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SOME TYPICAL DATA FROM CASES OF PINK DISEASE*

BY

Sir C. STANTON HICKS, Kt., M.D., M.Sc., Ph.D., F.R.I.C.

Professor of Human Physiology and Pharmacology, University of Adelaide

It is almost a century since Thomas Addison penned the following words of introduction to his immortal treatise *On the Constitutional and Local Effects of Disease of the Suprarenal Capsules*:

"If Pathology be to disease what Physiology is to health, it appears reasonable to conclude, that in any given structure or organ, the laws of the former will be as fixed and significant as those of the latter; and that the peculiar characters of any structure or organ may be as certainly recognized in the phenomena of disease as in the phenomena of health. When investigating the pathology of the lungs, I was led, by the results of inflammation affecting the lung tissues, to infer, contrary to general belief, that the lining of the air cells was not identical and continuous with that of the bronchi; and microscopic investigation has since demonstrated in a very striking manner the correctness of that inference—an inference, be it observed, drawn entirely from the indications furnished by pathology. Although pathology therefore, as a branch of medical science, is necessarily founded on physiology, questions may nevertheless arise regarding the true character of a structure or organ, to which occasionally the pathologist may be able to return a more satisfactory and decisive reply than the physiologist—these two branches of medical knowledge being thus found mutually to advance and illustrate each other. Indeed as regards the functions of individual organs, the mutual aids of these two branches of knowledge, are probably much more nearly balanced than many may be disposed to admit; for in estimating them, we are apt to forget how large an amount of our present physiological knowledge, respecting the functions of these organs, has been the immediate result of casual observations made on the effects of disease. Most of the important organs of the body, however, are so amenable to direct observation and experiment, that in respect to them the modern physiologist may fairly lay claim to a large preponderance of importance, not only in establishing the solid foundation, but in raising and greatly strengthening the superstructure of rational pathology. There are still, however, certain organs of the body, the actual functions and influence of which have hitherto entirely eluded the researches and bid defiance to the united efforts of both physiologist and pathologist. Of these not the least remarkable are the 'Supra Renal Capsules,' the atra-biliary capsules of Caspar Bartholinus; and it is as a first and feeble step towards an inquiry into the functions and influence of

these organs, suggested by Pathology, that I now put forth the following pages."

His words apply with equal force to-day, and it is hoped that the observations which are the occasion for this address will provide an example not only to illustrate the interdependence of physiology and pathology but also to show that young medical graduates should not feel intimidated by the imposing façade of laboratory science.

It was care of the patient, which is, after all, the objective of medical study, that led in the present instance to that combination of pathology and physiology which, as it happened, culminated in a successful clinical result.

In 1914, H. F. Swift, of Adelaide, speaking as the result of much clinical experience of the disease, proposed the name of erythroedema. Later it was suggested that a more non-committal term, such as "the pink disease," might be more conducive to research into its true nature and aetiology than the 30 different names under which it was described in the literature. In 1921 he read a paper on 14 cases seen in his own practice in the previous two years. From this it will be apparent that this elsewhere relatively uncommon disease has local conditions favourable to its development. Southby's (1949) very complete study indicates that Australian physicians see not only more cases but also more often see severe cases than is the experience of European paediatricians.

An ex-student of mine, Dr. Donald Cheek, during his year as resident medical officer at the Adelaide Children's Hospital, became sufficiently interested in the disease to search the hospital records, with the result that in 1949 he was able to report that during the preceding 10 years 136 cases had been treated. Of those remaining as in-patients, 18 had died; 9 of these deaths had been attributed to bronchopneumonia, and dangers from cross-infection had been made the basis of a policy advocating domiciliary care wherever possible.

Dissatisfied with existing theories of aetiology, and with accepted therapeutic measures, the main feature of which consisted in continued administration of powerful sedatives, he decided to study the condition more closely. The causative role of cobalt deficiency in the

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disease known as "sway-back" in sheep was discovered in Adelaide, and the dietary importance of trace elements and their regional deficiency in soils led Cheek to think of an analogous aetiological cause for pink disease.

