and the presence of such resistant organisms might prove to be of importance if it was desired to give prolonged treatment.

Toxic symptoms were often encountered, but could usually be controlled by slightly reducing the dosage.

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URINARY SYMPATHIN EXCRETION OF NORMAL INFANTS AND OF INFANTS WITH PINK DISEASE

BY

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The condition known variously by the name of "pink disease" and by a number of other descriptive or eponymous titles was described by Feer (1923) as a disorder of the vegetative nervous system. The fact that he employed atropine in treatment, however, suggests that he may have failed to appreciate the full significance of his hypothesis.

A very severe case of pink disease which was admitted to the Royal Edinburgh Hospital for Sick Children in October, 1953, appeared to one of us (J. W. F.) to show so many suggestive features of an overacting sympathetic nervous system that it was thought justifiable to embark on the determination of the infant's urinary sympathin (adrenaline and noradrenaline) excretion. The result was of sufficient interest to stimulate the investigation of further cases and of control subjects.

Method of Investigation

Urine was collected accurately for 24-hour periods from 19 healthy infants, most of whom were resident in nurseries under the care of the local authority, usually because of some temporary dislocation of family life. A number were

convalescing from minor illnesses in hospital, and in these cases the collections were obtained over the 24 hours immediately before discharge. Urine was collected similarly from four infants who presented the undoubted clinical features of pink disease.

All the control subjects and three of the affected infants were males in whom accurate urine collection was possible by means of small-sized latex colostomy tubing which was strapped to the penis and allowed to drain into a specially prepared collecting bottle. The fourth patient with pink disease was a female, and great difficulty was experienced in obtaining an accurate collection of urine despite the use of an indwelling catheter.

The urine was collected in bottles containing 5 ml. of 2N H₂SO₄ and 0.5 ml. of chloroform to stabilize the sympathin. Aliquots of the measured 24-hour specimen were used for assay. One aliquot (50–100 ml.) was submitted to acid hydrolysis by heating at pH 2 (adjusted with 2N H₂SO₄) for 20 minutes in a boiling-water bath. This treatment releases some (Euler and Hellner, 1951) but not all of the catechol amines excreted in a conjugated form (Euler and Orwén, 1955). The sympathin excreted in the free state was determined, using another aliquot of the urine which was not submitted to acid hydrolysis.

The sympathin determinations on the hydrolysed and unhydrolysed urine were carried out by a method to be described in detail elsewhere by Crawford and Law. It consists essentially in the extraction of the sympathin by passage of the diluted urine at pH 7 through a column of a weak cation exchange resin "amberlite IRC-50" previously buffered to pH 7–7.5. The adsorbed sympathin is recovered from the column by elution with dilute sulphuric acid. Most of the inorganic salt in the eluate, brought to pH 3.5 with dilute sodium hydroxide, is precipitated by the addition of 2–4 volumes of a mixture of equal volumes of acetone and ethanol. The supernatant is evaporated to dryness at 35° C. under reduced pressure. The residue is dissolved in distilled water (3 ml.) to give the "final urine extract." The sympathin content of this solution is determined fluorimetrically, using Lund's (1949, 1950) method modified in such a way that equal quantities of adrenaline or noradrenaline or mixtures of the two amines give similar intensities of fluorescence (Crawford and Law, unpublished).

When individual determinations of adrenaline and noradrenaline in the urine extract were required, separation of the two amines was effected by submitting an aliquot of the final urine extract to paper chromatography (Crawford and Outschoorn, 1951, modified as described by Vogt, 1954). The concentrations of the separated amines in the eluates from the appropriate paper strips were determined fluorimetrically.

The method of extraction of urinary sympathin described by Euler and Hellner (1951) was used in the first case of pink disease investigated (Table III). The sympathin in the urine aliquot is adsorbed on to aluminium hydroxide formed in the urine by the addition of aluminium sulphate followed by adjustment of the pH to 7.5 with dilute sodium hydroxide. The separated precipitate is dissolved in dilute sulphuric acid and the inorganic salts are removed by precipitation with acetone-ethanol mixture (see above) after adjusting the pH to 3.5. The supernatant is evaporated to dryness under reduced pressure at 35° C. The residue was dissolved in 0.9% (w/v) sodium chloride and the sympathin concentration in terms of noradrenaline determined by bio-assay, using the rat's blood pressure preparation (Crawford and Outschoorn, 1951).

