and soon spread to the rest of the world and (albeit in older children) to continental Europe.**

**By the 1940s it was quite common; most family doctors had 3-4 cases in their practices (especially in industrial towns) and pink disease accounted for 3%-4% of all pediatric hospital admissions in some cities. Within a decade, following the pinpointing of the cause, it had virtually disappeared. Today's doctors have never seen a case and are not taught about it; a new epidemic of pink disease would probably catch us as unprepared as were our fathers.**

**Breast fed and bottle fed babies were equally susceptible. The child became restless and listless, unable to play, occasionally irritated by light. The arms and legs hung passively and children who had been old enough to walk before the disease stopped walking, although there was no true paralysis. The fingers and toes, then the palms and the soles became swollen, cold and clammy and assumed the dusky red color that gave the disease its name.**

**The cheeks and nose were often bright red. The hair fell out. The teeth loosened in inflamed gums and there was even patchy erosion of the jawbone in some. The child lost interest in food although it salivated excessively and was often thirsty. Most wearing of all was the dreadful insomnia which kept child and parents awake night after night. The mortality was about 10% and we can assume that some of that was due to battering by overtired parents driven beyond breaking point.**

**There was no shortage of theories to explain this disease varying from emotional disorder and neurosis through to endocrine or electrolyte disturbance, photosensitivity, allergy, virus infection, ergotism and arsenic or thallium poisoning. There was also no shortage of reported cures. Tonsillectomy, liver powder, vitamin supplements, hormone injections and electrolytic adjustments all enjoyed transient popularity as first glowing claims, then negative counter claims, appeared in the medical and lay press.**

**Controlled clinical trials were still in their infancy and many hopes were raised time after time only to be cruelly dashed as the uselessness of the touted cure became obvious. Disease states similar to pink disease were induced in laboratory rats by depriving them of pyridoxine, but this vitamin proved another disappointment when tried in patients.**

**Then in 1945 a severely affected child was admitted to hospital in Cincinnati, Ohio, under the care of Dr Josef Warkany. The disease was rare in Cincinnati and Warkany's interest was aroused (as well as his compassion). He had a hunch that heavy metal poisoning might be implicated, so he asked his laboratory to measure the levels of the common, industrial heavy metals in the child's urine.**

The results were all negative. But one element-mercury-had not been measured as there was no adequate test for it at the time. By luck, Warkany discovered that in Cincinnati there was a young chemist, Mr Donald Hubbard, who had recently developed a sensitive method for measuring urinary mercury, so for the sake of completeness he asked Hubbard to do the measurement on his patient. The result was strongly positive.

Over the next 3 years Warkany appealed for urine specimens from the patients of his fellow American pediatricians (pink disease was too rare in Cincinnati to allow him to do the study on his own patients) and slowly a pattern emerged. In every case of pink disease there was a history of mercury use, a positive urine mercury test or both. In a group of control patients from Warkany's own practice, urinary mercury was virtually never seen.

Mercury and its salts were, and are, commonly used in industrial processes and prior to the introduction of effective health legislation in the 19th century cases of mercury poisoning were quite common among factory workers. The element was especially used in the manufacture of felt hats and the touchiness and irritability of 'mad hatters' became legendary.

Years later, in 1966, Warkany wryly commented that if a case of pink disease had been seen by a competent 18th century physician the diagnosis would have been immediately obvious. But by 1940, industrial mercury was tightly regulated by law and, frankly, mercury poisoning was vanishingly rare; doctors had never seen it.

The only continuing source of mercury was in medicine. Mercury salts are effective against intestinal worms and syphilis and are also effective diuretics and purgatives. In the days when nothing was safer, these drugs were widely prescribed.

In the early 19th century mercurous chloride also made an appearance in 'teething powders' which were given to irritable crying babies in the hopeful belief that the resulting brisk purgation would 'cleanse the system'. The more irritable the child became the more teething powder he was likely to be given. Steedman's teething powder was the most popular in Britain, containing 26.3% mercurous chloride. Similar powders were popular throughout the English speaking world, though they never took hold in continental Europe.

Warkany and Hubbard published their findings in 1948 and by 1950 the hypothesis that pink disease was caused by the mercury in teething powders had become quite popular. The FDA attempted (unsuccessfully) to ban the products. But there were dissenting voices. Why was pink disease rare in comparison with the enormous intake of teething powders?

(Steedman's sold an incredible 7 million doses a year). Why was it more common in some parts of the country than in others, although the sales of teething powders were the same? Why did some patients have no history of mercury exposure, in spite of intense and pointed questioning by the doctors? Why did many pharmacists swear that they had sold thousands of teething powders over the years and had never seen a case of pink disease?

