A SYNDROME IN THE RAT RESEMBLING PINK DISEASE IN MAN

BY

G. MARSHALL FINDLAY, Sc.D., M.D., and RUBY O. STERN, M.B., B.S.

(From the Laboratories of the Imperial Cancer Research Fund and the National Hospital, Queen Square, London.)

Of the diseases which have come into prominence since the War none is of more interest or importance than the condition first described in Australia by Swift¹¹ as occurring in infants and young children, and now known as Swift's disease, erythrœdema polyneuritis, or more colloquially as 'pink disease.' The syndrome was recognised in America by Weston¹⁴ and in this country by Thursfield and Paterson¹². Cases have since been recorded from France, Holland, Switzerland and Sweden. As Paterson and Greenfield⁹ point out, the disease appears to have become commoner during the past few years, some hundreds of cases having now been recorded. The ætiology of the condition is unknown.

The object of the present paper is to point out the close resemblance between the clinical symptoms and pathological findings in Swift's disease and those which occur in a disease of the rat possibly caused by absence from the diet of a vitamin-like factor distinct from the vitamins at present recognised. For the sake of brevity the disease in the rat will be referred to as the 'pink disease,' but without prejudice.

'PINK DISEASE' IN YOUNG RATS.

The clinical symptoms of this syndrome in the rat were first described by Boas² who produced the condition in young rats by feeding them on a complete diet except that the sole source of protein was supplied by fresh, crude egg-white which had been dried. The clinical symptoms as described by Boas are as follows:—For the first two or three weeks the young rats grow well and are usually in good health. Then red scaly patches appear at the corners of the mouth, the coat becomes rough and sticky and the long hairs fall out. The fur on the abdomen shows at first a characteristic ribbed appearance, followed by the development of bald areas. Meanwhile the red patches spread to other parts of the body and the picture is one of an eczematous dermatitis. There are even skin hæmorrhages in severe cases. The region round the mouth is always the most severely affected, though there is often such severe blepharitis that the eyes are closed. The loss of hair is often extensive. In a few cases œdema of the feet occurs. The rats always have a distinctive, somewhat musty, smell. The body weight remains stationary for a week or two, but falls slowly during the second stage of the disease. This is reached two or three weeks after the development of the first signs of deficiency. To the dermatitis symptoms of nervous upset are now added. There is pronounced spasticity of the limbs, particularly of the hind legs, and the back is arched. The rat assumes in many cases a kangaroo-like posture. Some of the rats do not show marked spasticity but assume a crouching attitude and display a curious swimming movement with the front paws. Death, which occurs

in the final phase, is preceded by a rapid loss of weight and the animal shows signs of extreme cyanosis. Rigor mortis sets in rapidly. Post mortem there is an almost complete absence of fat, and the skin is infiltrated and vascularised, but these are the only apparent abnormalities, the organs seeming perfectly normal. No extensive histological study was carried out, but sections of liver, kidney, thyroid, spleen and adrenals failed to show any marked change.

During histological investigations of the changes in rats due to lack of vitamin B₂ which have been described elsewhere (Findlay⁶), attention was drawn to the syndrome described by Boas and an attempt was made to repeat her observations.

Young rats bred from laboratory stock were, when 20–30 gm. in weight placed on the following diet :—

Dried egg-white ...	100 gm.	Cotton seed oil ...	75 gm.
Wheaten starch ...	250 „	Lemon juice ...	25 c.cm.
Salt mixture (McCollum,		Marmite ...	25 gm.
Simmonds and Pitz ⁸) ...	25 „	Distilled water ...	300 c.cm.