A recovery of 82% (S.D. 6) was obtained by the amberlite IRC-50 method in 51 experiments in which adrenaline or noradrenaline (3–30 µg.) was added to urine. No significant difference ($P=0.05$) in the recoveries of adrenaline or noradrenaline, or in the recoveries from hydrolysed and unhydrolysed urine, was found. Similar control experiments in which the two amines were separately determined following extraction by the amberlite IRC-50 method and separation by paper chromatography showed a recovery of 50%

(S.D. 9) for 2 to 15 $\mu\text{g.}$ of either amine (10 estimations). Again the recoveries for adrenaline and noradrenaline did not differ significantly ($P=0.05$).

The figures cited in the tables are corrected values, the correction factor for each experimental result being obtained from a recovery experiment carried out concurrently with the analysis.

Excretion of Sympathin in Normal Infants

Determinations of the sympathin excretion in single 24-hour urine samples from each of 14 healthy male infants aged 6–18 months gave a mean value of 16.5 $\mu\text{g.}$ (S.D. 4.0) for hydrolysed urine and 13.2 $\mu\text{g.}$ (S.D. 3.4) for the sympathin excreted in the free state (Table I). The results for

TABLE I.—*Urinary Sympathin Excretion by 14 Normal Male Infants*

No.	Age in Months	Body Weight (Kg.)	Volume of Urine (ml.)	Sympathin ($\mu\text{g.}/24$ hours)		% as Free Sympathin
				Hydrolysed Urine	Unhydrolysed Urine	
1	6	6.5	405	13.9	11.6	84
2	6	7.45	645	23.4	13.4	58
3	6	7.2	370	22.8	14.3	63
4	9	10.3	430	16.3	11.7	72
5	9	10.0	410	15.4	12.7	83
6	10	8.8	360	16.7	15.3	92
7	12	10.4	370	13.3	10.8	81
8	12	10.4	370	14.4	11.0	77
9	12	9.6	152	16.8	16.3	97
10	12	7.25	418	13.1	10.1	77
11	12	7.75	570	18.1	16.3	90
12	13	10.0	305	17.6	14.9	85
13	13	6.4	448	7.6	6.4	84
14	18	10.9	199	21.5	20.4	95
Mean	10.7	8.78	389	16.5	13.2	81
S.D.				4.0	3.4	11.3
Fiducial limits ($P=0.05$)				14.1–18.9	11.3–15.2	74–88

hydrolysed urine are similar to those given by Burn *et al.* (1953), who found 12–18 $\mu\text{g.}$ (in terms of noradrenaline) in the 24-hour urine samples of three children aged 3–24 months.

Separate determinations of the adrenaline and noradrenaline excretion by five normal male infants of 10–12 months showed 69% (S.D. 4.7) of the free sympathin to be noradrenaline, while of the sympathin in hydrolysed urine noradrenaline accounted for 61% (S.D. 5.8) of the total (Table II).

Clinical History and Sympathin Excretion of Infants with Pink Disease

Case 1

The patient, aged 9 months, was the second child of healthy unrelated parents. His original progress was entirely satisfactory, but at 7 months he developed chicken-pox, complicated by a severe attack of bronchitis, which was clearing at 8 months when he developed whooping-cough and further respiratory infection. His symptoms of increasing anorexia

and irritability had followed the onset of pertussis. There was no history of exposure to mercury in teething, grey, or worm powders, in ointment, disinfectant, or nappy washes. The development of classical and very severe pink disease was progressive, and the infant became so profoundly anorexic that tube-feeding was necessary. He was extremely miserable, had typical cold and puffy red hands with peeling developing after some weeks; sweating was profuse, and resulted in the typical body rash which the infant rubbed and scratched continuously. He was uncomfortable in any position, had a persistent tachycardia, was hypertensive (140/106), was photophobic, and had marked dilatation of the pupils. He shed his four teeth, and his tongue became small, hard, and blanched, the tip eventually sloughing. The abdomen became progressively distended with gas until it caused him distress.

At this stage rectal examination revealed his bladder to be grossly distended, the wall apparently being thin and relaxed. Micturition was hesitant and dribbling, the difficulty being similar to that sometimes observed after a dose of ephedrine. After an ounce or so of urine had been passed by dribbling micturition, catheterization produced a large residuum. Neither then nor later was any obstruction demonstrated, and it became the practice to assist the infant to empty his bladder completely twice daily by pressure on the abdominal wall and from the rectum.