**(In fact, only 1 in 500 children exposed to the teething powders developed the disease). In 1950 authoritative British medical opinion was still cautious about the mercury hypothesis-an understandable caution, yet responsible, as it turned out, for the prolongation of the epidemic, with uncountable cost in human and financial terms, for several years later.**

**But slowly the evidence was stacking up against mercury. Dimercaprol (British anti-Lewisite; BAL) is a chelating agent developed for military use against possible gas attacks and in the 1950s was the standard treatment for industrial mercury poisoning. Several physicians gave their pink disease patients dimercaprol with gratifying cures. (The drug was never tested in a proper controlled clinical trial as the disease disappeared before such a trial could be organized.)**

**Warkany and Hubbard's reports of an association between mercury exposure and the disease was confirmed by several other workers, though these later reports also noted that urinary mercury levels were often high in healthy children too. In the rare cases of industrial mercury poisoning that occurred, astute clinicians noted that in the recovery phase after the acute illness, a condition indistinguishable from pink disease could be seen for a few weeks. Clearly, if mercury was responsible for the disease, it could not be simple poisoning, or all exposed children would suffer in a dose related manner; the children who became ill must be excessively sensitive to the poison (idiosyncrasy).**

**And there the matter rested at impasse between the mercury hypothesis and the manufacturers of mercurials. In the absence of decisive evidence, Parliament declined repeated calls to ban the products (although several states in USA and Australia did so), and the disease remained a chronic and fearful curse.**

**The impasse was finally broken in 1953 by Dr J G Dathan of Stokes-on-Trent. Upset and incensed by the miserable deaths of 2 of his young patients and refusing to certify the deaths as due to natural causes, he referred the cases to the coroner. The scientific cases for and against the mercury hypothesis were arrayed against each other in an English court of law-surely an unusual setting for a scientific debate.**

**The jury found that the deaths were caused by mercury poisoning from Steedman's teething powder-in one case by frank overdose and in the other because of unusual sensitivity of the child-and fearing litigation or Parliamentary action the manufacturers immediately removed the mercury from their preparations and recalled all old stocks.**

**The other manufacturers gradually followed suit. 3 years later, in Sheffield, the intake of mercurials and the incidence of pink disease had both dropped sharply and by 1966 Warkany, the originator of the mercury hypothesis was able to write a final 'post mortem' article on pink disease in the "American Journal of Diseases of Children"-a rare, but deserved accolade for a dedicated (and lucky) medical scientist.**

**The story illustrates the difficulty of achieving change when doctors are**

**confronted by powerful commercial interests, and finds an echo in the 1980s in the continuing sagas of tobacco and lead. This is specially so when the companies can muster 1 or 2 experts who will say that “the evidence is not yet decisive”.**

**In truth it is still not proven beyond doubt that mercury caused pink disease and it is still possible that an epidemic virus, now fortunately passed, caused it. Of course, that explanation is very implausible and now that the disease is departed no one is sufficiently interested to do more experiments. It is also true that had the world had waited for 100% proof of cause and effect, our children would probably still be ravaged by this dreadful, but preventable disease.**

**It would be dishonest to close the pink disease story without one last remark, though as scientists we are embarrassed to have to make it. Warkany and Hubbard’s original 1948 study on urinary mercury were drawn from Warkany’s own practice in Cincinnati where the disease was rare and where teething powders were rarely used. Had the control urines been taken from the geographical areas where patients came from, mercury would have been found in several apparently normal, healthy children, thus making the association far less striking. If Warkany and Hubbard had done a scientifically impeccable trial, the cause might never have been noticed.**

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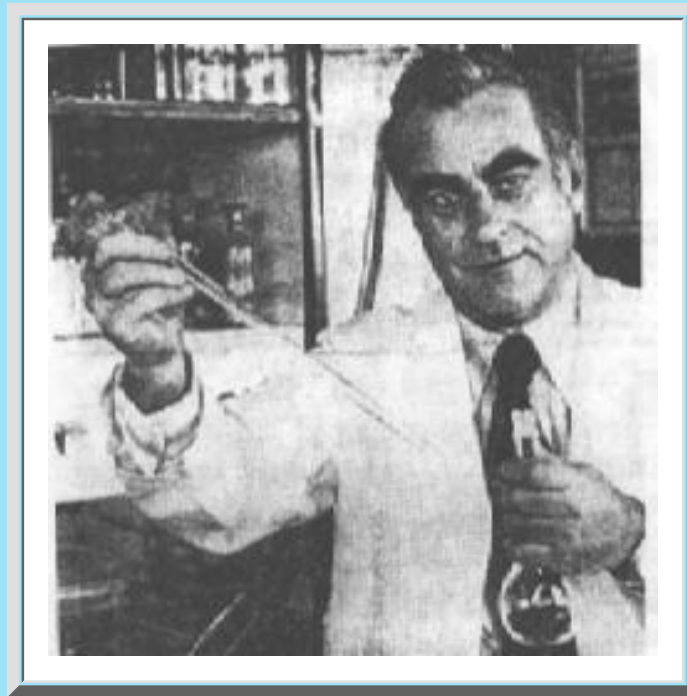
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**ACRODYNIA by DONALD B. CHEEK, MD, DSc  
BRENNEMANN'S PRACTICE OF PEDIATRICS  
Chapter 17D**

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Professor Donald Cheek MD Dsc.

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Don Cheek, father of 2 daughters, was born in South Australia. By the time he was 25 he had received 10,000 letters from grateful mothers around the world. The reason was the medical breakthrough he made with Pink Disease.

The disease was affecting young children and the cause was traced to the mercury compounds then being used in teething powders and ointments prescribed for children. The clue to the breakthrough was young patients complaining of constant thirst. He was to go on to spend another 10 years proving his thesis that the adrenal gland was vitally involved in Pink Disease.

He was Professor of Pediatrics at Johns Hopkins Uni Hospital, Baltimore and had won the Borden Award of the American Academy of Pediatrics.

