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PINK DISEASE*

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Pink disease has been known to man for less than half a century, and physicians of many lands have striven to solve the mystery of its causation and cure. So far but little light has been shed on the obscurity of this distressing malady.

The name "pink disease" has been adopted for this paper as it is non-committal so far as the cause of the malady is concerned, and, connoting as it does one outstanding feature, the pink rash, it is easily understood, and thereby leads to the diagnosis of many cases that might otherwise pass undetected. Also this name has been adopted by common consent throughout the British Empire. In America the disease is known as "infantile acrodynia."

Historical

Rocaz[1] of Bordeaux has recently drawn attention to an excellent description of pink disease by Selter[2] of Solingen, the Ruhr, which was published as far back as 1903. At a congress in Cassel this German physician related his observations on a new disease, the report of the congress appearing as follows:

Herr Selter (Solingen) reported eight cases of an illness for which he found no analogy in literature and which he termed "trophodermatoneurosis." The malady occurred in girls of 1½ to 3½ years. It was of gradual onset, and manifested itself in loss of interest, nervousness, and progressive loss of speech. Other features were delirium in sleep, mental disturbances (hallucinations, coprophagy), and profuse sweating with its consequences (sudamina, eczema, and sodden skin). The hands and feet were swollen, reddened, and cold. The patients had a constant sense of coldness and itchiness, and there was a loss of hair (mostly temporal) sometimes amounting to complete baldness. As clearly secondary phenomena, paronychia and boils appeared. The internal organs showed no abnormalities. The illness ended favourably in all cases in weeks or months.

This must undoubtedly be accepted as the first authentic description of pink disease. Unfortunately no one present recognized the condition, and so this important communication remained hidden in the obscurity of a medical journal until Swift[3] of Adelaide restated the syndrome, which he called "erythroedema." Swift's contribution was read at Auckland, New Zealand, in 1914, and was based on the study of fourteen cases. One of us (A. J. W.), a former student of William Snowball, was present, and in conjunction with Hobill Cole an immediate start was made to collect cases in Melbourne, Victoria. By the time the next Australasian Medical Congress met at Brisbane, in 1920, it was possible to review the signs, symptoms, prognosis, and treatment of ninety-one cases.[4] About 150 cases have now been personally studied in private practice by one of us (A. J. W.), and these form the basis for discussion in this paper. The biochemical changes in pink disease are not included, but will be reported later. As far as Australia is concerned this is not a new disease, for during the past fifty years it has been recognized by medical men specializing in diseases of children in Melbourne and Sydney. In 1883 William Snowball of Melbourne pointed out to his students a child with what he described as "raw beef hands and feet." He thought that this condition followed an attack of gastro-enteritis, and after a prolonged course recovery took place.

At about the same time Charles Clubbe of Sydney also recognized the malady, and called it "pink disease," from the sudaminal rash that was usually present. When asked whether he had invented the name he wrote: "I have always called these cases 'pink disease,' but I do not know if I originated the name."

Being certain that cases of pink disease existed before 1914, when Swift's paper was read, a search was recently made through the records of private cases belonging to one of us (A. J. W.). Three typical cases were quickly found between 1898 and 1901, and the first one is summarized here as being one of the earliest Australian case records of the disease:

K. B., a female aged 12 months, was first seen on September 21st, 1898. She had been ill for seven weeks, and a diagnosis of influenza made. Her gums had been lanced. She was sweating freely and was weak, being unable to sit up properly. Two months previously she had been able to walk. She was irritable about the body and legs, and the buttocks were ulcerated. Her toes were red and "beefy-looking," with vesicles on the soles of the feet, which had been scratched. She was treated with a mercurial binder and eventually recovered.

Swift, in a personal communication, says that he saw cases of pink disease when he was a house-physician at Great Ormond Street Children's Hospital, London, in 1885. In 1914 when again in London he discussed the disease with Still and Garrod, who both agreed that they recognized the syndrome, but could not help with regard to the causation or pathology. They both confessed that they knew of no literature on the subject.

