SOME SKIN MANIFESTATIONS IN HYPOPARATHYROIDISM

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A complex disease picture prevalent in this country has been traced (Spira, 1928) to the protracted ingestion of drinking water derived from the tap, and of food prepared in aluminium cooking utensils. No indication could at that time be given of the exact irritant, beyond stating that a mineral or metal seemed to be involved. Further observation revealed a frequent association with paraesthesiae affecting the hands and fingers, especially those supplied by the dorsal cutaneous branch of the ulnar nerve. The feet were affected to a lesser extent. Since there is, in the present state of our knowledge, only one poison which affects the ulnar nerve, namely, fluorine, Spira (1933) concluded that it may be this halogen which was one of the aetiological factors concerned. It was the widespread occurrence of mottled teeth in this country (Spira, 1942*a, b*), known to be produced by a drinking water with a content of not less than 1 part of fluorine per million parts of water (1 p.p.m.), equivalent to gr. 1/120 of fluorine to a pint of water, ingested during the period of calcification of the teeth, which helped to establish the fact that it is indeed fluorine which is the causative agent producing signs and symptoms of a hitherto obscure origin.

Mottled teeth have already been recognized by various writers as bearing a striking resemblance to a dental lesion produced by Erdheim (1906, 1911) in his parathyroidectomized rats. Independently, however, of this important finding, Spira (1942*c, d*) appears to have been the first, so far as can be ascertained, to draw attention to the frequent co-existence of mottled teeth with dystrophies of other organs of ectodermal origin, namely, the skin and its appendages, the nails and hair. As all these organs are regulated by the parathyroid glands, and also because frequent attacks of paraesthesiae are known to be pathognomonic of hypoparathyroidism, he came to the conclusion (Spira, 1942*c, d*) that, in the protracted action of fluorine, the parathyroids are vitally involved. The disease picture of chronic fluorine poisoning (fluorosis) has thus been established to be identical with that produced by Erdheim (1906, 1911) in his experimental parathyroidectomy (tetania parathyreopriva).

On further study of the symptomatology of fluorosis, Spira (1946, 1947) found, in perfect harmony with well-known facts concerning the relationship of the vegetative nervous system with

the endocrine apparatus, that there is a close association between the parathyroids and the vegetative nervous system. It is as yet impossible to state whether it is the sympathetic or the parasympathetic which is primarily involved when this association is disturbed by the action of fluorine. It is, however, likely that it is the disturbance of the equilibrium of the two great divisions of the vegetative nervous system, which brings about a decreased function of the parathyroid glands, with subsequent disturbance of the calcium metabolism of the body. The solution of the all-important problem whether it is the vegetative nervous system alone which is attacked by fluorine, or whether some higher part in the central nervous system is attacked first, must be left to further research. Lachmann (1941) suggests the possibility that in the process of hypoparathyroidism a calcium-regulating centre in the brain is involved.

Fluorine may be found in many media. It may be present in the soil as a natural constituent and find its way into the water. Spira (1943*b*) has shown that the filter powder frequently employed in this country to purify, by means of metal filters, water derived from rivers, lakes, ponds, etc., may contain fluorine as an impurity, and thus affect the drinking water. The iron and cement tanks, and the pipes conducting the water from its source to the tap from which it is drawn for drinking and cooking purposes, may all contain fluorine as an impurity. In the production of aluminium cooking utensils the mineral cryolite of the chemical composition Na_3AlF_6 (or $3\text{NaF} \cdot \text{AlF}_3$), which after purification contains roughly 50% fluorine, is employed as an essential raw material. In the process of preparing food the aluminium is readily corroded by both acids and alkalies, with the result that the fluorine compounds contained therein are set free and contaminate the food.