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**J G Dathan \*, C C Harvey \*\*  
1 May 1965 British Medical Journal  
pp 1181-1182**

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**N.B. copied from hardcopy supplied by Heather Thiele from 3M Pharmaceuticals pty ltd.**

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Since pink disease was described by Swift in 1914 there has been no unanimous view concerning the causation of this disease. Warkany and Hubbard (1948) first suggested that the cause might be chronic metallic poisoning, incriminating mercury, particularly that administered to infants in the form of teething powders.

This view received support from Bivings (1949) who found mercury in 28 out of 31 consecutive cases of pink disease and was reinforced by Gainsford (1949) in Manchester. 3 years later, however; in a reply to a question in the House of Commons, Miss Hornsby-Smith (1952), for the Minister of Health stated: "Inquiries are already in progress at various children's hospitals and, although the indiscriminate use of teething powders is clearly undesirable, there is not yet definite evidence to justify general publicity."

The deaths of 2 infants in 1953 were reported to H M Coroner in Stoke-on-Trent and the verdict at each inquest showed that the death was from bronchopneumonia due to pink disease resulting from chronic mercurial poisoning from teething powders.

On 10 December 1953 the attention of the Home Secretary was drawn to the first of these inquests and he was asked whether, in view of the evidence, action should not be taken to prohibit the use of these substances. During the course of his reply the Home Secretary stated that "inquiries were not yet complete." Thus his reply differed little from that made on behalf of the Minister of Health some 20 months earlier.

However, as a direct result of these 2 inquests which received wide publicity, the manufacturers of the teething powders concerned, ceased production and subsequently advertised "new and improved powders", made to a formula which did not include mercury.

The "British Medical Journal " 1954 commenting upon the paper incriminating mercury that appeared in the same issue (Dathan, 1954) stated that "there will be a good opportunity for investigating the residual cases which occur after the present supply of powders containing calomel have disappeared from the chemists' shops." This opportunity is now taken after 10 years and results show how correct earlier authors had been in their belief that chronic mercury poisoning was the main, if not the only, cause of pink disease.

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### **Our Experience Since 1953**

Up to 1953, the children's wards in Stoke-on-Trent were hardly ever without cases of pink disease and during the 3 or 4 months following the 1953 events several more cases were seen, which gave rise to some concern lest other sources of mercurial ingestion might have been overlooked. In 1954 the medical officer of health for the city therefore arranged for the collection of teething powders of the old formula from all the chemists' shops and the small mixed businesses and their free replacement by the harmless powders containing no mercury.

The results of this withdrawal of mercury containing powders was most

dramatic—there has not been an authentic case of pink disease in the city of Stoke-on-Trent during the 10 years that have now elapsed since this action was taken. Evidence collected in this area therefore supports strongly the view that pink disease was the direct result of chronic mercurial poisoning and that the disease is now practically extinct.

Evidence collected independently in another industrial area of the north of England provides figures which leave little room for further doubts regarding the etiology of this disease. In all, 65 cases of pink disease occurring in one pediatrician's practice (C H) in industrial South Yorkshire since 1948 have been reviewed; the results are shown in Table 1. The sharp fall in the case incidence of pink disease from 1954 onwards coincides with the withdrawal by the manufacturers of mercury containing teething powders.

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## Discussion

### Etiology

That the role of mercury in the causation of pink disease was not universally accepted even as late as 1956 is suggested by Farquhar, Crawford and Law (1956), who belittle the role of mercury and pointed out that the symptoms and signs were essentially manifestations of gross overactivity of the sympathetic nervous system.

They expressed the view that “pink disease may represent the misdirected zeal of an inexperienced defense mechanism to a number of noxious stimuli in certain predisposed infants.” The association between pink disease and mercury ingestion is still not wholly accepted, as is shown by correspondence in the “British Medical Journal” as recently as 1963, when Braithwaite (1963) disputed Lightwood and Butler's (1963) “unjustified acceptance of a transatlantic theory,” on the uncertain evidence of 21 patients who had suffered pink disease in infancy, of whom, only 9 had been given teething powders.

He had to admit, however, that he had only seen 1 case since 1953. Farquhar (1963), in reply, referred to the ever increasing weight of evidence incriminating mercury, only to have further doubts expressed by Frances Braid (1963), though without supporting evidence. McGregor and Rayner (1964) adduce fresh evidence for a mercurial cause, in the form of calomel dusting powder in siblings—one presenting with renal acidosis and the other, 5 years later, with pink disease.

W P D Logan (1949) from the General Register Office showed that the death rate from pink disease varied little between 1923-1947. It seems probable that the slight decrease during the years 1950-1953 may have resulted from a lessening in the use of teething powders resulting from approved propaganda in welfare centers and elsewhere, but the death rate was halved in 1954 and halved again in 1955 and now is practically nil.

Any remaining doubts about the cause of pink disease must surely be resolved by the comparison of Tables 1 and 2, bearing in mind that the withdrawal of mercury containing powders occurred early in 1954.

A nation wide survey compiled by the chief medical statistician of the General

Register Office (C C Spicer, personal communication, 1964), shows deaths registered as being due to pink disease during the years 1950-1962 (table 2). The marked national decline in deaths from pink disease parallels to a remarkable degree the local incidence of the disease quoted in Table 1.

It seems somewhat tragic that isolated deaths can still occur through shops still holding stocks of the old type of teething powders containing mercury.