Each rat received 5 drops of cod-liver oil daily. This diet thus contains an ample supply of vitamins A, B₁, B₂, C and D. Its content of vitamin E is, however, low. The weight curve of a typical rat fed on this diet is shown in Chart I, together with the time of onset of the cutaneous and nervous symptoms. The terminal loss of weight would seem to be correlated with the extreme muscular weakness which prevents the animal from feeding properly. Before the onset of the nervous symptoms the animal feeds well and there is no loss of appetite such as occurs in deficiencies of the antineuritic vitamin. There is little to add to the description of the clinical symptoms as given by Boas. The temperature remains normal throughout except during the terminal

CHART I.

phase of inanition when it becomes subnormal. The earliest skin lesions are usually seen around the mouth, on the lower jaws and front of the neck. At a later stage when the skin lesions are fully developed and fissured, the rats tend to keep their mouths constantly open, due possibly to the irritation of the skin lesions or to weakness in the muscles of the lower jaw. Blepharitis is a very constant symptom but keratomalacia never developed. The earliest nervous symptoms consist in a slight straddling of the hind legs. Later the characteristic gait develops. When the animal wishes to move forward the back is arched to the kangaroo position. Then slowly one hind leg is raised until the foot is from a half to three quarters of an inch from the ground ; still very slowly the foot is lowered and the process is repeated with the other hind leg. The gait is thus more reminiscent of an ataxic than of a spastic type of paralysis. After lasting for from two to three days this stage is followed by one of intense muscular weakness. If the animal is placed on its side it can right itself only with the greatest difficulty, if at all.

Blood examinations were made from the tail veins of a number of rats. The average leucocyte count for normal rats of the same weight was 8,750 per c.mm. : for the deficiently fed rats 10,600 per c.mm. Differential leucocyte counts did not show any significant variation, while the number of red blood corpuscles varied only within normal limits.

Pathological Observations. Apart from the skin lesions, the most conspicuous changes at death were the disappearance of the subcutaneous and peritoneal fat, and the wasted condition of the muscles, more especially those of the hind legs. The spleen and thymus also showed atrophy, while the adrenals were slightly enlarged. In rats killed before the onset of the nervous symptoms, however, the changes due to inanition were absent. Death, in the majority of cases, appears to be due to inability to take food as, post-mortem, the stomach is usually empty. Broncho-pneumonia was present in a small number of animals. The papillomatous condition of the cardiac portion of the stomach which is common in rats fed on diets deficient in vitamins A and B₂, was also not infrequently seen.

Histological Changes. Zenker's fluid and formol saline solution were used for the fixation of the internal organs, followed by staining with Weigert's hæmatoxylin and van Gieson. Boveri's solution was also used for fixing the skin, while for the adrenals, Cramer's osmic vapour method was employed for the demonstration of adrenalin.

In a typical rat dying in the terminal stages the histological appearances were as follows : No significant changes were noted in the liver, kidneys or pancreas. In the alimentary tract the papillomatous condition of the cardiac portion of the stomach was not infrequently encountered, while in the intestine both the muscular walls and lymphoid structures had undergone atrophic changes. In the spleen and thymus there was a reduction in the number of lymphoid cells. Broncho-pneumonic changes were sometimes seen in the lungs. The pancreas, thyroid, and genital organs did not show any deviation from the normal. In the bone marrow certain rats showed signs of early

gelatinous degeneration. Sections of the muscles of the hind legs showed a general thinning of the muscle-fibres which had shrunk to two-thirds or less of their normal size, with the result that the sarcolemma nuclei appeared more prominent and more numerous than in the normal muscle. The intermuscular connective tissue septa stood out very clearly with an increase in the cellular elements. In some cases the intramuscular nerve branches also showed a slight excess of cell nuclei.

Skin. The cutaneous lesions were very similar to those described by Denton⁵ in black tongue in dogs, and by Findlay⁶ in rats fed on diets deficient in vitamin B₂. The earliest changes were congestion in all the small vessels of the cutis vera, with oedema of the surrounding tissues. Later, there was a proliferation of the reticulo-endothelial tissue around the vessels and hair follicles, the nuclei being increased and deeply stained. There was no polymorphonuclear exudate round the hair follicles, except when ulceration and an invasion of saprophytic micro-organisms had occurred. The cells of the hair follicles appeared shrunken and atrophic. The cells of the epidermis were not hyperplastic, but the whole process of keratinisation was very active, there being an excessive scaly desquamation of the horny layer. In some places where desquamation had occurred the epidermal cells were reduced to a single layer. Similar changes to those described in the skin, though in less degree, were seen in the epithelium forming the mucous membrane of the mouth.