He was given permission by the honorary staff of the Children's Hospital to investigate the possibility of a mineral deficiency in cases of pink disease, and he obtained the co-operation of the spectroscopist of the Commonwealth Division of Soils in the conduct of this troublesome research.

Cheek and Stace (1950) published the results obtained in a study of 16 normal infants and 16 infants suffering from the disease, the only significant finding being a consistently subnormal plasma sodium in the latter instance.

Disappointed with this superficially unimpressive outcome of the research, which nevertheless contained the clue to a solution of the problem, Cheek decided to study the condition from the standpoint of a functional overactivity of the adrenal medulla, evidence for which seemed to be presented by increased pulse rate, raised diastolic blood pressure, initial pyrexia, and the characteristic sweating. The work of Selye also had caused him to think in terms of the stress syndrome. Advice and assistance to this end were sought of the Department of Physiology, where, by chance, many years had been devoted to studies in water metabolism. The description of severe non-pitting oedema in a fatal case therefore led me to think in terms of a movement of water from plasma to tissue cells, and an explanation of signs and symptoms in terms of water and ionic imbalance.

Treatment of Pink Disease with Salt

For at least 50 years both polycythaemia and leucocytosis had been reported as a consistent feature of this disease, and I therefore advised careful haematocrit and haemoglobin estimations, to test the possible existence of haemoconcentration. Haemoconcentration being found, treatment was directed to restoration of extracellular water and sodium, using daily oral administration of 8 g. of common salt alone in milder cases, and in more severe cases the intramuscular injection of deoxycortone acetate on alternate days in doses of 3 mg. In extremely severe cases, which experience had shown were likely to develop vascular "shock," intravenous administration of normal saline and plasma, together with injections of the corticosteroid, was found to be dramatically effective.

A successful appeal was made to the medical profession to provide cases for investigation. Extended study of these cases soon disclosed the fact that response to this treatment was uniformly good and rapid.

To those who carried the burden of nursing these troublesome cases the therapeutic results came as a great relief, and we were soon faced with the ethical question, Should we investigate in greater detail the scientific aspects of the disease, or should we inform the profession of a certain means of alleviating suffering and, in severe cases, of preventing death? We decided on the former course.

Acting on the assumption that the facts could be reasonably explained in terms of hypofunction of the suprarenal cortex, a search of the paediatric literature was made, with the result that pink disease seems quite naturally to fit into place in a jigsaw puzzle of which already many of the essential pieces had been discovered by other investigators in many lands.

Clinical Features of Pink Disease

Before developing the major topic, it may be advisable briefly to recapitulate the clinical features of pink disease, which have for so long evaded elucidation.

As Craig, of Liverpool, has expressed it, "the appearance of the child is one of abject misery." It flies into tantrums when disturbed but is otherwise quite apathetic. Food has no interest for it; photophobia can be intense, but may be absent. When it is present the child burrows face down into the pillow. Scratching, rubbing, and hand-chewing all indicate disturbed reflex responses; and, because the child is so often weak and muscular hypotonia is constant, it wriggles and writhes incessantly. Exhaustion is the only cause of fitful sleep. Otherwise insomnia is a very trying feature of the condition. The colour which has given rise to the name pink disease is best seen in the hands and feet, which are cold to the touch in most cases. It is noteworthy that the colour is cyanotic when the skin is cold. It is more truly pink when the skin is warm to the touch. There may be non-pitting oedema of the extremities, and the skin is then taut and shiny and may desquamate. The clinical term applied to this appearance makes homely reference to "raw beef" or "washerwoman's hands."

Older children are able to describe the sensory changes in the skin. They feel warm water as hot or scalding. They describe numbness and tingling. Another striking manifestation is excessive sweating, especially noticeable about the head. Sudaminal rash is thus an additional cause of misery to the patient. Craig draws attention to the curious contrast seen in some cases in which the swollen hands and feet have a sodden appearance, oddly contrasting with the dry skin covering the emaciated trunk. Hypotonia is commonly extreme. The flabby muscles feel as if shrunken and jelly-like, and tendon reflexes are weak or absent. Tachycardia and raised diastolic pressure are constant features, and raised temperature may be seen only at the outset, accompanied as it usually is by a "running nose," which may persist throughout the course of the condition. The accompanying leucocytosis has led to search for an infectious cause. The associated polycythaemia has been recorded, but owing to the unconscious prejudice in favour of a bacterial leucocytosis its significance has been overlooked.