On 30 September 1963 a 6 month old firstborn girl was referred to one of us. (C C H) by her doctor as a case of pink disease, with restlessness, slight cough and loss of appetite and with the significant comment, "these symptoms are said to have developed since she started teething."

She had between 3.5-4.5 months of age received 9 mercurial teething powders of the old pre 1954 formula containing 26% calomel, purchased from a store in Oxfordshire. Classical symptoms began at 4 months of age: irritability, insomnia, anorexia, with excessive sweating at 5 months of age, cold discolored hands and feet and hyponia. She was found dead in her cot at home on the morning following consultation and no urinary excretion studies were made.

At the inquest the pathologist's evidence led to a verdict that the child had died from pink disease due to mercury poisoning from these powders.

Public health inspectors have since this recent fatality been on the alert; and in one urban district in the West Riding 60 packets have been collected from the local shops, each containing 20 powders, including 1gm (65mg) of calomel per powder, manufactured by a firm which went out of business 7 years earlier.

Action now by medical officers of health similar to that taken in Stoke-on-Trent in 1954 and more recently in the West Riding could remove most of the remaining risks that there might be further deaths from pink disease. At the same time, the risk of mercurial ointments, lotions and vermifuges should continue to receive publicity internationally within the medical profession (Blattner, 1964).

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## Summary

The incidence and mortality rate of pink disease have fallen dramatically since teething powders containing mercury were withdrawn from the market in 1954. In one pediatric practice in South Yorkshire an average of 9 new cases had been seen annually during the period 1948-1954, whereas only 4 cases have occurred since.

The national death rate from pink disease shows a similar decline, from 57 in 1950 to 7 in 1955 and to 0 in 1961-1962. A fatal case occurring in 1963 is described where out of date mercury containing teething powders bought from a village shop in Oxfordshire, had been administered. The divergent views on the causation of pink disease are discussed and the results of this survey interpreted as conclusive evidence that this disease is caused by ingestion of mercury.

2 of the children with proved mercury powder risk in 1951 and one in 1953 were later found to have bronchiectasis.

Table 1-New cases of pink disease in one South Yorkshire area

year	mercury powders definite	mercury powders unproved	Total
1948	2	5	7
1949	2	2	4
1950	5	4	9
1951	9*	3	12
1952	7	5	12
1953	9*	3	12
1954	5	0	5
1955	0	0	0
1956	0	1	1
1957	1	0	1
1958	0	0	0
1959	0	0	0
1960	0	0	0
1961	0	0	0
1962	0	1	1
1963	1	0	1
	31	24	65

Table 2

Year	Male	Female	Total
1950	34	23	57
1951	34	19	53
1952	15	13	28
1953	19	17	36
1954	8	7	15
1955	4	3	7
1956	3	1	4
1957	2	1	3
1958	0	1	1
1959	1	1	2
1960	1	1	2
1961	0	0	0

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Our thanks are due to Dr J L Emery, Consultant Pathologist, Sheffield Children's Hospital, for information and advice.  
to Dr C C Spicer, Chief Medical Statistician, General Register Office;  
to Dr E C Butterworth for many hours of biochemical work during the original series of cases in Stoke-on-Trent.  
We also thank Dr R W Elliott, West Riding County Medical Officer  
Dr J S Hamilton, Medical Officer of Health for Stoke-on-Trent, for their co-operation and example in the collection of obsolete powders containing mercury.

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**RETURN to MAIN MENU** 



**Clinical Pediatrics Aug 1963  
John L Chamberlain MD; Warren W  
Quillian**

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Nashville, Tennessee.

# Acrodynia

## SUMMARY

The literature concerning acrodynia is briefly reviewed. Experience with 62 cases is recorded. Children with acrodynia exhibit signs and symptoms of autonomic hyperactivity. There is an association with increased urinary mercury levels. BAL seems to be the therapy of choice, with Priscoline and ganglionic blockers helpful in initiating symptomatic relief. Our last patient was encountered in 1958.

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62 cases of acrodynia have been recognized at Vanderbilt University hospital since 1926. Significantly, perhaps, no instances have been encountered during the past 3 years. A similar decrease in incidence has also been noted by Dodd at another institution where, in the past, acrodynia was commonly seen. It would appear that acrodynia is becoming a disease of the past in the U.S.

Acrodynia has occurred sporadically in this country and affects infants and young children. The term is derived from the Greek roots meaning "extremity" and "pain". First reports of this disease in the US were in 1920 when 10 cases were reported by Bilderback. These cases, although collectively grouped as acrodynia, still had little resemblance to a similarly described disorder due to arsenic poisoning.

The first accurate description should probably be credited to Swift who, in 1914, presented a paper before the Australasian Medical Conference entitled, "Erythroedema". In recognition of his discovery acrodynia is often termed "Swifts's disease". The term "pink disease" is often used interchangeably because of the characteristic red hands and feet.

This paper represents a study of 62 infants and children with acrodynia, describes the status of 57 of these cases in a follow-up survey and discusses the etiology and therapy of the disorder.

## CLINICAL DATA

The diagnosis in the 62 patients with acrodynia was based on the clinical manifestations and in some instances on the associated findings of high urinary mercury excretion. Of these cases, 47 were recognized between 1936-1955. and the last was encountered in 1958. 51 of the children were under 2 years of age. There was an even sex distribution.

Inquiries concerning exposure to inorganic mercurial compounds were recorded in 24 cases. Of these, 22 were found to have been exposed to mercury, primarily in the form of teething powder.