Investigation of the patient's urinary output of mercury in 24 hours at an early stage failed to reveal anything abnormal and his serum sodium and chloride were normal, although it should be stated that he had been receiving half-strength saline frequently each day as the excessive loss from the skin was obvious.

Much of the clinical picture suggested overactivity of the sympathetic nervous system, and the urinary sympathin excretion was determined. The result was given as 74 $\mu\text{g.}$ of pressor substance (in terms of noradrenaline) in 24 hours (Table III).

TABLE III.—*Urinary Excretion of Sympathin ($\mu\text{g.}/24$ hr.) in All Cases*

Case	Collection	Unhydrolysed Urine	Hydrolysed Urine	% as Free Sympathin
1	1	Not done	74*	
2	1	41	41	100
	2	20	21.5	93
	3	42	49	86
3	1	43	Not done	
	2	40	" 36"	100
	3	37		
4	1	13	17	77
	2	19	23	83

* Extraction by the method of Euler and Hellner (1951). Extracts assayed on rat's blood pressure preparation with (—) noradrenaline as standard.

It was decided to observe the effect of reflex heat and of an anti-adrenaline drug on the patient, and the result may be seen on the graph. Skin temperature readings were recorded with a thermistor and the rectal temperature with a

TABLE II.—*Urinary Excretion ($\mu\text{g.}/24$ hr.) of Adrenaline and Noradrenaline by 5 Normal Male Infants*

No.	Age in Months	Body Weight	Volume Urine in 24 Hours	Hydrolysed Urine			Unhydrolysed Urine		
				Adren.	Noradren.	Total	Adren.	Noradren.	Total
1	10	5.45 kg.	475 ml.	8.3 (45%)	10.2 (55%)	18.5	3.9 (37%)	6.7 (63%)	10.6
2	10	5.5	540	8.8 (46%)	10.3 (54%)	19.1	3.7 (32%)	7.9 (68%)	11.6
3	12	9.1 "	495	5.9 (34%)	11.4 (66%)	17.3	2.4 (24%)	7.4 (76%)	9.8
4	12	9.1 "	485	5.5 (36%)	9.8 (64%)	15.3	3.0 (30%)	7.1 (70%)	10.1
5	12	9.4 "	670	8.2 (35%)	15.2 (65%)	23.4	5.5 (30%)	13.0 (70%)	18.5
Mean	11.2	7.7 "	533	7.3 (39%)	11.4 (61%)	18.7	3.7 (31%)	8.4 (69%)	12.1
S.D.				1.52	2.22	2.99	1.17	2.6	3.6
Fiducial limits ($P=0.05$)				5.4–9.2	8.6–14.1	15.0–22.4	2.25–5.15	5.2–11.6	7.6–16.7
				Mean noradrenaline %=61 S.D., 5.8 Fiducial limits, 53–68			Mean noradrenaline %=69 S.D., 4.7 Fiducial limits, 63–75		

premature-baby thermometer. The pulse and blood pressure were also recorded, and as some measure of the effect on the relaxed bowel the abdominal circumference was measured around its maximum point. As may be seen, reflex heat (provided by an electric blanket to the right arm, leg, and half of trunk) failed to produce release of the vasospasm, but within five minutes of injecting tolazoline ("priscol") the skin temperature was rising to normal and remained there, the bowels opened copiously, and urine passed normally. There was only a slight fall in the blood pressure, but it is known that tolazoline may not influence hypertension successfully because of its potentiating effect on cardiac output.

The results were so satisfactory that it was decided to begin treatment with this substance. Initially the oral route was employed, but, possibly owing to delayed gastric empty-

Effect of reflex heat and tolazoline in Case 1.

ing, the signs of pink disease were uninfluenced. Intramuscular injection of 5 mg. every six hours was started, with complete control of the vasospasm. The hands and feet were warm, and sweating became normal. The baby was happier, abdominal distension decreased, and urinary function improved but was impeded by a more or less continuous priapism which seemed to be due to the drug. The tongue became normal in appearance apart from the healing irregular anterior margin.

Treatment was continued for five days, and at that time only the gross wasting, some fullness of the abdomen, and weakness remained. On the fifth day of treatment, however, the temperature rose steeply and widespread signs of bronchitis appeared. Chlortetracycline was given, but the patient rapidly deteriorated, dying in 24 hours.