In South Australia the course of the disease lasts on the average three to four months, and is more commonly followed by many months of subnormal health. In the absence of known aetiology, therapeutic measures have been directed to maintaining adequate nourishment and to sedation, mainly by chloral hydrate. But, as already indicated, fear of the consequences of infection in the upper respiratory or alimentary tract has been the guiding factor in advice to parents.

Infection and Mercury Poisoning

There are two aetiological theories which must be mentioned. The infection theory has had its basis in the leucocytosis, which is explicable in terms of haemoconcentration, and in the fact that the onset may be marked by pyrexia. A recent study of the good therapeutic effect of tonsillectomy in this disease led to its advocacy in terms of removal of a source of infection. In my opinion this work may well disclose a non-specific positive response of the suprarenal cortex.

The role of infection as an initiating disturbance cannot, however, be entirely overlooked. There is often a history of illness from which the mother dates the decline in health. In the case of older children who fail to thrive, this illness may be more clearly remembered as the starting-point. Demand on cortical function in excess of capacity to comply may, in certain circumstances of post-natal involution, be the starting-point either in terms of Selye's (1949) general theory of adrenal cortical function, or more specifically in terms of oxygen utilization by the tissues (Hess, 1921; Scott, 1922; Messerle, 1926; Sasaki, 1930; Goldzieher, 1934).

The mercury-poisoning theory, supported in this country by Warkany and Hubbard (1948) and in Switzerland by Canconi, is based upon the finding of mercury (from soothing powders) in the urine of these patients. Here again we may be dealing with a depression of function of the suprarenal cortical cells by chronic mercurial poisoning. A closer consideration of the anatomical and functional condition of this organ in the circumstances is therefore indicated.

Suprarenal Cortex in Infancy

As early as 1908 Husnot had drawn attention to the fact that the cortex of the human suprarenal gland is not fully developed until approximately the eighth year. In 1911 three independent groups of workers in this field reported a remarkable haemorrhagic involution of the cortical tissue beginning immediately after birth. Thomas was the first to report the complete degeneration of the inner zone by the end of the first 12 months. He thought that the destruction was to make room for the growing medulla. Elliott and Armour noted the important fact that the foetal suprarenal owed its relatively large size to the presence of a very vascular inner zone of cells lacking the characteristic doubly refracting granules of the adult cell. They found that the involutionary change involved special foetal cortical tissue, but not the peripheral subcapsular cells, which early in foetal life assume the appearance of adult cells and store lipid material. It is from these that the adult cortex ultimately develops. In a case of hemicephaly these investigators found that the gland was small and the inner vascular cortical zone was absent, but the rim of cortical cells was normal. Kern described the changes in detail.

In the newborn there is capillary hyperaemia in this atypical mass of cortical tissue. The columns of cells are separated and their alignment deranged. Degenerative changes such as nuclear shrinkage and appearance of colloid droplets in the cytoplasm mark this stage. At 30 days a completely degenerated cellular zone is established between the scanty phaeochrome cells forming the rudimentary medulla and the outer thin layer of subcapsular cortical tissue. The degenerating cells appear to flatten in a plane parallel to the capsule. There is phagocytosis of erythrocytes, and shrinking of the reticulum between the degenerating cells. At 12 months this zone has been replaced by a thick zone of fibrous tissue which becomes progressively thinner as the medullary mass increases in bulk, until, finally, cortical and phaeochrome tissue are practically in contact. Kern found that this involutionary phenomenon could not be demonstrated in guinea-pigs, rats, rabbits, calves, sheep, pigs, or horses. This lends support to the observations of Elliott and Armour that the vascular cortical zone is involved in cerebral development.