Nervous System. The brain and spinal cord of each rat were fixed in formol saline, together with one sciatic nerve, whilst the other was fixed in Muller's fluid. Sections were taken from the cervical, dorsal and lumbar regions of the spinal cords. The following staining methods were used:—on frozen sections toluidin blue and Scharlach R; on celloidin sections toluidin blue and hæmatoxylin with van Gieson counter-stain. Nerves fixed in formol saline were teased and used for the study of π granules with toluidin blue staining after mordanting with Muller's fluid. Marchi preparations of the nerves fixed by Muller's fluid were made and embedded in celloidin.

The outstanding lesion was that in the spinal cord. Here there was diffuse infiltration with small round cells, greater in the grey matter, but apparent also in the white matter and extending in most cases throughout the length of the cord. This finding was practically constant, being completely absent only in two rats. The infiltration varied somewhat both in amount and extent, but where it did not involve the entire cord the dorsal and lumbo-sacral region appeared to be most affected. With the toluidin blue stain, the small round cells stained an intense blue which did not allow of any differentiation of the chromatin. With iron hæmatoxylin they stained very deeply, but appeared to be slightly granular. In some rats the infiltrating cells were distinctly larger and stained less deeply, their appearance resembling that of small neuroglial cells. A few sections from the spinal cords of these rats were stained with Anderson's Victoria blue stain for neuroglia, but this failed to reveal any excess of neuroglial fibres. The infiltration occurred diffusely; it was not limited to white or grey matter, but it was certainly most obvious in the region of the

posterior horns. In several cords it was possible to see the infiltration extending into the posterior nerve roots but unfortunately it is difficult to be certain about the condition of the anterior nerve roots as most of these had been torn off in the process of preparation of the sections. In one or two sections, however, in which the anterior nerve roots were still present, no infiltration could be seen in them.

Most cords were greatly congested and there seemed to be an excessive number of capillaries present. No perivascular infiltration, however, could be determined.

The nerve cells in the anterior horns were relatively healthy. In a few, early vacuolation could be seen, but nowhere could we find the intense vacuolation and swelling which was so pronounced a feature in the cords of rats fed on a diet deficient in vitamin B₂ (Stern and Findlay¹⁰). A few cells also had pale-staining Nissl granules, but there was no evidence anywhere of acute chromatolytic changes.

In Scharlach R. preparations there was no trace of lipochrome pigment in the nerve cells, neither could we demonstrate any products of myelin destruction.

The changes in the peripheral nerves were slight but definite. In most sciatic nerves early degeneration could be seen by the Marchi method. Minute droplets of black-staining lipoid were found lying along the course of the nerve fibres. These droplets were most obvious at the nodes of Ranvier. In two rats the brachial plexus was stained by the Marchi method. Neither of these nerves showed any evidence of degeneration. Preparations of peripheral nerves which were stained for π granules were negative. Only a very few granules could be found, not more than were present in the nerve of a normal rat.

The brains appeared perfectly normal, no infiltration with cells being found above the cervical region of the cord.

'PINK DISEASE' IN BREAST-FED RATS.

Boas² in attempting to explain the action of dried egg-white in giving rise to the clinical syndrome described above, suggested that the phenomena observed might be explained by one of the following hypotheses:—

(1) When fresh crude egg-white is dried an essential dietetic factor in it, the existence of which has been hitherto unrecognised, is destroyed. In the absence of this factor from a diet in which the nitrogen is entirely supplied by the egg-white and is complete in all other respects, young rats develop a characteristic disease, associated with dermatitis and nervous symptoms.

(2) When fresh crude egg-white is dried some toxic product is formed which is responsible for the development of the symptoms when rats are fed on a diet containing dried egg-white as a sole source of protein.

Since egg-white is the only crude protein mixture which is yet known to be susceptible to this deterioration of its nutritive properties on drying, it

appeared to be of importance to determine whether it was possible to produce the 'pink disease' syndrome in young rats by a diet which did not contain dried egg-white.