Post-mortem examination was carried out by Dr. A. R. Macgregor. The main features noted were a purulent bronchitis and a patch of bronchopneumonia. Nothing peculiar to pink disease was noted. Chromaffin tissue was subjected to careful histological examination and no abnormality was found. The genito-urinary tract was normal. Sections of the tongue showed that muscle necrosis formed the floor of the ulcerated margin, granulation tissue was forming, and there was much polymorph and mononuclear infiltration. Beyond the areas of necrosis cellular infiltration was noted for some distance, but the arteries in the healthy parts showed no pathological changes, and in the infiltrated areas nothing was found that could not be explained as secondary to the surrounding inflammation.

Case 2

A boy aged 6 months, the second child of healthy unrelated parents, had been well until six weeks before admission, when he began to lose weight and to be restless, fretful, and sleepless. His appetite deteriorated. For one week he had been very photophobic, and for a few days had been sweating profusely, a rash had appeared on the trunk and limbs, and his hands and feet had become pink and cold. There was no history of exposure to mercury.

On examination he had clearly lost weight and there was obvious photophobia. A sweat rash was present and the hands and feet were typically pink, puffy, and cold. The heart rate at rest was 144 a minute, and the systolic blood pressure 130 mm. Hg. The abdomen was a little full and the bowel was constipated, but the bladder was not enlarged. Blood biochemistry, urinalysis, and lumbar puncture gave normal results. No abnormal urinary excretion of mercury was found.

During the next few days his appetite improved, but the clinical condition was unchanged. One week after admission a 24-hour collection of urine was obtained and the sympathin excretion determined (see Table IV). On the following day

TABLE IV.—Urinary Excretion of Sympathin ($\mu\text{g./24 hr.}$) in Case 2

Collection and Date	Treatment to Urine	Extract from Amberlite IRC-50	Eluates from Paper Chromatograms		
			Adren. Fraction	Noradren. Fraction	Total
1 9-10/5/54	Hydrolysed	41	13.9	26.8 (66%)	40.7
	Unhydrolysed	41	11.2	26.2 (70%)	37.4
2 23-24/5/54	Hydrolysed	21.5	4.1	15.4 (79%)	19.5
	Unhydrolysed	20	3.7	13.6 (81%)	16.7
3 26-27/5/54	Hydrolysed	49	Not done		
	Unhydrolysed	42			

his temperature rose to 101°F. (38.3°C.) and after 24 hours pus cells appeared in the urine. The infection was cleared with sulphadimidine, but during the next week the signs of pink disease became more pronounced. In the third week of his stay in hospital his response to reflex heating (see Table V) was negative, and a further 24-hour collection for

TABLE V.—Case 2, Skin Temperatures in Degrees Centigrade

Date		Cubicle Temperature	Hands		Feet	
			Right	Left	Right	Left
24.5.54	Original	20.5	28	27	22	22
	1/2-hour Heat	22	25	22.5	21	21
	1 hour	21.5	37	23	21.5	21.5
	1 1/2 hours	21.5	34	26	21.5	21.5
26.5.54	Original	23	33	26.5	24	24
	1/2-hour Heat	23	29.5	24.5	23	23
	1 hour	23	37	24.5	22.5	22
	1 1/2 hours	23	35	35	21.5	21
1.6.54	Original	20	33	32.5	21.5	22
	1/2-hour Heat	21	33	33	21	21
	1 hour	21	37	35	21.5	21
	1 1/2 hours	21	35.6	34.5	22	22

Temperatures were recorded at five-minute intervals, but, for reasons of space, only selected time intervals are given here. The temperatures were always stable for 20 minutes before heating began, and the latter was applied for 30 minutes by means of a pre-heated electric blanket.

sympathin determination was obtained. Chlorpromazine treatment was begun at once in dosage of 10 mg. six-hourly by intramuscular injection. After 48 hours his clinical condition appeared to be worse, and although his right hand was warm the other extremities did not respond to reflex heating. Urine excreted over 24 hours was again collected and the sympathin content determined. His temperature, which had been unstable, rose again owing to a coliform urinary infection, which was treated with sulphonamide. It was decided to observe the effect of "hydergine," which is a

mixture of equal parts of dihydroergocornine, dihydroergocystine, and dihydroergokryptine. This was given by subcutaneous injection in dosage of 0.03 mg. three times a day, but his signs remained uninfluenced. While the question of using hexamethonium was being discussed he began to improve and no treatment was given. He was discharged convalescent, and remained well.