In 1916 Lewis and Pappenheimer, in a detailed study of this phenomenon, confirmed the results of these investigators and found that in the first three years of life no increase in the subcapsular cortical tissue had taken place. They believe that degeneration of the foetal inner cortical mass is complete in 14 days. Expressed in terms of weight, there is a shrinkage in the post-natal weight amounting to 30% within two weeks and 50% in two months, and when the gland has reached adult development it is 1/30 of the kidney weight compared with 1/3 at birth. Goldzieher reported three cases of congenital heart disease in which this involutionary change of the suprarenal cortex did not occur, and examined in detail the evidence which pointed to involvement of the foetal cortical cells in respiratory function under conditions of low oxygen tension.

We know that there is massive destruction of foetal erythrocytes after birth, and recent work has shown that the dissociation characteristics of foetal haemoglobin differ from those of the post-natal type. Foetal arterial blood is only 63% saturated, compared with 95% saturation of the free-breathing infant. Moreover, in the adult the average oxygen tension of venous blood is about 25 mm. It may fall as low as 4 mm. in the foetus. Increased blood volume and erythrocyte count, together with a meionectic haemoglobin, are aspects of adjustment of the organism to anoxaemia, but there is evidence of further adjustment by the tissue cells themselves, because the foetal oxygen utilization of 75% is more than double that of the maternal 31%.

It has been suggested that the atypical cortical cells of the suprarenal are involved in maintaining the high rate of oxygen utilization necessary in the circumstances. In this connexion the work of Armstrong and Heim (1938) calls for further study. They were working on animal adaptation to intermittent anoxia as part of a research in aviation medicine, and the only significant fact that emerged was hypertrophy of the suprarenal cortical tissue. They found that intermittent anoxia produced by exposure to half atmosphere for four hours daily led to hypertrophy and degeneration of the suprarenal cortex, and that the animals died from the effects of the anoxia. On the other hand, injections of cortical extract greatly improved the survival rate, apparently owing to increase of oxygen utilization by tissues. Further investigation along these lines may well disclose valuable information on this aspect of suprarenal function.

Another remarkable change in the body economy at birth is that affecting water sodium and chloride, to select only the main features of the picture. So far as water distribution is concerned, the infant has indeed been likened to an oedematous adult. Although it contains only 10% more total water than the adult, more than twice the amount—that is, 50%—is extracellular, whilst in the adult only 20% is in this phase. At birth the muscles contain only 18% of the total body water. In the adult 50% of the body water is held in the muscle cells. The newborn infant has little power either to concentrate or to dilute its urine. Excretion of solute requires disproportionately more water than is needed after the infant reaches the age of 3 months, and most investigators agree that glomerular filtration does not reach the adult value until 5 to 6 months.

McCance (1950) states that, "much as our knowledge of kidney function has advanced in the last 30 years, these discoveries about the infant kidney have served

only to indicate how little we really do know about the reabsorption of sodium chloride."

Other clinical evidence of neonatal hypofunction of the suprarenal cortex in certain instances is provided by Goldzieher and Gordon's (1932) study of pseudo-pneumonia of the newborn. Increased pulmonary ventilation following suprarenalectomy led Swale Vincent to postulate the production by the suprarenal of a controlling hormone which he termed "pneumin." Marine and Baumann interpreted absence of the increased ventilation after suprarenalectomy as evidence of the existence of accessory tissue, and there is a wealth of 25-year-old research on this interesting relation between the suprarenal and the respiratory function which would repay extended investigation (Hess, 1921; Aub *et al.*, 1922; Scott, 1922; Bornstein and Gremels, 1925; Messerle, 1926; Kuehl, 1927; Kisch, 1928; Sazaki, 1930; Harrop and Weinstein, 1933).

In 1944 Vogt was able to demonstrate what Cramer (1928) on histological grounds had postulated—namely, control of cortical activity from the medulla of the gland—and we begin to see the mechanism of climatic acclimatization in clearer detail. This is a third major adjustment required of the newborn (cf. Conn and Louis, 1950).

From the foregoing necessarily brief references it will be evident that the function of the suprarenal gland undergoes changes commensurate with post-natal anatomical involution and regeneration.

Cortical Insufficiency in Infants

Bruch and McCune (1936) were unable to find evidence of cortical hypofunction by examination of plasma-sodium levels of normal infants up to 3 weeks of age. This might be expected because of large sodium reserves in the bones. Hypofunction might be expected to manifest itself only when functional demand exceeds the capacity of the cortical tissue. I am therefore more impressed by evidence provided by the successful treatment of 12 cases of foetal shock with saline and deoxycortone acetate as reported by Berling (1941).