In the case of the deficiency diseases, beriberi and scurvy, it has long been known that a deficiency of the appropriate vitamin in the diet of the pregnant or lactating female results in the appearance of the deficiency disease in the suckling young, while the mother remains in apparently normal health. Thus Andrews¹ found that the milk of mothers who had infants suffering from beriberi produced that disease in puppies when given to them as their sole source of food, while Ingier⁷ produced very severe scurvy in the foetal and newborn guinea-pig by feeding the mothers on a diet lacking in vitamin C. An experiment was therefore undertaken to determine the effects of placing pregnant rats on a diet capable of producing 'pink disease.' The following protocol gives the results of one such experiment.

Rat 1496 fed on dried egg white when ten days pregnant; delivered of four young at full time. The young rats began to show loss of hair when from 18 to 22 days old and died with nervous symptoms in from 28 to 35 days. Histological examination showed the characteristic

CHART II.

changes in the skin, cord and peripheral nerves. Under optimal conditions young rats cannot be weaned before the 25th day, while if deficient in vigour they usually continue to suckle for a longer period. In the present experiment the young were not observed to take any of the food themselves but were seen to suckle their mother until just before death.

There is thus evidence to show that rat's milk may give rise to 'pink disease' when the mothers are fed on dried egg-white.

Other experiments have been undertaken to determine the effects of placing female rats on the dried egg-white diet just prior to impregnation. In these experiments a normal pregnancy results, but the young are either born dead

or only survive their birth four or five days. Histological examination of these infant rats has shown cellular infiltration in the spinal cord. These experiments suggest that the 'pink disease' syndrome in the rat is a true deficiency disease analogous to beriberi or scurvy.

'PINK DISEASE' SYNDROME IN ADULT RATS.

The mothers of certain of the litters which had received the diet of egg-white have continued on this régime after the death of their offspring.

Rat 1481, adult female, died after 12 weeks on the diet, having decreased from 130 gm. to 98 gm. in weight. There was loss of the long hairs on the abdomen and flanks, but no nervous symptoms. Histologically the only lesion was early round-celled infiltration of the spinal cord.

Rat 1496, adult female, after 20 weeks on the diet, had blepharitis of the right eye but no other skin symptoms and no nervous symptoms.

Rat 1494, adult female, after 13 weeks, showed loss of hair and dermatitis on the lower jaws and front of neck together with bald patches on the back. There were no nervous symptoms. The skin lesions gradually improved but the general condition became worse and after twenty-three weeks on the diet the animal died (Chart II).

Adult rats are therefore far more resistant than young rats to the effects of the dried white of egg diet, but do nevertheless develop lesions if the diet is persisted in.

EXPERIMENTS ON THE INFECTIVITY OF 'PINK DISEASE' IN THE RAT.

In order to exclude the possibility that 'pink disease' in the rat is due to an infection with some bacterial or ultra-microscopic organism cultures were made from the heart-blood and spleen of affected rats in broth and serum broth. The cultures were invariably sterile. Attempts to transmit the disease to normally fed rats by intraperitoneal injections of blood or emulsions of spinal cord were negative, as were the results of intra-cerebral inoculations with blood or emulsions of cord. Normally fed rats placed in the same cages as those suffering from 'pink disease' were not infected and remained in perfect health.

There is thus no experimental evidence that 'pink disease' in the rat is an infectious condition.

PINK DISEASE IN CHILDREN.

A brief résumé of the clinical and pathological findings in Swift's disease will now be given in order that they may be compared with those described in 'pink disease' in the rat.

Clinical Symptoms. The disease occurs in infants and young children aged from 4 months to 3½ years, but most commonly between 9 months and 2 years. The majority of the children are breast fed, though others may be on a mixed diet. Other members of the family are not as a rule attacked, and there is no evidence that the disease is infectious. There is usually a history of a cold some time before the onset of the disease. The condition is generally afebrile and the majority of cases eventually recover after some months, unless carried off by an intercurrent infection, such as broncho-pneumonia. According to Warthin¹³ certain cases have recovered by forced feeding. The symptoms may be grouped under three headings (i) nutritional, (ii) cutaneous, (iii) nervous.

(i) Anorexia is constant and extreme.