Case 3

A boy aged 11 months, the first child of healthy unrelated parents, had made good progress from birth until the age of 9 months. He then became progressively irritable, miserable, anorexic, photophobic, and sleepless. His mother commented on the redness of his hands and feet, and she had noted him to be "soft and floppy." For one month before the development of symptoms he had been having one mercurial powder each day. When seen by one of us (J. W. F.) his condition was beginning to improve. He weighed 1.5 lb. (680 g.) less than he had done two months previously. He was apyrexial, but the heart rate was 168 a minute at rest. He was hypotonic, photophobic, and miserable; his feet and particularly his hands were pink and cold, and there was slight peeling. The blood pressure was 160/100 at rest. His abdomen was a little distended with gas, and the rectum was filled with small pellet-like scybala. The bladder was not palpable. The lower two central incisor teeth had erupted and were obviously loose. The pupils were not abnormally dilated. Other pathological processes were excluded, and the diagnosis was in no doubt. Urine was collected over three 24-hour periods and analysed for sympathin (Table III).

As the infant was clearly improving no treatment was attempted, and it was possible to discharge him for convalescence at home.

Case 4

The patient, a girl, aged 7 months, was the fifth child of healthy unrelated parents. From the third month she had appeared to be restless, "wriggling as if in pain," and miserable at night. Three weeks before admission she developed photophobia of increasing severity. Her appetite rapidly deteriorated, she lost weight, and she became increasingly irritable.

On admission she was very cross and obviously uncomfortable. She wriggled about in the prone position and on her knees with her head firmly buried in the pillows. When faced with the light she closed her eyes tightly and often attempted to cover them with her hands. There was no obvious eye trouble. The hands and feet were cold and distinctly pink, but showed only minimal peeling. A mild heat rash was visible over the abdomen. The heart rate was 180 a minute at rest, and the systolic blood pressure was 130 mm. Hg. The abdomen was a little full but there was no loading of the bowel, and although the bladder was palpable rectally it was not abnormally distended. Other pathological conditions were excluded and the diagnosis was certain.

Urine collections were attempted, but the sex and the baby's extreme restlessness rendered accuracy impossible. All faecal contamination had to be excluded. An indwelling catheter was inserted, and a plastic apron was so attached to the perineum that urine escaping from around the catheter should have been directed into the collecting-bottle. The volumes of urine were so small in each 24 hours (60-70 ml.) that their completeness must be doubted. The results are given in Table III. This infant improved steadily on oral tolazoline.

Discussion

Many and widely varying hypotheses have been advanced in attempts to explain the cause and clinical features of this strange condition. Among these are encephalitis (Francioni and Vigi, 1928), preceding bacterial infection (Rodda, 1925), viral infection (Cobb, 1933), mercurial hypersensitivity (Warkany and Hubbard, 1948, 1951), arsenical poisoning

(Meyer and Weise, 1933), "arseno-plumbism" (Calvin and Taylor, 1935), ergot poisoning (Debré and Nevot, 1939), avitaminosis B (Orton and Bender, 1931; Warthin, 1926), avitaminosis E (Forsyth, 1941), emotional deprivation (Leys, 1950; Leys and Cameron, 1952), allergy (Helmick, 1927; Fanconi and Botsztein, 1948), adrenocortical hypofunction (Cheek and Hicks, 1950), adrenocortical hyperfunction (Cheek, 1954), and a neurosis of the vegetative nervous system (Feer, 1923; Selter, 1927). Of these the possible part played by mercury has attracted the greatest attention in recent years.

Hamilton (1819), in Edinburgh, wrote a classical description of the clinical features of mercurialism, and attention was drawn to their resemblance to pink disease by Warkany and Hubbard (1948, 1951). Not all the features of mercurialism are present, however, in pink disease, nor are all the features of the latter to be noted in mercurial poisoning. Not all affected babies excrete abnormal amounts of mercury in their urine. Hypersensitivity of some infants to the mercury content of medicaments absorbed from the alimentary tract or from the skin has been postulated, but Holzel and James (1952), in comparing two regions in England, found that the disease appeared to be commoner in the region using less mercurial teething powder. Dimercaprol has not fulfilled its earlier promise in treatment (Southby, 1953), and it has even been reported as having been used successfully in patients who excreted no mercury before, during, or after treatment (Houet, 1952). Doubt concerning the role of mercury in the causation of pink disease has been expressed recently by McCance (1955).