The most frequent symptoms were rash, irritability, pruritus, hypertension, excess sweating, hypotonia and photophobia-Table 1. The rash was protean, being erythematous, macular, papular or vesicular.

The children frequently demonstrated irritability and pain by rubbing their hands and feet excessively. Pruritus and burning were distressing and prominent. Perspiration was often excessive and night sweats were common. Blood pressure readings were not consistently recorded in these patients, but a significant number (39 of 44 cases with recorded bp values) had hypertension.

The pathognomonic posture of a child with acrodynia and hyperextensibility was often assumed. (Fig 1) Fever was not a prominent feature. 4 children were noted to lose hair and nails and there were 2 cases of autoamputation.

Laboratory studies were usually noncontributory. 33 cases had a white count of 10 000 to 25 000 per cubic ml. Hemoglobin values below 10gm per 100 ml were noted in 6 cases. The spinal fluid was normal in 14 cases so studied. 12 patients had abnormal routine urinalysis. Other laboratory determinations were for the most part normal.

Mercury values in the urine of 19 cases varied from 0 to 401 mcg/L. Although there is some discrepancy in the literature, a value below 10 mcg/L is generally deemed to be within normal limits. By this criterion, 15 of 19 cases (83%) in our series had abnormal amounts of mercury in the urine.

Therapy was usually with nonspecific agents such as multivitamins, brewer's yeast and blood transfusions, with chelating agents, and with peripheral vasodilators. Cases for this analysis were selected on a basis of adequate clinical follow up and relation to overall drug effect.

10 cases were treated with multivitamin preparations. 2 patients received Priscoline alone (12.5 to 25 mg orally every 3-4 hours). One responded dramatically and the other showed little improvement. 3 were treated with dimercaprol (BAL) alone (3mg/Kg/day), and all had prompt improvement. These had received BAL relatively early in the disease.

12 patients were given a combination of BAL and Priscoline. The addition of Priscoline to the BAL regimen produced immediate alleviation of symptoms in almost all cases (Table 2). Of the 62 children, 5 died during hospitalization and were autopsied. No specific post mortem abnormalities were noted except for bronchopneumonia in 3 cases.

19 of the remaining 57 cases were followed from 4 to 36 years after discharge. The most recent information was gained from correspondence with the patients and private physicians. Development is thought to be normal in 82%. "Nervousness", obviously a subjective complaint, is recorded in 42% and allergy, manifested by asthma or urticaria, in 21% (Table 3).

## DISCUSSION

Most of the cases of acrodynia in the US have been reported from the

**South.** There appears to be a geographical variation in this country as well as elsewhere throughout the world. For example, there are approximately 80-100 cases a year in South Australia which has a population of only 500 000. Some investigators feel that unnecessary use of mercurial compounds may account for the distribution of the disease. Seasonal variation apparently does not occur.

For years the treatment of acrodynia was unsatisfactory. Because acrodynia has a general similarity to vitamin deficiencies, large doses of multi-vitamins including brewer's yeast were used without apparent effect on the course of the disease. In 1948, with the discovery by Warkany and Fanconi of mercury in the urine of patients with acrodynia, great interest was aroused. Warkany was able to demonstrate significant amounts of mercury in the urine of 38 of 41 cases of acrodynia.

Idiosyncrasy to mercury has been proposed as the cause of the disease. Many children appear to ingest and excrete mercury without manifesting acrodynia and it is not known why certain individuals develop an idiosyncrasy. No correlation has been noted between the amount of mercury excreted and the severity of symptoms, though agreement is general that children with acrodynia excrete more mercury than normal children. Cheek believes that mercury may inhibit enzymatic reactions and thus the patient becomes sensitive to the metal.

Adrenal cortical insufficiency under conditions of stress with increased adrenal medullary activity has been suggested as contributory to acrodynia. Cheek, when studying the role of mercury and sympathetic activation in animals, produced hypertension in rats by giving them both calomel (a mercurous chloride preparation used in teething powders) and epinephrine.

He found that more response could be obtained when these were used in combination than when either was given alone, and concluded that mercury potentiates the tissue response to epinephrine. In addition, a distinctive lesion was found in the outer area of the renal medulla, an area thought by some to be important with respect to hypertension in animals.

Another manner in which mercury could potentiate sympathetic activity is by inhibiting sulfhydryl groups and thereby impair the function of methyltransferase which is important in the degradation of epinephrine. Cheek found that the serum, levels of sodium and chloride are depressed in acrodynia and that cellular potassium is also decreased.

The association of acrodynia with mercury by Warkany suggested to Bivings that dimercaptol (BAL) might be helpful in therapy. When a heavy metal reacts with receptor cells in a way to inactivate essential enzymes, it does so by combining with sulfhydryl groups. BAL, being a dithiol, forms a fairly stable complex with heavy metals and in this case mercury is excreted from the body in a dithiol complex.

In 1949, most of Biving's cases showed prompt improvement when treated with BAL. Our 3 cases treated with BAL alone showed a prompt improvement, but as already noted these patients were treated early in the

disease.

Versene, the tetrasodium salt of EDTA, has a stronger affinity for calcium than for other alkaline earths and can be used to abstract calcium from the body. When it has been chelated with calcium outside the body (Ca-EDTA) no calcium abstraction will occur in the body, nor does the compound exchange for alkali metals. It does, however, exchange specifically for yttrium, americium, plutonium, copper, nickel and lead.