Since the appendages of the skin, namely, the teeth, nails and hair, have been clinically found to be damaged through the protracted action of toxic amounts of fluorine upon the vegetative nervous system, with subsequent involvement of the parathyroid glands (Spira, 1942*c, d*, 1943*a*, 1944*a, b*, 1946), the question arose as to how the skin itself reacts in the process of hypoparathyroidism. The object of the present paper is to record the results of clinical observation on such dermatoses as were found frequently, though not invariably, to

accompany signs and symptoms of chronic fluorine poisoning; and also to discuss certain skin diseases which were for a long time, even before the subject of the deleterious action of fluorine came under closer scrutiny, believed to be due to parathyroid insufficiency which in turn leads to a reduction of the calcium content of the body. The ectodermal lesions concerned are in the main characterized by mottling of the teeth, mottling of the nails, and by alopecia.

In the course of investigating great numbers of apparently healthy young men and women in this country for any effects of hypoparathyroidism caused by the protracted ingestion of toxic amounts of fluorine (Spira, 1942*a, b, c*, 1944*b*), seborrhoeic dermatitis over the typical areas in the interscapular region and over the sternum has been found to be a common occurrence. It was often a matter of surprise to observe with what resigned indifference the victims looked upon their skin disease, so long as it was not causing them too much inconvenience. The incidence was considerably greater amongst the males than amongst the females. A similar divergence in the degree of alopecia, so prevalent in this country, between the sexes has been tentatively explained (Spira, 1946) by the possibility that smaller quantities of fluids containing toxic amounts of fluorine may have been ingested by females, rather than by the possibility that the ovarian hormones act in an antagonistic manner upon the function of the parathyroids.

Probably no dermatological problem has ever been studied more extensively than seborrhoeic dermatitis. Yet the knowledge of its aetiology is as scanty as that of the great majority of other skin affections. Whilst, in this era of bacteriology and parasitology, the condition is still widely held to be due primarily to an infection (Dowling, 1939), evidence is accumulating to show that the old conception of 'seborrhoeic diathesis' is being revived. Barber (1929) emphasizes that the condition is the result of a faulty metabolism, the effects of which are not only visible on the skin, but produce such systemic disturbances as gingivitis, chronic nasopharyngeal catarrh with frequent exacerbations, marked hypertrophy of the lymphoid tissue, and flatulence. According to him, this faulty metabolism causes an alteration in the secretion and composition of the cutaneous fat, thus producing an environment which enables harmless saprophytes normally inhabiting the skin to become parasites. It is noteworthy that the same author (Barber, 1921*a, b*) adduces most of the features shown by him to be characteristic of 'seborrhoeic diathesis' as belonging also to the syndrome of alopecia areata.

Ingram (1939) denies that micro-organisms play any important rôle in producing seborrhoeic skin lesions. He states that the seborrhoeic diathesis

manifests itself in a great variety of changes. Apart from the characteristic eruptions, vasomotor instability leads to perniosis and chilblain development. There is an increased susceptibility to infections such as boils, pustules and carbuncles, perionychia and fissures. Changes in the mucous membranes of the upper respiratory tract leading to chronic catarrh, bronchitis and asthmatic disorders, rhinorrhoea and hay fever, infected antra and other sinuses, pyorrhoea and gingivitis, and so-called 'soft teeth', all belong to its symptomatology. Dyspepsia, flatulence and chronic constipation are its outstanding features.