(ii) The rash appears at the same time as the other symptoms. It begins as a diffuse erythema over the trunk but more especially on the extremities; the hands, feet, cheeks, nose and forehead are all affected. The skin becomes red and swollen though there is no pitting on pressure. The redness is followed by a fine desquamation especially on the palms of the hands and soles of the feet. The extremities appear extremely irritable, the child continually scratching and tearing at them, while if the face irritates he rubs it into the pillow in a burrowing manner, so that the tip of the nose becomes bright red. Ulceration of the tongue or buccal mucosa is common, but rarely extensive. The hair usually falls out in patches or is pulled out by the child, leaving large bald areas. In rare cases the nails become loose or drop off.

(iii) Although there is no evidence that the mentality of the child becomes affected he is extremely miserable and irritable: insomnia is a constant symptom. The movements are slow and there is great hypotonia of the muscles. This is shown by the lower jaw hanging down so that the mouth is open, an appearance aptly described as that of 'a young gosling.' There is no actual motor paralysis but sensation over the extremities appears to be diminished. The reflexes are either diminished or absent. According to Paterson and Greenfield⁹ the attitude in bed is most characteristic. The child who from the first seems to show dislike of the light, keeps the face turned to the pillow. The body is in a crouching attitude, the back being curved and the knees drawn up. If the child should sit up in bed he keeps up continual movements with the upper extremities and upper part of the body. A curious mouse-like odour has been noted in most cases. There is a constant leucocytosis of from 15,000 to 40,000.

Pathological Changes. Comparatively few post-mortem examinations have been made but the most important findings are atrophy of the lymphoid tissues and changes in the skin, nervous system and muscles. Warthin¹³ states that in the thymus and spleen there is a reduction of the lymphoid tissue, while the Peyer's patches and solitary glands of the intestine also exhibit a decrease in lymphocytes. Broncho-pneumonia is usually the actual cause of death.

The same observer found in the skin a reticulo-endothelial proliferation about some of the small nerve trunks, the sweat glands and hair follicles. The epidermis was hyperplastic with definite hyperkeratosis. The papillæ were enlarged and lengthened, and the capillaries of the papillæ dilated, the endothelium being swollen. The peri-vascular reticulo-endothelium was hypertrophied. Butler³ found hyperkeratosis but no parakeratosis or acanthosis. The cells of the granular layer exhibited ballooning. In the corium there was considerable œdema and a lymphocytic infiltration.

Byfield⁴ found that in the spinal cord an occasional nerve cell in the anterior horn had undergone degeneration. Some œdema was present in the sensory roots and in the myelin sheath of the sciatic nerve.

Warthin found that the main changes in the nervous system consisted of congestion and cedema of the meninges of the brain and cord, with proliferation of the reticulo-endothelial cells. Paterson and Greenfield described very definite lesions both in the central and peripheral nervous systems. In the peripheral nerves there was a considerable myelin destruction in some fibres of the peripheral nerves, increasing in degree and extent on passing to the peripheral parts of the nerves. In the central nervous system there was diffuse increase of small cells in the grey matter especially in the lumbo-sacral enlargement of the cord. The nerve roots also showed some cellular increase, but very little meningeal or perivascular exudate was found. In one case there were grave changes of the motor nerve cells of the ventral horns, particularly in those supplying the distal portions of the limbs. These changes consisted in moderate perinuclear chromatolysis with eccentricity of the nucleus, and the presence of large vacuoles in the cytoplasm of the cells. In the muscles there was considerable atrophy of the fibres, an excess of sarcolemma nuclei and an increase in the cellular content of the connective tissue septa.

By kind permission of Dr. Donald Paterson under whose care at the Hospital for Sick Children, Great Ormond Street, the child was, the courtesy of the Medical Superintendent of the North-Western Fever Hospital, where she died following an attack of measles, and the kindness of Dr. J. G. Greenfield who performed the autopsy and thereafter placed the pathological material at our disposal, we are able to refer to the pathological findings in a recent fatal case of Swift's disease.