Jaudon's (1946a, 1946b) contributions provide such a mass of detail and critical evaluation of data that they deserve first consideration in a communication of this kind. He surveys the clinical and experimental field which encompasses his own extensive human studies, and considers that his own cases of hypofunction of the adrenals in the first weeks of life are due to fractional cortical disturbance only. He demonstrated that salt and deoxycortone were necessary for long periods to sustain life, although there were no other signs of endocrine disturbance in either the infants or their parents and relatives. Treatment can, moreover, be discontinued without regression of signs and symptoms, and there are imperceptible amounts of corticosterone in the urine.

His cases suffered no difficult birth, and the signs developed from anorexia, through regurgitation and vomiting, into full gastro-intestinal disturbance. Two were mistaken for pyloric stenosis. Weight loss was disproportionate to food regurgitated, and administration of fluids was necessary to maintain hydration. After administration of salt and deoxycortone acetate, tone and appearance improved rapidly, together with reversal of the excessive loss of urine of low specific gravity and high chloride content. The negligible excretion of

corticosteroids, together with absence of any sign of macrogenitosomia, is taken to indicate freedom from hyperplastic encroachment of the androgenic zone of the cortex. Oddly enough, in a personal communication he states that he has not seen cases of pink disease. This fact emphasizes the unwisdom of criticizing, without local knowledge, published accounts of endocrine disease in other countries. In 1923 no one had seen, in England, the severe types of hyperthyroidism reported by Plummer, of the Mayo Clinic, and they could not therefore understand or believe his clinical account of the effect of large doses of tincture of iodine. I could not believe my own eyes when I myself saw many of his cases. They were so extremely emaciated, and were in muttering delirium. Only recently, Professor Freudenberg, of Basle, told me that he had seen but few cases of pink disease, and none fatal.

Jaudon's infants provided the following consistent data: moderate lowering of plasma- CO_2 combining power; slight rise of non-protein nitrogen; associated lowering of plasma sodium and plasma volume; and abundant chloride in the urine.

Treatment consisted in giving deoxycortone acetate, ranging, according to the needs of the case, from 0.5 to 5 mg. daily, with salt ranging from 2 to 3 g. The steroid alone gave only temporary relief.

Suprarenal Cortex and Pink Disease

Our satisfaction in finding these papers of Jaudon's can be imagined. As Dr. Basil Hetzel, of the Institute of Medical and Veterinary Science, was working on glucocorticoid excretion in urine of hypertensive patients, he suggested that these cases of pink disease be investigated along similar lines. Using the technique of Venning *et al.*, and after overcoming technical difficulties, he has shown that there is a normal output of glucocorticoids in this disease. A preliminary communication on the work has already appeared (Hetzel, 1950).*

Owing to the often poor state of health of the child after "recovery" from pink disease, we suspected that there might be subacute or chronic forms of hypofunction of the suprarenal cortex, and were supported in this by the following statement in Cameron's classic textbook on the nervous child. If one ignores the obvious confusion of medullary and cortical function, which was excusable at the time, his words provide once again that refreshing reminder that insight, which is a product of clinical observation and acumen, is often more important in medicine than too ready recourse to the application of statistical methods:

"We know that the suprarenal glands are exhausted and that their function becomes impaired under the stress of great exertion, great emotional excitement, and persistent infection . . . and they are the same conditions which in practice we are forced to regard as productive of the bouts or attacks of pallor, prostration, and vomiting of the nervous child. If speculation is permitted where certainty is not yet, we may surmise that in Addison's disease we are observing the effects of the gross destruction of the suprarenal medullary tissue; in an attack of cyclical vomiting we are encountering the temporary exhaustion and functional impairment of the same gland."