Since all these signs and symptoms were shown to constitute the disease picture of chronic fluorine poisoning (Spira, 1942*c*, 1944*a, b*), it appears that fluorosis and 'seborrhoeic diathesis' are identical conditions, and that it is the fluorine which is at the root of the diathesis. Any infection present is of a secondary nature (Spira, 1944*a*), and is brought about by the tissues having become less resistant to an attack by endogenous or exogenous agents, when their calcium content has fallen below the normal level. It is a well-established fact that the action of this halogen consists in precipitating calcium salts, which are stored in the body as a material indispensable for sustaining the vitality of most of the organic functions, and substituting sodium or potassium for the calcium which has been removed. It is suggested that Barber's (1929) conception of a faulty metabolism as a cause of 'seborrhoeic diathesis' can now be narrowed down to denote a faulty calcium metabolism as the *fons et origo* of the condition. Thus, contrary to the time-honoured explanation, it may be not the seborrhoea which causes the dermatitis, the eczema, and such dystrophies as seborrhoeic warts, seborrhoeic alopecia, etc., but fluorine which, in its ultimate effect, simultaneously damages some or all of the organs of ectodermal origin, the skin as well as its appendages, the teeth, nails and hair. Buschke (1911) describes seborrhoea on the bridge of the nose, Kerley (1930) and Fleischmann (1931*a, b*) seborrhoea capitis, and Schwarz (1935) an impetiginous rash over the scalp in association with ectodermal dysplasias, and Lévy-Francé & Juster (1926) incriminate the disturbance of the sympathetic and endocrine systems in the aetiology of seborrhoea. In Roholm's (1937) series of sixty-eight cryolite workers, eight men (11.8%) were affected by a rash on the upper part of the chest and back, consisting of chronic folliculitis with a varying degree of suppuration, scars and pigmentation.

In view of the fact that chemically fluorine belongs to the group of halogens, two other members of which, namely, bromine and iodine, are known to produce, amongst other diseases acne vulgaris, it is reasonable, in the absence of these halogens, to

assume that the frequent occurrence of this chronic inflammatory disorder involving the sebaceous glands is, in a country in which fluorosis is endemic, attributable to the protracted action of toxic amounts of fluorine. Tendlaw (1902), Wheelon (1925), MacQuaide (1944) and Spira (1947) found an association of acne with ectodermal dystrophies, and Richter & Herzfeld (1932) recorded two cases of toxicodermias produced by iodine and arsenic respectively, which were cured by the administration of parathyroid extract. Dermatology is also familiar with those numerous cases of dermatitis affecting the beard region and designated seborrhoeic sycosis barbae, an eruption which is often refractory to every form of local treatment. A few such cases, unsuccessfully treated at various skin hospitals for several years by means of local applications only, were permanently cured within 6-8 weeks, mainly by a régime directed against chronic poisoning by an irritant contained in the drinking water and aluminium cooking utensils, any additional local treatment having played only a secondary rôle. In his experiment on two dogs, extending over a period of 587 and 626 days respectively, Roholm (1937) administered perorally daily doses of cryolite to one of them, and sodium fluoride to the other. Towards the close of the experiment a scaly and itchy dermatitis developed in both animals on the facial skin, especially around the mouth.

Gaul (1937), in studying the elemental constituents of psoriatic lesions, administered sodium fluoride in doses varying between 0.05 and 0.125 g. to patients suffering from psoriasis vulgaris. He states that this resulted, after a week or 10 days, in the development of a pustular dermatitis on the area generally affected by seborrhoea, and that the eruption was indistinguishable from that following the ingestion of bromides and iodides.

It is known that the increased sebum excretion is frequently associated with hyperhydrosis. In fact, seborrhoeic dermatitis is by some believed to be the result of an interaction of sebum and sweat. The following case, however (Spira, 1947), which I attributed to the action of fluorine begun already in intra-uterine life, demonstrates the fallacy of this conception. A man, 31 years old, suffered from congenital ectodermal dysplasia with involvement of the skin and its appendages, the hair, teeth and nails. His chief complaint was intolerance to heat due to inability to perspire. Even intravenous injection of 7.5 mg. (0.0075 g.) of pilocarpine hydrochloride succeeded in producing no more than small glistening beads of sweat on his forehead and frontal scalp, but none on any other part of the body. Yet, over his sternum and between the shoulder blades and in the scalp follicular seborrhoeic dermatitis was present, with occasional areas

of acne. There was also follicular hyperkeratosis over the chest and back.