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

Aetiology and Pathology

Pink disease attacks males and females in practically equal numbers, and does not occur in definite epidemics. One of the features of the disease is that it occurs in young children, the majority being between 9 and 18 months of age (Fig. 1). We have seen over 200 cases in Australia, and they have all been under 4 years of age. This makes us wonder if the affection does occur here in older children, as reported in other countries, especially in France.[1]

It is of great interest to consider the site, nature, and causation of the pathological changes which occur in pink disease. In recent years the attention of many authorities has been focused upon the nervous system. Blackfan and McKhann[5] have discussed the role played by the various parts of this system, and have shown how many of the signs and symptoms of pink disease could be produced by its disordered function. They have again stressed the importance of the sympathetic system, as was originally suggested by Feer in his early work on the disease. The post-mortem results, which have recently been reviewed by Cobb,[6] show that although there may be microscopical changes in practically any portion of the central nervous system, these findings are variable, and usually of a minor degree. Briefly, it may be stated that on various occasions the following changes have been noted: round-cell infiltration, demyelinization, cellular degeneration, and oedema in the spinal cord, and degenerative changes with demyelinization in the peripheral nerves. Wolf, Paterson, and Davison[7] have made interesting observations on the brain, showing changes in the cerebrum and cerebellum. These writers state that many of these changes could be produced by starvation and exhaustion alone. This hypothesis was further borne out by animal experiments.

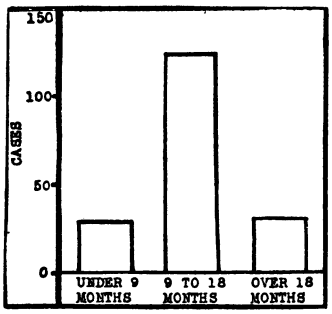

FIG. 1.—The age incidence of pink disease (192 cases).

In reviewing the post-mortem findings in his three cases, Blackfan also concluded that the microscopical changes in the central nervous system were no more extensive than could be accounted for by the terminal infections from which the patients died. It seems that the pathology of pink disease is the pathology of its complications.

It is of importance to realize that prior to death all the organs, including the various components of the nervous system, have usually been subjected to the toxins liberated from three sources: first the toxin of pink disease *per se*, secondly the various coccal infections of the skin, mouth, etc., and thirdly the superadded disease which usually terminates life, such as pneumonia or gastro-enteritis. To these toxic products the harmful effects of prolonged under-nutrition must be added.

As nearly every organ in the body is controlled either directly or indirectly by the central nervous system, and especially by the sympathetic system, it is a simple matter to postulate that the primary lesion lies in that situation. It should be remembered, however, that no matter where a toxin may originate in the body, it will inevitably gain access to the blood stream and so bathe every organ. Thus if there is a widespread upset in bodily function, as seen in pink disease, it is just as rational to conclude that the organs themselves have been attacked by some toxin, and that the influence of a deranged sympathetic system plays but a minor part. The organs have a common blood supply as well as a common nerve supply. At present we prefer to maintain an open mind as to the site of attack of the noxious influence, and would rather visualize it as a toxin which is diffusely distributed throughout the body, rather than acting entirely through the medium of the nervous system.

Theory of Causation

The cause of pink disease is not known. There are many theories, however, and some of the more interesting ones have been selected for discussion.

Vitamin Deficiency.—The post-mortem changes in the nervous system are often in keeping with this theory, and the disease tends to occur at an age when vitamin deficiency is most common. On the other hand, pink disease may develop in a child who is receiving a liberal supply of the known vitamins, and also large amounts of these vitamins do not produce the cure, although they assist in maintaining bodily health. Moreover, compared with other lands, pink disease is relatively common in Australia, yet the standard of living here is high and vitamin deficiency is rare.

Light Hypersensitivity.—Braithwaite[8] considers that pink disease may be due to an abnormal reaction to daylight following on a recent infection, and this might explain the prevalence of pink disease in Australia. Improvement is claimed by keeping the children in a light from which the rays from the violet end of the spectrum have been filtered by means of ruby glass. We do not subscribe to this theory for several reasons. We consider that children who are nursed in the open air do not run a prolonged course. They usually tend to recover more rapidly and are less prone to secondary infection than the children who are nursed indoors. Even more convincing is the fact that graded sun baths with tanning of the skin have been most beneficial in a number of cases. In no case did the rays of the sun appear to be definitely detrimental to the course of the disease, although it must

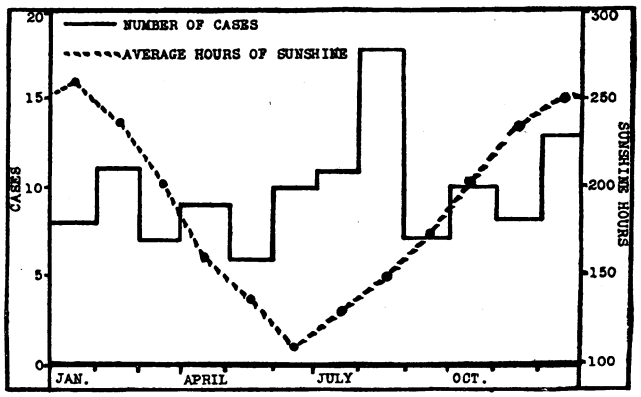

FIG. 2.—An increase in the average hours of sunshine does not produce more cases of pink disease (analysis of 116 cases).