In an experimental study, McCoy treated 5 cases of acrodynia with Ca-EDTA and kept 5 patients as controls. There were no significant difference in the course of the disease between the 2 groups, suggesting that Ca-EDTA is not effective in treatment of acrodynia.

Bower in 1954 reported treatment of 9 cases of pink disease with ganglionic blockers. Hexamethonium seemed to abolish sweating, coldness and hypertension. Photophobia seemed to be aggravated, but symptomatic relief occurred in 7 of the 9 cases.

The action of Priscoline is complex. it is related chemically to both the sympathomimetic amines and histamine. Its peripheral effect is one of vasodilatation. In 1954 Peterson reported dramatic symptomatic response to this drug in 7 patients treated with acrodynia at Vanderbilt University. Both peripheral temperature and blood pressure responded significantly after oral Priscoline. These cases also received a course of BAL. It was Peterson's impression that this drug was more effective than BAL in producing early symptomatic relief.

Prompt improvement was seen in approximately 75% of patients treated with the combination of BAL and Priscoline. BAL therapy alone employed by Bivings and at Vanderbilt showed similar results as did those treated with ganglionic blockers. The edathamil treated group showed no improvement. 2 cases treated with Priscoline alone are too few to draw conclusions.

In our series, the overall course of the disease did not seem to be altered by any method of treatment except among those treated with BAL alone (Table 2). The combination of BAL and Priscoline produced prompt improvement in the majority of cases, but the overall course remained essentially unchanged. These observations suggest that initial therapy should be with BAL alone. If this regimen does not bring about prompt improvement it is suggested that Priscoline be added to the therapy.

Autopsies performed on children dying from acrodynia have revealed no consistent changes. None of the 5 postmortem examinations performed here shed light on the nature of the disease. Several pathologists have found changes in the brain, spinal cord, ganglions and peripheral nerves, but these lesions appear to be nonspecific.

Follow up studies of patients with acrodynia are few. In the US especially there is a paucity of case reports with follow up evaluation. Our mortality rate of 8% (5 of 62 cases), 3 dying with bronchopneumonia and 2 of unknown causes, is comparable to a 17% mortality rate (37 of 213 cases) in the English

**study of Holzel and James. Bronchopneumonia accounted for death in 12 of those cases.**

**In our series, normal development was present in 82% of cases with follow-up evaluation. “Nervousness” was recorded in 42% and allergy, manifested by asthma and urticaria occurred in 21%. Findings were similar in the English study of 110 cases. Allergic diathesis and other findings were thought to be within the expected range found in the general population (Table 3). It is noteworthy that children can recover from acrodynia without apparent sequelae.**

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Table1 Clinical Features of  
Acrodynia

Symptom	# of cases
rash	55
irritability	51
itching	41
hypertension	39

sweating/coldness	38
hypotonia	35
photophobia	29
loss of hair	4
autoamputation	2

Table 2 Prompt improvement with therapy

.	%
1 Priscoline alone 2 cases- 1 unimproved	50
2 BAL alone a) 3 cases- 0 unimproved b) 14 cases- 4 unimproved (Bivings 1949)	76
3 BAL with Priscoline 12 cases- 3 unimproved	75
4 Edathamil 5 cases- 5 unimproved (McCoy 1960)	0

Table 3 Long term followup

.	19 cases (Vanderbilt series) %	110 cases Holzel %

1 normal development	82	73
2 nervousness	42	27
3 allergy	21	15
4 skin disorder	16	-
5 urologic symptoms	10	-
6 convulsions	5	-
7 poor dental hygiene	5	-

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**Was Young's syndrome caused by  
exposure  
to mercury in childhood?**

**W F Hendry, R P A'Hern, P J Cole**

**British Medical Journal December 1993**

## Abstract

### Objective-

to determine whether the incidence of chronic sinusitis, bronchitis or bronchiectasis in men with obstructive azoospermia (Young's syndrome) has fallen in men born after 1955 when calomel (mercurous chloride) was removed from teething powders and worm medication in the United Kingdom.

### Design-

A prospective study of etiological factors in subfertile men with epididymal obstruction operated on between 1975 and 1993.

### Setting-

Central London.

### Subjects-

274 men with obstructive azoospermia undergoing epididymovasostomy; date of birth was recorded and illness in childhood, persistent nasal or respiratory symptoms and previous urinary or genital infection were asked about.

**Main outcome measure-**Site of epididymal block and association with possible etiological factors related to date of birth.

**Results-**146 men had hold up in the head of the epididymis (capital blocks): 119 (82%) had Young's syndrome and 11 gave a definite history of pink disease (mercury intoxication) in childhood. 128 had obstruction lower down towards the tail of the epididymis (caudal blocks): 64 (50%) had a history of genital or urinary infection and only 3 had Young's syndrome; none had had pink disease. The incidence of Young's syndrome fell significantly from 114 (50%) of 227 men born up to 1955 to 8 (17%) of 47 men born since then.

**Conclusions-**The decline in incidence of Young's syndrome in those born after 1955 is similar to that observed with pink disease, suggesting that both conditions may have had similar etiology-mercury intoxication.

## Introduction

The presence of chronic sinusitis and bronchitis or bronchiectasis in over half of men with obstructive azoospermia was first described from the north of England by Young in 1970, and further cases were documented shortly thereafter in France. Since then, large series of patients with Young's syndrome have been documented in reports from the United Kingdom, Australia and France, but only sporadic cases have been reported in the United States.