It has been recently suggested (Sayer, 1942) that the seborrhoeic dermatoses are an external manifestation of a syndrome caused by vitamin B deficiency. Pillsbury & Sternberg (1937) draw attention to the close relationship which exists between vitamins, hormones and the vegetative nervous system. Spira (1944*b*), too, quotes several authors whose experimental work led to the conclusion that vitamin D and parathyroid extract not only act in a similar manner upon the calcium metabolism, but are also capable of replacing each other, should the body be deprived of either of them for any reason.

An inspection in this country of the feet of 850 men and 850 women (Spira, 1944*b*) revealed the fact that as many as 62 % of the former and 55 % of the latter were afflicted with a condition known as 'dhobi-itch'. The degree of the affliction was variable, and the disorder at one time or other incapacitating. Since the eruption was frequently associated with ectodermal dystrophies and other signs of chronic fluorine poisoning, Spira (1942*c*, 1944*b*) suggested that 'dhobi-itch' is another manifestation of fluorosis, and that any fungus that may be found should be looked upon as a secondary infective agent.

'Dhobi-itch' was often found to be associated with a similar eruption on the hands and fingers known as dysidrosis and cheiropompholyx, an association which has also been emphasized by Dowling (1932). Like 'dhobi-itch', dysidrosis has for many years been held to be due to an infection by a fungus. Darier (1919) goes so far as to state that 'the dysidrosiform eruptions are mostly, and probably always, of mycotic origin and due to the epidermophyton'. Since, however, a mycelium could in many cases not be detected, these dermatoses have been divided into at least two groups, namely, epidermophytosis and occupational dysidrosiform eruptions. Industrial medicine is, no doubt, acquainted with the fact that cheiropompholyx occurs frequently amongst cement workers. Spira (1943*b*) examined several samples of the ingredients employed in the process of cement mixing, such as 'clay', 'chalk', 'lime' and 'cement', before tap water has been added to mix the concrete, and found that some of them contained fluorine. In his view, cheiropompholyx which attacks susceptible cement workers is attributable to their handling such ingredients as contain fluorine as an impurity. Burckhardt (1938), in discussing the aetiology of the cement- and chalk-eczema encountered in plasterers, states that skin tests with various cements, chalk, and ingredients of cement on healthy skins may produce in every person a reaction which, both clinically and

histologically, is an eczema. He holds that the cement-and-chalk-eczema is in most cases a toxic, not an allergic, manifestation. In view of the frequently expressed belief that dysidrosis is sometimes associated with excessive sweating, and therefore due to a disease of the sweat apparatus, it is interesting to note that Spira's (1947) patient suffering from 'congenital ectodermal dysplasia of the anhydrotic type' was found to have recurrent attacks of cheiropompholyx, although biopsy of the skin taken from one of his fingers revealed absence of sweat glands and the pilocarpine test failed to produce sweat at his finger tips.

Cheiropompholyx, however, frequently affects also people whose occupation does not bring them into contact with any of these or other minerals which might act as irritants on their fingers and hands. Moreover, the symmetrical distribution of the affected parts also in this group of victims of the disease is an additional reason for the belief that the eruption is of a central origin. Both the frequent co-existence with each other and with the dystrophies of the teeth, nails and hair, singly or in combination, and the similarity in the appearance of the dermatoses seem to indicate that 'dhubi-itch' and cheiropompholyx are identical, and that they are external manifestations of a systemic disease. Dowling (1932) draws attention to the well-recognized fact that seborrhoeic eczema of the scalp and other parts may be accompanied by an eruption of the palms and soles, identical with dysidrosis.

Darier (1919) states that the victims of cheiropompholyx are almost always dyspeptic, neurasthenic and depressed, and Mitchell (1929) found that in dysidrosis a history of furunculosis and of severe pustular paronychia is common. Milian & Périn (1921) found an association of dysidrosis with malformation of the teeth, with mottled teeth, and with the ear lobules attached to the sides of the face. Darier (1921), Sabouraud (1921), Scheuermann (1938) refute the suggestion, made by Milian & Périn (1921), of a syphilitic origin of dysidrosis, and Darier (1919), Sabouraud (1921) note a frequent co-existence of intertrigo (Hebra's eczema marginatum) with dysidrosis.