Results so far obtained by Dr. Cheek confirm a conclusion which has been reached by others, that in cases of marasmus and in the nervous child fractional

*This information has been received since the lecture was given.

cortical insufficiency of the suprarenal may in many instances be a contributing, if not a causal, factor. Hislop (1938) reported his good results in cases of marasmus from the daily administration of 1 min. (0.06 ml.) of "eucortone" per 2 lb. (0.9 kg.) of body weight. He was influenced in his decision by the experimental work of Simpson, Dennison, and Korenchevsky. Szasz (1939) reported a similar group between the ages of 7 weeks and 6 months. All, it is important to note, had been weaned early and fed artificially. She reports a clinical impression which we ourselves have gained from observations following the administration of corticosteroid. "It appeared that the functional capacity of the organism dramatically (*sturmisch*) improved. Meteorism ceased, the lilac colour of the skin disappeared, stools became firm, hypostasis and hydro-lability cleared up."

Cheek (1951) has already reported a study of 11 cases between the ages of 2 and 7 years of what may be termed cryptic manifestation of the pink disease syndrome, which includes psychological instability, failure to thrive, and lassitude. There is also some tendency to recurrent catarrh and to allergic manifestation, and plasma-sodium levels tend to be subnormal. Although there is no evidence of pink disease, some cases had a previous history of it. Restoration to normal vigorous health and psychological stability followed treatment with salt alone in milder cases, and with corticosteroid in addition in more severe instances. The duration of the treatment was more prolonged in proportion to the duration of the ill-health. Since leaving Adelaide, I have been informed by Dr. Cheek that a further 15 cases of pink disease at the Babies' Hospital have responded promptly and successfully to the same treatment. The average confinement in hospital has been reduced from 3-4 months to 3-4 weeks.

Why there are so many and such acute cases of pink disease in the States of South Australia and Victoria

remains to be elucidated. There is widespread belief among mothers, fostered by the teaching of infant-nurses and welfare agencies, that salt should not be added to the diet when weaning, not even in cooking the vegetables for purée. There is, too, owing to a warm arid climate, a large water loss from the skin due to the high evaporation rate, and this may be sufficient to deplete foetal salt reserves in certain cases, especially when on a salt-free diet. Manifestly these can be only exacerbating factors. There is recent evidence that the outward movement of sodium is not merely due to altered renal threshold. Conn and Louis (1950) have been able quantitatively to correlate the loss of sodium and chloride in the thermal sweat with adrenal production of corticoids similar in action to deoxycortone. They followed the course of sodium and chloride movement under the influence of A.C.T.H. and unexpectedly disclosed an important pituitary adjustment in the course of acclimatization to heat.

Whatever the local contributing cause, the result has been to create conditions favourable to a recognition of the basis of the disturbance known as pink disease, in infants between 6 and 18 months, and a related group of more chronic disturbances classified as "failure to thrive" or "the nervous child."

TABLE I.—Some Typical Data from Cases of Pink Disease

Case No.	Sex	Age in Years	Plasma Sodium*		Cell Volume %		Haemoglobin (g. %)		Plasma Protein (g. %)		48-hour Urine Volume in ml.	
1	F	2½	300	315	42	40	13.2	13.0	7.3	7.2	545	1,540
2	F	3	290	300	45	38	14.0	12.0	7.5	7.2	640	1,700
3	F	2½	300	330	40	38	12.8	12.3	7.7	7.5	500	1,290
4	F	2½	290	315	43	40	13.9	12.8	7.5	7.2	500	1,500
5	M	2½	290	300	41	40	13.6	13.0	6.8	7.2	530	1,300
6	F	3	280	360	45	38	13.6	12.0	7.5	7.0	350	1,200
7	M	5	270	335	48	40	15.0	12.0	8.0	7.5	700	1,100
8	F	2½	260	340	55	40	17.0	13.5	8.3	6.8	720	1,030

* The accuracy of these figures is of the order of $\pm 5\%$.

TABLE II.—Incidence and Duration of Main Signs and Symptoms in Pink Disease

	Day of Disappearance of Symptoms																						
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Photophobia			.		.		°			..	.							..					
Insomnia ..			.		..	..	°		.	..		.						..					
Hypotonia ..			.		.	.	..°	.		.	.	.											
Redness ..									.	.							.	..		..	°	.	
Anorexia ..			.		..		°		..	..		.	.				..		.				
Irritability ..				.			.		.	.		.		..				..					

° Deoxycortone administered from onset.