Similarly, the parts played by other toxic materials, by vitamin deficiency, and by emotional deprivation have been called in question, and it is clear that no one of these factors is responsible for all cases of pink disease.

There is no convincing evidence of the presence of an encephalitis, although it must be remembered that the condition is sometimes seen in association with the Guillain-Barré syndrome. Feer (1923) was impressed by the apparent disturbance of autonomic balance, and he described pink disease as a "disorder of the vegetative nervous system." Orton and Bender (1931) reported finding in their cases degeneration of cells in the lateral horn of the cord, which they considered to be the effector cells of the splanchnic sympathetic. Like the other inconstant histological changes in the central nervous system, however, these may have resulted from the prolonged illness rather than have been evidence of the basic disorder. Stolz and Woring (1926) claimed to have found hyperplasia of chromaffin tissue in pink disease, but this has not been substantiated by others.

Many of the clinical features of our cases, and particularly of the first, provide evidence which is suggestive of overaction of the sympathetic nervous system. Arteriolar spasm and the closure of the precapillary sphincters produce capillary anoxia and are responsible for the production of the cold pink, puffy hands and feet, and they were responsible for the necrosis of the tongue in the first case. Hypertension is a logical sequel. Sympathetic activity may be seen in the tachycardia, the bowel and bladder relaxation, and the pupillary dilatation which may be observed. Objection has been raised, however, to the condition being a pure sympathetic overaction in view of the excessive sweating which is such a feature of pink disease. Although cholinergic, it is nevertheless a sympathetic function, and could be explained on the basis of the disturbance being a diencephalic one with resultant stimulation of both the adrenergic and the cholinergic sympathetic nerve endings. It had been hoped that further information on this point might have been obtained by treating the second case with chlorpromazine, but this controversial drug shed no light on the matter.

Alternatively it is possible that the excessive sweating may be a compensatory mechanism for losing heat, in view of the impaired heat regulation resulting from arteriolar spasm. Undoubtedly the heavy sweating is responsible for the prickly-heat rash which so many infants show, and for the reduced plasma chlorides, especially in less temperate

climates than our own. It is more difficult to explain the excessive salivation and the hypotonicity, although the latter may be the result simply of anorexia, poor calorie intake, and sleeplessness, while these in turn may be due to itching, discomfort, and even pain. Excessive salivation may result from sensory stimulation of the mouth, and in Case 1 this may have arisen from the necrotic changes in the tongue. No explanation for the photophobia presents itself, although spasm of the retinal vessels was suspected in our first case. The arteriolar spasm responsible for the pinkness and coldness of the hands and feet is variable. It is common to discover the hands more severely affected than the feet at one examination, only to find the position reversed in the same child a little later. Furthermore, spontaneous relief of spasm in the hands may take place when the feet are still involved, or vice versa, and while the blood pressure is still raised and the heart rate rapid.

These observations would be compatible with a centrally determined variation in sympathetic stimulation in various efferent nerves, or changing sensitivity of end organs to a circulating sympathomimetic substance. Leys (1950) considered that the signs could be explained only on the basis of a disturbance of the whole autonomic system at the diencephalon, and suggested that the condition was a "diencephalopathy." McCance (1955) was of the opinion that pink disease is essentially a manifestation of gross overactivity of the sympathetic system.

Vulliamy (1952) demonstrated very clearly that the arteriolar spasm existing in pink disease was too intense to allow of release by reflex heat, whereas the injection of an adrenergic blocking agent, tolazoline, resulted in almost immediate vasodilatation. Relief of symptoms in six of seven cases treated with tolazoline was noted by Peterson and Laughmiller (1954). It is possible that this is the result of the histamine-like action of tolazoline, and not of its anti-adrenaline activity; but Bower (1954), who reported failure or delay in the response of infants with pink disease to reflex heating, confirmed the release of arteriolar spasm by such ganglion-blocking agents as hexamethonium bromide and pentolinium tartrate. All of these drugs are capable of abolishing most of the signs of pink disease, with the exception of photophobia. These observations on the results of treatment provide suggestive evidence of a possible part played by sympathetic overaction.

Attempts to prove such overactivity, however, by demonstrating the presence of abnormal amounts of sympathomimetic substance in the plasma have met with variable success. Glanzmann (1937) suggested that the adrenal medulla produced an increased secretion of adrenaline in children with pink disease. He found that plasma from affected cases when diluted with Ringer's solution resulted in dilatation of the pupil of the enucleated frog eye, whereas similar dilutions of plasma from normal children had none. This mydriatic effect he attributed to adrenaline. Cheek (1951) investigated the adrenaline content of the plasma in affected and control cases, and found no significant difference, but scrutiny of his results has led to doubt about their value.