Spira (1928) attributed cheiropompholyx to the protracted ingestion of an irritant contained in drinking water and aluminium cooking utensils. He recorded a case of this affection which occurred, in addition to a papular eruption on the forehead and to rectal haemorrhage and albuminuria, in a newborn child delivered by Caesarean section of a woman suffering from eclampsia.* Since cheiro-

pompholyx was found by him frequently to be co-existent with ectodermal dystrophies and other signs and symptoms of chronic fluorine poisoning, he suggested that cheiropompholyx, too, is caused by the protracted ingestion of toxic amounts of fluorine. He reported (Spira, 1928, 1933, 1942*c*, *d*, 1944*b*) that several cases of cheiropompholyx, including his own, which for a long time failed to respond to any method of local treatment, yielded promptly within a few weeks to a régime based chiefly on avoiding food prepared in aluminium cooking utensils, substituting a pure and wholesome drinking water for tap water, and eliminating the amount of poison accumulated in the body by an effective adsorbent (charcoal) and an aperient. Scheuermann (1938), too, obtained good results in some cases of haematogenous toxic dysidrosis by means of a protracted administration of an aperient and charcoal.

A disturbance of the sympathetic and endocrine systems in dysidrosis has been stressed by Lévy-Franckel & Juster (1926), and the importance of the association of the vegetative nervous system with the endocrine apparatus as a factor in the causation of dysidrosis is also emphasized by Leszczynski (1929*a*). In his view, the equilibrium of the vegetative nervous system is disturbed in dysidrosis either by the tonus of the sympathetic being increased or by that of the parasympathetic being decreased.

In discussing vesicular eruptions of the hands and feet, Lehmann (1930) states that in dysidrosis internal influences are important predisposing factors. He observed a frequent association of this dermatosis with hypochlorhydria, with attacks of indigestion and constipation, with bad teeth and pyorrhoea, with rhinitis, and with nervousness and marked tremor of the fingers. He holds that the underlying pathological changes are trophic in nature, and governed by the sympathetic nervous system. Administration of calcium lactate, and thyroid and parathyroid extracts proved distinctly helpful in his case.

Cumming (1876), quoted by Leszczynski (1929*a*) and Dowling (1932), considers cheiropompholyx to be a sign of gout because the fingers are thickened in a fashion similar to that seen in arthritis, and Kémeri (1929, 1930*a*, *b*) found a frequent co-existence of dysidrosis with rheumatism, which was caused by a focal infection, such as chronic rhinitis, bad teeth, tonsillitis and tonsillar abscesses. Frey & Orzechowski (1920), who were the first to note an association of otosclerosis with latent tetany, mention peeling of the skin of the palms due to dysidrosis in one of their cases.

changes in some of the parathyroids in cases of eclampsia, and Vassale (1906) obtained good results from the administration of parathyroid gland in the treatment of this condition.

* It is in this connexion of great interest to note that Erdheim (1906) quotes Jeandelize (1903) for the statement that eclampsia gravidarum is due to a disturbance in the action of the parathyroid glands. According to the same source, Pepere (1905) found degenerative

Cheiropompholyx is sometimes accompanied on the mucous membranes by tiny vesicles and pustules which break down to form shallow ulcers and fissures. Ulcerative and aphthous stomatitis, when occurring simultaneously with ectodermal dysplasias, has been shown (Spira, 1944a) to belong to the symptomatology of fluorosis. Those afflicted with 'dhobi-itch' are often found also to be suffering from intertrigo in the groins, axillae and the intergluteal region, a condition designated by the collective name of tinea, although a fungus cannot always be detected. It is this co-existence of the lesions of the hands and feet, and on the mucous membranes, which sometimes renders the differential diagnosis from foot-and-mouth disease difficult.