TABLE III.—Distribution of Main Signs and Symptoms among Different Cases

Symptoms	Case No. (See Table I).								
	1	2	3	4	5	6	7	8	9*
Irritability ..	+	+	+	+	+	+	+	+	+ Subject to colds
Sleeplessness ..	+	+	+	+	+	+	+	+	
Running nose ..	+			+		+			
Adenoids ..	+						+		+
Tonsils ..			+	+	+	+	+	+	
Muscle weakness ..	+	+			+			+	
Apathy ..	+			+				+	+
Cold hands ..	+						+		
? Asthma ..	+						+		
Anorexia ..	+	+	+	+	+	+	+	+	+
? Precipitating illness	Measles aged 18 months	Pink disease aged 15 months	P.U.O. aged 26 months	Pink disease aged 9 months	Teething aged 2 years	Not known	Pink disease aged 5 months	Measles aged 12 months	Measles aged 2 years

* This patient, a girl aged 5½ years, vomited once or twice weekly. In Cases 1 to 8 there was a tendency to sweat at night and intolerance of hot weather.

Conclusion

If I may return to the analogy of the jigsaw puzzle, I would describe the present survey as an attempt to construct a composite picture of fractional hypofunction of the suprarenal cortex from the mass of anatomical, pathological, and physiological data which seems to me to elucidate the phenomenon known as pink disease, and, to some extent at least, to explain part of the aetiology of certain types of the nervous-child syndrome or the child that fails to thrive.

All the symptoms and signs can be explained in terms of the recognized results of loss of sodium with accompanying dehydration, always bearing in mind the insidious development of the condition. With the fall in plasma sodium there may be a fall in chloride or bicarbonate, or both; a fall in plasma volume and rate of blood flow; and an increase in corpuscular volume. The bluish-pink colour seen in pink disease indicates the slowed capillary circulation which is associated with capillary dilatation, and the severe and fatal cases represent true vascular shock, which can readily be precipitated by any rapid loss of body fluid.

There are unexplained physiological features of the recovery from pink disease—for example, the well-being of the child is recovered long before the pink colour disappears. But, as McCance pointed out in his report on the effect of salt deprivation, the results of acute experiment cannot be expected accurately to follow those of chronic disease. For one thing, the retreat of the organism before maladjustment is highly complex and effective. It is reasonable, however, to assume that from birth to the age of 8 years the morphological developmental changes in the structure of the suprarenal gland may be associated with functional disturbance arising perhaps from demands in excess of capacity and which acts as either a causal or an exacerbating factor.

Detailed biochemical investigation of the condition is now in progress. My friend, McCance, who tortured himself and his colleagues by extreme deprivation of salt, concluded from his experiments that the symptoms and signs of Addison's disease could, with explicable exceptions of pigmentation and cramps, be described in terms of sodium deficiency.

In his Goulstonian Lecture for 1936 he repeated a bold prophecy made in 1836 by Prout, that, in the future, chemistry would ultimately be to medicine what anatomy was to surgery—a most unpalatable opinion at the time. McCance, speaking in, dare we say, a more enlightened age, ventured to extend the prophecy in the following words: "I feel that the influence of biochemistry on medicine is only in its infancy. I see, for example, no reason why certain problems of psychology and even human behaviour should not be solved in the future by intelligent hormone therapy; or why neurology should not become just as biochemical a subject as nutrition."

It would seem that to some extent at least our Australian contribution confirms this opinion.

My thanks are due to the paediatricians and general practitioners of South Australia who so willingly co-operated in providing cases, and to the firm of Ciba Limited for the prompt and liberal supply of "percorten" brand of deoxycortone acetate.

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When speaking on the vote of thanks to Sir Stanton Hicks, after his address at the Ciba Foundation, Dr. Leonard Simpson expressed his appreciation of the fact that the speaker had been at pains to put forward the work of a younger colleague. He compared the case to that of Professor J. J. R. Macleod and Dr. Banting (as he then was). Dr. Simpson added that Dr. Donald Cheek, of the Children's Hospital, Adelaide, was to be congratulated not only on his tenacious investigation of pink disease, but also on his good fortune in having at hand someone with research experience in the field of water metabolism.