The urinary excretion of sympathin is probably a more reliable index of the daily output of adrenaline and nor-adrenaline than efforts to detect them in the plasma. Burn *et al.* (1953), in a preliminary report, recorded normal urinary sympathin excretion in two cases of pink disease. The present investigation was undertaken shortly after the publication of their letter and before it had come to our notice. The result in the first case indicated that sympathin excretion might in fact be increased in pink disease and stimulated further studies, and the determination of the normal range became necessary (Tables I and II). The results obtained in Cases 1 and 3, and with one exception the results obtained in Case 2, demonstrate that urinary sympathin excretion in these infants was greater than in the normal control group (Table III). The results in Case 4 were apparently within normal limits, but there was some doubt about the completeness of the urine collection. The results of separate determinations of adrenaline and nor-

adrenaline in two of the urine samples from Case 2 (Table IV) indicate that there was no marked change from the normal in the proportions of adrenaline and nor-adrenaline in the urinary sympathin.

The variability of the physical signs in individual cases suggests that if they are the result of sympathetic overactivity the intensity of sympathetic stimulation varies from time to time along the various efferent nerves of the sympathetic outflow. Should such clinical features be the result of stimulation at the sympathetic nerve endings rather than the response to a circulating sympathomimetic substance, then more intensive signs would be expected to follow the production of a very much smaller total quantity of pressor substances. This would explain why the urinary output of sympathin in pink disease is less than in pheochromocytoma, although the clinical pictures may resemble each other so closely as to be mistaken for one another (Hubble, 1951; Vulliamy, 1952).

The sympathetic nervous system is known to be responsible for the maintenance of the *milieu intérieur*. Stress results in its increased activity, and many different physical or emotional insults could produce its overaction. At an age when the immature central nervous system may react to the stress of febrile or other incidents in certain children by convulsive seizures it seems at least plausible that the posterior hypothalamus may react to certain insults in certain predisposed subjects by prolonged and exaggerated activity on the part of the sympathetic system. Pink disease has been recorded in the course of Schüller-Christian disease, and was attributed to granulomatous irritation of the posterior hypothalamus (Stahlie and Winkel, 1950).

The physical signs of the condition, its resemblance to the effects of a pheochromocytoma, and its response to ganglionic and adrenergic blocking agents are suggestive of such a mechanism.

The present investigation has shown that in infants suffering from pink disease the urinary excretion of sympathin may be greater than in normal control infants who were subjected to similar restraint during the period of urine collection. While these results indicate that sympathetic overaction can be present in children with pink disease, they do not provide evidence that this is invariably so. Definitive treatment of pink disease will require to be the treatment of the underlying case, whether that be toxic, infective, or emotional, but ganglionic and adrenergic blocking agents may be used to relieve symptoms by decreasing sympathetic tone.

Summary

The physical signs of pink disease and their response to adrenolytic substances suggest that they may be produced by an overacting sympathetic system.

Such babies may have a higher daily excretion of sympathin than controls of the same age.

Pink disease may represent the misdirected zeal of an inexperienced defence mechanism to a number of obnoxious stimuli in certain predisposed infants.

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HYPERTHYROIDISM DEVELOPING DURING P.A.S. THERAPY

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Since the bacteriostatic effect of P.A.S. on tubercle bacilli in man was described by Lehmann (1946), its relative clinical value and toxicity have been amply confirmed. Among its many toxic effects one must include its effect on the thyroid gland. Medical reports on this subject are few. Madigan *et al.* (1950) were the first to mention an increase in skin temperature in patients who were receiving P.A.S. therapy, although the rectal temperature remained normal. They attributed the finding to the direct pharmacological effect of P.A.S. resulting in peripheral vasodilatation—an effect seen in febrile as well as afebrile patients. The increased heat loss in afebrile patients was compensated by an increase in the basal metabolic rate.

Komrower (1951) drew attention to the fact that P.A.S. was responsible for the thyroid enlargement in his patient, who developed clinical myxoedema during P.A.S. therapy over a period of about six months. Clausen and Kjerulf-Jensen (1951) reported somewhat similar findings in three cases, and four more cases were reported by Bergqvist and de Maré (1952). Further reports came from Librach (1952) and Davies and Galbraith (1953).