The testicular obstruction in these cases lies in the efferent ductules in the head of the epididymis, whereas in cases occurring after an infection, the block is lower down towards the tail. The efferent ductules are lined by ciliated columnar epithelium similar to that lining the nasal and respiratory passages, whereas the duct of the epididymis is lined by stratified columnar epithelium with microvilli. The association between obstructive azoospermia and chronic nasal and respiratory



disease is therefore likely due to a common defect in the function of the ciliated columnar epithelium, which is found in both sites.

Earlier studies have shown significantly impaired mucociliary clearance in patients with Young's syndrome even though ciliary beat frequency was normal and electron microscopy showed no ultra-structural defects in the cilia. The viscous, creamy yellow fluid seen at operation within distended tubules in the head of the epididymis in patients with Young's syndrome is recognisably different from the runny, milky white fluid found in caudal epididymal blocks occurring after infection.

Histochemical studies using frozen sections showed that this difference was due to abnormal accumulation of lipid within the epithelium and lumen of the efferent ductules in men with Young's syndrome; this was not seen in the other groups.

The history given by the patients with Young's syndrome was nearly always the same: a febrile illness in early childhood, usually associated with a respiratory infection, followed by development of chronic sinusitis with nasal polyps, persistent cough, recurrent bronchitis and in some cases, bronchiectasis. The medical features of the respiratory aspects of Young's syndrome have been documented by Handelsman et al.

In some men with Young's syndrome, a definite history of pink disease in childhood was forthcoming, suggesting a possible etiological connection. Pink disease was caused by mercury intoxication, the mercury being released from normally insoluble calomel (mercurous chloride) in teething powders or worm medication under certain intestinal conditions.

After considerable controversy, products containing calomel were withdrawn from sale in the United Kingdom and Australia in 1955. Pink disease then disappeared (fig 1), apart from a few isolated cases. If Young's syndrome and pink disease shared a common etiology, the syndrome would also be expected to disappear in men born after 1955. To test this hypothesis we related the dates of birth of a large number of subfertile men with obstructive azoospermia to the site of epididymal obstruction, coexisting nasal or respiratory disease, and any past history of pink disease.

### **Patients and methods**

Between 1975 and 1993, 274 azoospermic men presenting to a single consultant urologist underwent epididymovasostomies for epididymal obstruction. The year of birth was recorded, and they were asked about any history of illness in early childhood of chronic or persistent sinusitis, bronchitis or bronchiectasis and previous genital or urinary infection.

After full investigation including physical examination, seminal analysis and measurement of hormone concentrations and antisperm antibodies, they underwent scrotal exploration under general anaesthesia. The site of obstruction in the epididymis was established by visual inspection with magnification, supplemented by a photographic record early in the series.

Patency of the vasa deferentia was tested by vasography and a testicular biopsy was taken. Patients were classified into those with distension, usually symmetrical, strictly confined to the head of the epididymis (capital blocks), and those with distended tubules extending further down the epididymis on one or both sides towards the tail (caudal blocks). These changes have been described in more detail and illustrated elsewhere. Epididymovasostomy was done, and the men were followed whenever possible by seminal analysis repeated at intervals of 3 months and inquiry was made about pregnancy in female partners. All men with capital blocks operated on since 1982 received carbocysteine 275mg 3X daily for 6-12 months.

## Results

Of the 274 men, 122 (45%) had Young's syndrome. This association was seen in 114 (50%) of 227 men born before 1956, but in only 8 (17%) of 47 men born since then. A total of 119 men with Young's syndrome had capital blocks and only 3 had caudal epididymal blocks. This confirms the close associations between chronic nasorespiratory disease and hold up in the efferent ductules in the head of the epididymis.

Among the 146 men with capital blocks, 12 claimed to have fathered children in the past, and progressive deterioration in the sperm count culminating in azoospermia was observed in 4. 33 (23%) had bronchiectasis, and 42 (29%) had persistent sinusitis, leaving 27 (18%) with no such complaints. 11 (8%) gave a definite history of pink disease in infancy (table 1). Only 12 (8%) of the men with capital blocks had had genital or urinary infection.

Among the 128 men with caudal epididymal blocks only 3 gave a history of either bronchiectasis (1), chronic bronchitis (1) or persistent sinusitis (1). None gave a history of genital infection.

Table 2 shows the years of birth of those with Young's syndrome and those with capital and caudal epididymal blocks where they may be compared with the national death rate for infant boys from pink disease in 1950-62. The fall in the incidence of Young's syndrome and capital blocks in those born after 1955 is obvious, resembling the decline in incidence of pink disease. 4 of the 9 men with capital blocks born after 1955 grew up abroad (Kenya 1, South Africa 1, Middle East 1, Sicily 1); if these are discounted, it can fairly be said that only isolated cases have been seen in the United Kingdom since 1955. No such decline in incidence has been seen in those with caudal blocks.

The age distribution of patients at presentation would be expected to be independent of year of presentation if there was no change in etiological factors. Figure 2 shows this independence in patients with caudal blocks and a positive correlation between age and year of presentation in patients with capital blocks. One of the contributing factors to this is that few patients who were born after 1955 presented with epidymal obstruction (fig 3). Men born before 1940 would have been over 35 years old when this study started and less likely to present with fertility problems.