be admitted that several children were rendered most uncomfortable by exposure to the sun. Finally an analysis of 116 cases failed to show that the greatest number occurred at the time of the year when the hours of sunshine were at a maximum (Fig. 2).

Infection.—An attempt was made in Victoria by Penfold, Butler, and one of us (I. J. W.)[9] to determine an infective factor in the aetiology of pink disease by a study of blood cultures, but it was felt that the results obtained were not conclusive. Although world-wide efforts have been made to prove an infection as being the cause of the disease, the results have been negative except in a few isolated and unconfirmed experiments. Moreover, the histological changes in the organs do not

as a rule indicate bacterial invasion, except where there has been a definite superadded infection.

A great deal of indirect evidence is available, however, which suggests either a passing bacterial invasion leaving a trail of chronically disordered body function, or else a prolonged mild infection which has evoked but little reaction. Many writers have stated that the onset of the disease is significant. In the present series 116 cases were studied with reference to this, and 24 per cent. were found to have had a febrile attack at the onset. The temperature rose to 100° or 102° F., and was usually accompanied by upper respiratory infections. Further, during the course of pink disease, the rectal temperature often shows slight elevations to 100° F. in the absence of secondary infection.

The history of direct contact as a possible cause of transmission has been recorded on several occasions. In the present series 140 cases were especially investigated from this standpoint, and four families were found where a second child was attacked by the disease, but only after the long intervals of fifteen months, three years, four years, and six years respectively. On another occasion a child who was taken to visit a baby with pink disease contracted the malady one month later. These figures may be of some significance, as pink disease is uncommon in Victoria when compared with other maladies.

The age incidence of the disease is in keeping with the infectious theory when an analogy is drawn to diseases such as measles and diphtheria, where towards the end of the first year and during the second year of life the immunity conferred *in utero* is lost. Adults do not contract pink disease, so it is rational to suggest that the mother possesses immunity and conveys it to the developing foetus. When the baby nears the end of the first year of life this immunity wanes and he becomes susceptible.

The infecting organism may be a virus which is widely spread throughout the community in a non-pathogenic state. These carriers would perhaps react slightly to the virus from time to time, and thus immune bodies would be produced. On rare occasions the organism would assume a pathogenic role in a highly susceptible individual, usually a child aged between 8 and 18 months, and an attack of pink disease would result. This theory would explain the infrequency of transmission by direct contact, and also the occurrence of sporadic cases in isolated parts of Australia.

Symptomatology

When discussing the symptomatology of a disease it is satisfactory to be able to correlate the clinical findings with the pathology of the condition. Unfortunately with pink disease this attempt is immediately doomed to failure, for the causation and the pathology still remain practically a closed book. As many excellent discussions of the disease are available in literature it will suffice to discuss but a few points of special interest.

In reviewing the case histories recorded by one of us (A. J. W.) during the past twenty years we have made a study of the onset, course, and duration of pink disease. Formerly various symptoms have been unduly stressed, and this has resulted in many cases being misdiagnosed during the early stages of the malady. This especially applies to the presence of the pink coloration of the hands and feet. An analysis of fifty-seven consecutive cases showed that the average time for the appearance of this symptom was the fifth week of the disease. Although it occurred in the initial stage in twelve of the cases, it is interesting to note that in five cases it did not appear until the third month. Several authentic cases have been recorded where the pinkness has not appeared at any stage.[1]

Three Clinical Phases

The symptoms of pink disease could well be divided into three stages, the first two each lasting one month and the third much longer.

First Stage.—During the first few days there may possibly be an acute phase consisting of coryza, a temperature varying from 100° to 102°, and general malaise. During the rest of the month the patient becomes irritable and sleep is greatly disturbed. The entire mental make-up of the child is distorted. He becomes petulant, vicious, and extremely miserable, as is illustrated by the following case records:

N. C., a female aged 15 months, was seen on October 1st, 1921. For the past two months she had been developing the classical signs of pink disease with red, swollen, and icy-cold hands and feet, anorexia, loss of weight, and intense pruritus. The mother stated that for the past six weeks she had been up practically the whole night trying to pacify the child, who rarely slept for more than two hours. She also stated that if her child had been an adult, she would have been considered to be insane, sitting up in her cot, banging her head with her hands, tearing out her hair, screaming, and viciously scratching anyone who came near.