The child, a girl, aged 1 year 7 months at the time of death, had been seen five months previously at Great Ormond Street by Dr. Paterson, who diagnosed her condition as a typical mild case of Swift's disease. There had been no definite nervous symptoms, the main complaints being those of restlessness and loss of appetite. The hands and feet were at that time the pink colour characteristic of the condition, but the general state of the child was not bad enough for institutional treatment. Five months later she developed measles and was admitted to the North Western Fever Hospital, where she died in April, 1928, of broncho-pneumonia.

At the autopsy extensive broncho-pneumonia was present in both lungs and in addition, both lungs contained minute caseous tubercles, grouped mainly around the hilus. The peri-bronchial lymph glands were infiltrated with tubercles, which showed early caseation on microscopic section. The heart was healthy except for two small nodules of atheroma at the base of the aorta. The liver showed early cloudy swelling. The kidneys were very congested, and microscopically the Malpighian bodies were enlarged. The tongue had a normal appearance macroscopically, but microscopically there was a slight excess of fibrous tissue throughout, with wasting of the muscle. The epithelium however was intact. The thyroid had the normal infantile appearance.

The brain and spinal cord were removed and fixed in formol saline. Portions of the gastrocnemius and triceps muscles and of the ulnar, radial, sciatic, phrenic and vagus nerves, the cervical sympathetic ganglia and the abdominal sympathetic chain were taken for section. The following staining methods were employed. Toluidin blue for Nissl granules in the brain and spinal cord, hæmatoxylin with van Gieson's counterstain, Marchi-Busch, Weigert-Pal, Bielschowsky and the Victoria blue method for neuroglia.

Above the level of the medulla, the brain appeared quite normal. In the medulla, there was a slight diffuse infiltration with small round cells, extending throughout the white and grey matter. These small cells somewhat resembled small neuroglial cells, but the neuroglia stain did not show any increase in the number of neuroglial fibres. In the spinal cord, the same infiltration was noted. It was most extensive in the grey matter of the cord and extended

along the posterior roots for some distance. The anterior roots were unaffected. The infiltration was more severe in some regions of the cord than in others. It was greatest in the eighth cervical, first and second dorsal segments and in the lumbo-sacral region. The mid-dorsal region was practically unaffected.

By the toluidin blue method the anterior horn cells appeared to be healthy for the most part. In the eighth cervical segment, the postero-lateral group of cells were seen to be rather pale. One or two of the cells in this group had eccentric nuclei and in one cell early vacuolation was seen. In the lumbo-sacral region some of the cells in the anterior horn were rounded and stained more faintly than normal, but their nuclei were central, so that the cellular change was a very early one.

Marchi and Bielschowsky preparations of the spinal cord were negative. No changes could be found in the cauda equina.

In the peripheral nerves, at first sight it seemed as though there were some demyelination of the median nerve and one of the branches of the sciatic, but both these nerves normally contain a large number of non-myelinated, sensory fibres and on comparing the median nerve with that of a normal child, no difference could be noted. All other nerves appeared well myelinated by the Weigert-Pal method.

There was no evidence of myelin degeneration by the Marchi method in any of the peripheral nerves except in one branch of the sciatic, where there was some swelling and globulation of a few nerve fibres, with some slight patchy blackening. It was difficult to be certain that this was true degeneration and not an artifact. The nerves in the muscles appeared well myelinated.

The muscles were small in bulk, but the individual fibres were not unduly wasted. They were a little smaller than normal, but had preserved their polygonal shape. There was no increase of connective tissue or fat, and the sarcolemmal nuclei were not increased in number.

The cervical sympathetic and abdominal sympathetic ganglia showed few deviations from the normal. A few cells appeared distorted in shape and had eccentric nuclei, but the majority appeared healthy. Some of the capsule cells had proliferated, but whether this was pathological is open to question. There was no cellular infiltration in the ganglia and no increase in interstitial tissue. The carotid ganglion was normal.

The slight changes in the nervous system in this case are not surprising when it is remembered that the case was clinically a mild type of the disease. The outstanding lesion, the small celled infiltration of the spinal cord corresponds exactly in extent, though in a lesser degree, with that described by Greenfield and Paterson in their three cases. This case would seem to suggest that the primary lesion is in the spinal cord and that the changes in the peripheral nervous system are secondary.