## Discussion

**Warkany, who established the link between mercury and pink disease, commented in a review that there is nothing more dead than a dead disease. The results of this study indicate that the resulting problems may, in fact, live on since there is a relation between pink disease in childhood and Young's syndrome in adult life and, by inference, between both conditions and mercury intoxication.**

Although the toxic effects of mercury are well documented, this long term effect on reproduction has not been described before. Mercury inhibits enzymes containing sulphhydryl by reacting with thiols to form mercaptides. Cilia, like spermatozoa, rely on glycolysis for energy, and impairment of sperm motility has been observed with exposure to mercury.

Other examples of enzyme inhibition have been well documented in spermatozoa and their effects noted in the epididymis. Chemicals such as alpha-chlorhydrin and 6-chloro-6-deoxy glucose, which block glyceraldehyde 3-phosphate dehydrogenase, lead to acute cystic change in the efferent ductules and infertility in animals. The stasis that developed in the ductules in our men with Young's syndrome was much more gradual, since some were previously fertile, and seemed to be due to accumulation of lipid in the ductules. It is not known why this should happen, although it may be noted that patchy hold up in the ductules has commonly been seen at necropsy in old men. Premature change in mitochondrial DNA has been put forward as one possible explanation.

The results of epididymovasostomy were much better in the group with postinfective caudal epididymal blocks (patency 52%, pregnancies 38%) than in those with holdup in the head of the epididymis, 82% of whom had Young's syndrome (patency 12%, pregnancies 3%). Significantly better results were obtained in the latter group in those receiving adjuvant carbocysteine (patency 23%, pregnancy 7%) compared with those who had no adjuvant therapy (patency 2.2%, no pregnancies).

Improvement in nasal and respiratory symptoms was noted subjectively by the men receiving adjuvant carbocysteine. Even with adjuvant therapy, however, the results were much poorer than those obtained in men with postinfective blocks lower in the epididymis, presumably partly because of poor flow characteristics in Young's syndrome. With the decline in incidence of capital blocks, surgeons can look forward to much better results of reconstruction for obstructive azoospermia.

The geographical differences in incidence of Young's syndrome are important. Sale of calomel was discouraged by the FDA in USA in 1933, and remarkably few examples of Young's syndrome have been reported there. On the other hand, as Warkany commented, wherever the British flag flew, calomel was an ingredient of popular medications, probably because it induced sweating and acted as a purgative. Although there were regional differences in incidence, it has been estimated that as many as a quarter of infants in Sheffield and a third in Warwickshire were receiving teething powders containing mercury.

The largest series of Young's syndrome have been reported from the United Kingdom and from Australia, where the incidence of pink disease was highest until the sale of calomel was prohibited.

It should not be expected, however, that Young's syndrome will disappear completely. Teething powders containing mercury were still on sale in the United Kingdom as late as 1966, and isolated reports of pink disease have continued to appear, associated with mercury in such varied sources as vermifuges, ointments, dusting powders, gammaglobulin and fungicides on wheat seeds. Mercury intoxication has also been recorded in dentists and from industrial pollution, house paint and metallic mercury.

Mercury is still on sale in London in 1993 in skin lighteners and is being prescribed in ethnic remedies. Previous studies suggested that there were no long term sequelae of pink disease. This study shows that this is not so and emphasises the vital importance of recognising and eliminating such toxic factors from our environment.

## TABLES and Figures for Young's Syndrome and Pink disease

**TABLE 1**  
**Characteristics of men with a definite history  
of pink disease in childhood.**

Case #	Year of birth	Sperm count (M/ML)	Chest problems	Findings at operation
1	1945	0	bronchiectasis	right capital block, left fibrosis
2	1951	0	bronchiectasis	bilateral capital blocks

3	1953	0	bronchiectasis	bilateral capital blocks
4	1947	0	bronchitis	bilateral capital blocks
5	1949	0	bronchitis	left capital block, right atrophic
6	1952	0	brochitis	bilateral capital blocks
7	1953	0	sinusitis	bilateral capital blocks
8	1946	0	none	left capital block, right atrophic
9	1948	0	none	bilateral capital blocks
10	1950	0	none	bilateral capital blocks
11	1952	0	none	bilateral capital blocks

**TABLE 2**  
**Year of birth of men with Young's syndrome,**  
**capital and caudal epididynal block.**

Year of birth	# with caudal blocks	# with capital blocks	# with Young's syndrome	Death rate from pink disease
1938	7	9	6	-
1939	2	1	1	-
1940	4	0	0	-
1941	1	2	2	-
1942	3	4	3	-

1943	6	4	3	-
1944	5	5	4	-
1945	3	7	6	-
1946	3	7	6	-
1947	5	17	14	-
1948	3	10	7	-
1949	4	10	7	-
1950	6	13	12	34
1951	5	13	11	34
1952	6	17	15	15
1953	7	7	8	19
1954	8	4	3	8
1955	12	7	6	4
1956	4	0	0	3
1957	6	3	2	2
1958	7	2	1	0
1959	3	1	1	1
1960	4	1	0	1
1961	4	0	1	-
1962	1	0	0	-
1963	4	0	1	-

1964	5	2	2	-
total	116	140	116	-

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**We thank Dr Chris Ford, scientist at the fertility unit, St Michael's Hospital, Bristol, for help with understanding the biochemical aspects of these cases.**

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