The appetite soon begins to wane, the weight falls, and there is great muscular weakness. This loss of power is a constant early finding, and deeply impresses the parents when their children are old enough to walk. During the infantile paralysis epidemic in Victoria in 1930 several cases of pink disease were sent to the Children's Hospital erroneously diagnosed as infantile paralysis on account of this muscular weakness. Towards the end of the first month the sudaminal rash may appear on the trunk, and is most prominent during the bouts of profuse sweating which so commonly occur. The miserable child begins to turn from the light and assumes the characteristic attitudes which are caused by the hypotonia, photophobia, and itchiness of the face, arms, and legs. The intense itching of the skin has actually been described by some of the older patients,[1] and when the younger children are closely observed the great distress produced by this symptom can be fully appreciated. They slowly twist and turn, rubbing and scratching the offending parts either with their hands or against the sides of the cot.

Second Stage.—During the second stage, which also lasts about one month, the various changes become fully established, and the child develops the classical picture of pink disease. The hands and feet are swollen, and either pink or slightly cyanosed, depending on the surrounding temperature. They feel icy cold, and the circulation is poor, for if the superficial capillaries are emptied by pressure on the skin the refilling is slow when the pressure is released. The vesicles which appear in the skin of the hands and feet break and then desquamate. Here staphylococcal infections frequently appear. Photophobia without apparent conjunctivitis, a rapid pulse and often a raised blood pressure, a running nose and excess salivation, severe bouts of sweating, a sudaminal rash on the trunk, marked muscular weakness and hypotonia, trophic changes and secondary infections, especially in the skin and mouth, and invariably a change in the mental attitude complete the distressing syndrome. Perhaps it is only now that the pinkness of the hands and feet appears for the first time and the correct diagnosis is made.

Third Stage.—This stage of gradual recovery begins in the third month and lasts for several months. There is a natural tendency for the great majority of cases of pink disease to improve in the third month, irrespective of the type of treatment. An analysis of sixty-two consecutive cases showed that the average duration before improvement set in was twelve weeks. This was prolonged by any severe secondary infection, notably stomatitis,

bronchopneumonia, gastro-enteritis, and skin infections. The first indications of improvement are usually an increase in appetite and sleep, and the weight no longer falls. The child becomes tolerant and peaceful instead of being miserable and antagonistic. He gradually regains his power and takes an interest in his surroundings. He may even smile. It is many weeks, however, before he is finally restored to normal health. An analysis of twenty-one consecutive cases showed that the average time which elapsed between the onset and complete recovery was seven months. The longest duration was eighteen months. The hypotonia is the last symptom to disappear, and we know of no children who have suffered from any sequelae.

Treatment

Specific.—Until the cause of pink disease is found it will be difficult to obtain a specific remedy. Before such a cure can be accepted it will have to ensure that the duration of pink disease must be consistently reduced to six weeks or less instead of the usual twelve or more weeks. Pink disease shows a natural tendency to improve during the third month, and yet this improvement is constantly being claimed as being due to some new form of treatment. It appears that up to the present no successful specific method of treatment has been fully established.

Symptomatic.—Although the course of pink disease cannot be greatly altered it is possible to lessen the discomfort of the sufferers, and to alleviate the mental and physical stress which falls to the lot of parents. In addition, the incidence of secondary infection can be reduced considerably. Treatment in the open air is of the greatest value, and if possible the children should sleep on open balconies. Most patients will be aided if their skins are well tanned by graded sun baths. If it is necessary to send cases of pink disease to a hospital it is wise to see that there is accommodation for them on the balconies and in the gardens, as they do not do so well in the wards with other ill children. Next to treatment in the open air emphasis should be laid upon the comfort gained by seeing that the body is lightly clad both by day and by night. This may best be shown by the following case:

R. L., male aged 18 months, was seen on October 12th, 1934. He was well up to four weeks before consultation, when he began to lie about with his face downwards and did not want to eat. His sleep had been very broken for three weeks and he had lost weight. At the same time he ceased to walk and his muscles became very soft. He sweated at intervals during the day and pulled out his hair in handfuls. He cried constantly day and night. The hands had been red and swollen for the past fourteen days, and a red rash was present on the trunk. When brought to the consulting room he was crying and throwing himself about, apparently as if he could not get comfortable. His pitiful wailing and look of distress lasted without intermission for twenty minutes. The child was wearing a knitted woollen pullover, a silk shirt, and a woollen Jaeger undershirt, a napkin, silk pants, and a pair of socks. For examination he was stripped, and lying naked he immediately went to sleep, and all through the examination slept peacefully. He was then dressed to go home in the silk shirt and the napkin. The shirt had short sleeves so that his neck, arms, and legs were bare, and thus covered he continued to sleep all the way home. Later, when he was thoroughly convalescent, his father stated that the least possible clothing had afforded the greatest relief. The child wore only a silk singlet and napkin except when the weather was very cold, when he wore a loose woollen garment in addition.

Clothing.—A sleeveless mercerized cotton singlet and napkin were all the clothes others wore all through their illness. Silk next to the skin is infinitely more comfortable than wool, especially when the skin is sweating freely. It has been shown experimentally that silk has a greater absorbing power than wool.[10] Cotton is next in preference to silk. Cases of pink disease are also more comfortable at night when lightly clad. Hospital nurses state that these children resent being tucked into bed at night, and immediately commence to crawl slowly out on top of the bed coverings. No matter how often the night nurse repeats the tucking-in process, out they crawl.

Local Applications.—The next factor in the child's comfort is a tepid bath given night and morning, and after careful drying with a soft sterile towel the skin of the whole body is gently rubbed with methylated spirit. This is followed by a liberal dusting with a talc or zinc and starch powder. If any irritation is present about the fingers and toes, painting them with equal parts of tincture of iodine and methylated spirit after the bath will prevent onychia. After these baths the patients are comfortable, and usually obtain two or three hours of sleep. The methylated spirit application undoubtedly keeps the moist perspiring skin free from coccal infections, and since adopting this treatment the ulceration of the buttocks, multiple pustules about the trunk and limbs, and loss of nails have been rarely seen. These are very serious complications, even causing death in some cases. Infections of the mouth are also very serious, so careful attention to the fingers, which are frequently in the child's mouth, is an essential point in the treatment. The mouth can be kept fairly sterile by letting the child chew on a swab of cotton-wool fastened in sterile gauze moistened with peroxide of hydrogen one part to four of water. The children seem to enjoy chewing this swab, which is controlled by a silk thread. It certainly does seem to lessen the incidence of stomatitis with loss of teeth, and helps to heal the ulcers that so commonly appear in the course of the disease. Chromic acid solution 1 per cent. may be used for obstinate ulcers. The irritable hands are best left exposed to the air, as any attempt to keep them warm seems to increase the discomfort. Wiping with spirit and fanning them makes them comfortable, and occasionally older children seek relief by immersing them in cold water. Gentle stroking or rubbing the hands and feet also seems to soothe the child.

General Care.—Nursing these children in the mother's arms only increases the heat of the body, so that the perambulator or cot is the best place for them to lie. They also seem to sleep better when the perambulator is being wheeled, so taking them for walks seems to be beneficial. During the first six weeks children with pink disease are ill and do not want to be amused. Parents should be warned not to allow the other children of the family to worry them, or encourage visitors to come and "cheer them up."

Diet.—Owing to the thirst that is such a prominent feature, milk will usually be taken in fairly liberal quantities. Under ideal conditions for preservation and sterility, cold unboiled cow's milk may be given with advantage. Otherwise one of the common modifications of milk may be used and vitamins added in generous quantities. Cocoa is appreciated by older children, and raw eggs may be mixed with the milk. Raw liver and meat juices have been highly recommended, and have been advocated as a possible specific cure,[11] [12] but apart from their high nutritive contents, which include protein, vitamins, and iron, we do not consider that they have any specific value. Children under 2 years of age show a great dislike for the solid foods which they have previously taken well, so every effort should be made to maintain a well-balanced diet by the addition of eggs and broths to the milk diet. Some children seem to enjoy raw vegetables, such as lettuce, and also raw fruits of all kinds, and

these may be given with advantage. The following letter from the parent of a child aged 18 months is instructive:

"A. lived on raw fruits, showing a marked preference for this kind of food. Lettuce leaves played a large part in his diet. Milk was given unboiled and cold, and he drank a quart daily. His appetite was poor at all times, but he would always eat raw fruit, and never objected to a drink of milk. The demand for repeated drinks was noticeable throughout his illness."