A series of 11 cases of thyroid enlargement during P.A.S. therapy was reported by Brinkman and Coates (1954) from the Trudeau Sanatorium, Trudeau, New York. Two of their cases developed myxoedema as well as thyroid enlargement. The enlargement appeared after 4 to 12 months' treatment with P.A.S., except in one case in which goitre appeared after seven weeks' treatment. In addition, Hamilton (1953) recorded an unusual finding of exophthalmos with a hyperplastic-hypothyroid type of enlargement.

The gradually increasing number of reports of the thyroid gland being affected during P.A.S. therapy are

all on the hypothyroid type. The following case presents the opposite picture—that is, hyperthyroidism, hitherto not mentioned, apart from the high basal metabolic rate alluded to by Madigan *et al.* (1950).

Case Report

A Thai married woman aged 32 attended the out-patient department for treatment of pulmonary tuberculosis in November, 1953. She had been treated by her doctor for the previous two years with apparently little improvement. Physical examination at that time proved the lesion to be in the left upper lobe, confirmed by x-ray examination. Sputum examinations were positive for tubercle bacilli. Her temperature was 37.7° C. (99.8° F.), pulse 118, respirations 24, and body weight 47.1 kg. (7 st. 5½ lb.). She was given P.A.S. (12 g. daily) and isoniazid ("rimifon") (300 mg. daily). After a pneumoperitoneum a few days later her condition improved steadily, and by December, 1954, her weight was 53.3 kg. (8 st. 5½ lb.), pulse 88, respirations 20, temperature 36.7° C. (98° F.), and sputum examinations were negative. However, she began to notice that her neck was somewhat enlarged, and by January, 1955, it was so obvious that she had to wear a scarf to conceal it. She felt easily tired, irritable, and hot even in relatively cool weather. Her weight dropped to 51.6 kg. (8 st. 1½ lb.) in spite of a voracious appetite.

The B.M.R. was +25.1%; cholesterol, 140.2 mg. per 100 ml.; neck measurement, 33 cm.; respirations 20; temperature 36.5° C. (97.7° F.); pulse 104. When the cause of the thyroid enlargement was realized P.A.S. was discontinued and streptomycin was given together with isoniazid. Subsequent to the withdrawal of P.A.S. the hyperthyroid state improved steadily—B.M.R. was +16.8%; cholesterol, 200 mg. per 100 ml.; neck measurement, 31 cm.—with no symptoms referable to hyperthyroidism. By November, 1955, the B.M.R. was +13.3% and the neck measurement 31 cm. (apparently her normal size).

Discussion

The clinical pattern and laboratory findings in this case leave us with no alternative but to conclude that P.A.S. caused thyroid enlargement and hyperthyroidism. It may be argued that the basal metabolism may be high even in afebrile cases, as previously noted by Madigan *et al.* in patients during P.A.S. therapy, but the fact that the B.M.R. changes in our case were correlated with blood cholesterol levels during and after cessation of the drug would be strongly in favour of hyperplastic hyperthyroidism. However, determinations of radioactive iodine uptake and of protein-bound iodine in the serum, especially the latter, could settle the problem, but unfortunately these were not available to us.

Isoniazid by itself is known to cause thyroid enlargement, but this was not the responsible factor in our case, as the drug had been given throughout the treatment period. Angel *et al.* (1955) discussed the role of P.A.S. in the production of thyroid enlargement with or without myxoedema. They investigated the iodine metabolism of the surviving thyroid slices, and were of the opinion that P.A.S. does not inhibit the accumulation of inorganic ¹³¹I in thyroid tissue, but is rather like thiouracil and somewhat weaker in action. P.A.S. inhibits the formation of di-iodotyrosine and thyroid hormone, and the action is a direct one, although the possibility of an additional indirect action cannot be entirely excluded. Macgregor and Somner (1954) and Brinkman and Coates (1954) found iodine ineffective in the relief of goitre due to P.A.S., but remissions of the symptoms and goitre were seen following the use of thyroid. Balint *et al.* (1954) reported some benefit from iodine.

The mechanism, outlined above, of the role of P.A.S. in the production of goitre does not seem to fit in with what happened in our case, undoubtedly a case of hyperthyroidism. It may be possible that in this case the P.A.S. in some way, (?) acting like thiocyanate, blocked the formation of thyroid hormone by excessive production of thyrotropin