THE PREVENTION AND CURE OF 'PINK DISEASE' IN THE RAT.

Boas in a survey of some of the commoner food stuffs capable of preventing 'pink disease' in the rat found that raw potatoes, yeast but not marmite, raw white of egg and egg yolk were all capable of preventing the onset of the condition. These results have been confirmed. Cow's milk, however, is not very potent. Experiments which will be published elsewhere indicate that a daily ration of more than 5 c.cm. of summer milk is necessary to cure 'pink disease' in the rat. By far the most rapid cure is obtained by adding raw liver to the diet.

DISCUSSION.

The experiments here brought forward fully confirm the findings of Boas that when dried egg-white is fed to young rats as the sole source of protein there results a syndrome characterised by nervous and cutaneous symptoms.

The fact that the same disease may be produced by feeding the mothers on dried egg-white as the sole source of protein suggests that in the drying process some essential dietetic factor is destroyed in the egg-white, rather than that a toxic substance is formed. If the existence of a hitherto unknown dietetic factor is postulated, there is a close analogy with the known occurrence of the deficiency diseases, beriberi and scurvy in infants fed at the breast.

Investigation of the pathological changes occurring in young rats fed on dried egg-white shows that very characteristic changes occur in the central nervous system. These pathological changes still further emphasize the similarities of the condition in the rat to Swift's disease in man. These similarities may be thus briefly summarised :—

- (i). Both diseases occur in young animals. Swift's disease has never been recorded in adults, while in the adult rat it is only after from three to five months that cutaneous lesions can be produced.
- (ii). The diseases may occur on a diet of mother's milk or a ration containing ample supplies of the known vitamins.
- (iii). The clinical symptoms of both diseases are nutritional, nervous and cutaneous.
- (iv). In rats there is a characteristic 'kangaroo' position, in children a knee-elbow position.
- (v). In rats and children there is a curious mousy odour.
- (vi). Death is often due to an intercurrent broncho-pneumonia.
- (vii). There is no evidence that the diseases are due to an infection with bacteria or ultramicroscopic viruses.
- (viii). The pathological changes in the skin and nervous system are similar.

Although the possible formation of a toxic substance during the drying of egg-white cannot be excluded the experimental evidence here brought forward strongly suggests that for the normal nutrition of both young and adult rats a factor is required in addition to the known vitamins. If Swift's disease in man is identical with this new syndrome in the rat then this new factor must also play a part in human nutrition.

REFERENCES.

1. Andrews, V. L., *Phillip. J. Sci.*, Manila, 1912, VII, 67.
2. Boas, M. A., *Biochem. J.*, Camb., 1927, XXI, 712.
3. Butler, J., *Arch. Dermat. & Syph.*, Chicago, 1925, XI, 166.
4. Byfield, A. H., *Am. J. Dis. Child.*, Chicago, 1920, XX, 347.
5. Denton, J., *Am. J. Path.*, Boston, 1928, IV, 341.
6. Findlay, G. M., *J. Path. & Bact.*, Edinb., 1928, XXXI, 353.
7. Ingier, A., *J. Exp. Med.*, N.Y., 1915, XXI, 525.
8. McCollum, E. V., Simmonds, N., & Pitz, W., *J. Biol. Chem.*, N.Y., 1915, XXIX, 521.
9. Paterson, D. H., & Greenfield, J. G., *Quart. J. Med.*, Oxf., 1923, XVII, 6.
10. Stern, R. O., & Findlay, G. M., *J. Path. & Bact.*, Edinb., 1929, XXXII, 63.
11. Swift, H., *Australian Med. Congr.* (1915) *Childrens' Sect.* (quoted by J. A. Wood, *Med. J. Australia*, Sydney, 1921, I, 145.)
12. Thursfield, H., & Paterson, D. H., *Brit. J. Child. Dis.*, Lond., 1922, XIX, 27.
13. Warthin, A. S., *Arch. Path. & Lab. Med.*, Chicago, 1926, I, 64.
14. Weston, W., *Arch. Pediat.*, N.Y., 1920, XXXVII, 513.