When the mouth is ulcerated cold foods will prove to be less painful than hot. A change from the city surroundings to the mountains or seaside is of the greatest benefit when the children begin to sleep better and their appetite improves. It should be emphasized, however, that during the worst months of the illness the parents are well advised to keep their children away from strangers and strange places. The resources of a nurse trained in the care of ill children are of great help if the anorexia is extreme. In some cases it may even be necessary to resort to tube feeding.

Drugs.—For insomnia occasionally a mixture containing bromides and chloral hydrate has been of help, but hypnotics are usually disappointing.

Prognosis

Under ideal conditions the mortality is low, most patients being restored to perfect health. Relapses are rare once the child begins to eat and sleep well and put on weight. Sequelae are unknown, and one attack apparently affords a permanent immunity. The complications that may appear during the prolonged course of this disease comprise the chief danger to life, although on rare occasions sudden death may unexpectedly occur in the absence of any obvious superadded condition. When the patients are treated in hospital wards cross infections such as bronchopneumonia and gastro-enteritis are especially liable to occur, in spite of careful nursing. Fig. 3 shows the grave danger to life which is incurred by admitting cases of pink disease to a public hospital, where the nursing is excellent but the risk of cross infection is always present. The treatment in both groups was practically uniform, but it must be admitted that the hospital group would naturally contain a higher percentage of severe cases. However, we consider that by diminishing the secondary infections of the skin and mouth, removing all possible sources of cross infection, and giving a well-balanced diet and plenty of fresh air the mortality rate of pink disease should be less than 5 per cent.

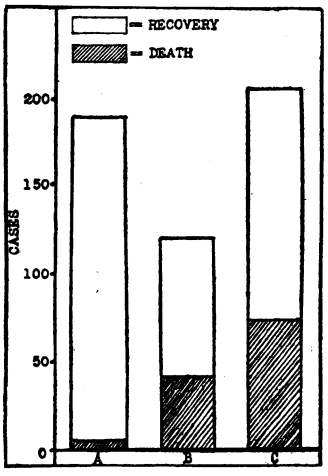

FIG. 3.—When cases of pink disease are treated in their own homes (A) the mortality is low (3 per cent.) compared with the results of hospital treatment both in Melbourne (B) (mortality 30 per cent.) and in Sydney (C) (mortality 29 per cent.).

The length of the illness should be impressed upon the parent when the case is first diagnosed, otherwise the patient will pass from one medical attendant to another. After three or four months the child will be finally "cured" by some form of treatment which, if used at the beginning of the illness, would have failed to shorten the attack.

Summary

1. The early work on pink disease is described, and honour is paid to Selter.

2. The aetiology and pathology is discussed, with special reference to the part played by infection.

3. The symptomatology is described and the natural course of the disease is emphasized.

4. It is considered that no specific method of treatment has yet been established, but great benefit is obtained by attention to the details of symptomatic treatment.

5. The great danger of cross infection is stressed.

Our thanks are due to Dr. Reginald Webster, pathologist at the Children's Hospital, Melbourne, for his constructive criticism of this paper.

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PREVENTION AND PROGNOSIS OF THE LATE TOXAEMIAS OF PREGNANCY*

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Definitions and Preliminary Observations

The "late" toxaemic manifestations exclude those arising before the twenty-eighth week, thus partially overcoming the difficulty of differentiating them from cases of chronic nephritis complicating pregnancy, in the large majority of which symptoms will have arisen earlier. It is not, however, so simple a matter to lay down what is or is not implied under the designation of the "toxaemias of pregnancy," as they form a group of disorders whose right to such a title, though justified on pathological grounds, has never been proved by the discovery of any definite toxin or toxins. Hence dependence for a definition of the conditions under consideration must be placed on their clinical features, of which a true albuminuria and raised blood pressure are the most consistently present. Associated therewith are others, such as oedema, headache, vomiting, insomnia, cramps, polyneuritis, jaundice, and ante-partum bleeding, in varying degrees of prominence and frequency. No useful purpose will be served by trying to do more than offer a syndrome of this kind for a well-recognized group of disorders, but the need for a period of observation before cases can be definitely placed in this category must be stressed. Albuminuria, for instance, even of proved renal origin, may mean much or little, and sometimes is late in appearance or even absent. I accept F. J. Browne's[1] conclusion, based on an analysis of 320 cases of so-called "pre-eclampsia," that the cause, whatever it may be, is capable of producing directly any one of the signs or symptoms ascribed to the condition.

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