Attention has been drawn on previous occasions to the frequent occurrence of furunculosis in chronic fluorine poisoning. In surveys of 1099 men and women with mottled teeth in this country (Spira, 1942c) and of 850 men and 850 women examined at random (Spira, 1944b) as many as 324 subjects (29 %) and 533 subjects (31 %) respectively, stated that they had suffered from boils at one time or other. It is noteworthy that of the 533 people in the latter survey no fewer than 368 were men, and only 165 were females. It may be justifiable also in this case to apply the same explanation of the marked divergence in the incidence of furunculosis between the sexes as was given in the case of alopecia and seborrhoeic dermatitis (*vide supra*). The prompt disappearance of furunculosis of whatever extent and duration in an otherwise apparently healthy subject, which is obtained by a régime directed against fluorosis is remarkable. The following is an illustrative case:

Some years ago a patient of mine who was acquainted with my views on the subject advised, without my intervention, his relative abroad who was suffering from intractable furunculosis which had resisted every kind of treatment for a long time, to avoid food prepared in aluminium cooking utensils, if any were used in his household, and to take large doses of charcoal and an aperient. I was subsequently informed by my patient that his relative had, in fact, used aluminium in his kitchen, and that the régime recommended resulted in a prompt cure within a few weeks.

The co-existence of dystrophies of the teeth, nails and hair, singly or in combination, with pathological changes of the skin has been recorded by numerous observers even before ectodermal dystrophies were recognized as forming a distinct group within the disease picture of chronic fluorine poisoning. Foerster (1916), Cooper (1930) and Hutton (1939) recall that in hypoparathyroidism the skin is in many cases secondarily involved, and Richter & Herzfeld (1932) draw attention to the

fact that several dermatoses were recorded to have been successfully treated by parathyroid hormone. Foerster (1916) believes that no one particular dermatosis is characteristic of parathyroid pathology. A careful analysis, however, of the numerous reports on cases in which dystrophies of the teeth, nails and hair were accompanied by dermatoses reveals some regularity in the appearance of certain skin changes. Amongst them the frequent occurrence of keratosis palmaris et plantaris is striking. It has been observed to accompany ectodermal dysplasias by MacKee & Andrews (1924), Tobias (1925), Janitzkaja & Rjabow (1928), Clouston (1929), Bloch & Stauffer (1929), Falconer (1929), Brain (1930), Gordon & Jamieson (1931), Fleischmann (1931b), Bowen (1932), Dodds (1935), Lord & Wolfe (1938), and Young (1944). Lévy-Franciel & Juster (1923, 1926) accuse a disturbance of the sympathetic and endocrine systems, and Spira (1947) a disturbance of the vegetative nervous system and the parathyroids of producing keratodermias. Kraus (1903) and Jadassohn & Lewandowsky (1906) give prominence to this anomaly of keratinization. Thus the frequent occurrence of palmar and plantar keratosis lends further support to the similarity of some of the features in chronic arsenical poisoning on the one hand and chronic fluorine poisoning on the other, a similarity which was emphasized by Spira on several occasions.

The cutaneous lesions associated with ectodermal dysplasias have been reported to be frequently papular in nature. The papular eruption may appear on any part of the body, but is found most often on the face. It was noted by Jadassohn & Lewandowsky (1906), MacKee & Andrews (1924), Jacobsen (1928), Janitzkaja & Rjabow (1928), Weech (1929), Falconer (1929), Gordon & Jamieson (1931), Hill (1933), Dodds (1935), Stephenson (1936), de Silva (1939) and Lowenburg & Grimes (1942). In the patient of Margolis & Krause (1939), who was suffering from tetany following strumectomy, the skin presented numerous dry scaly areas over which there were numerous minute dry papules; with improvement of the tetany the skin has resumed a normal appearance and texture.

The skin lesions in hypoparathyroidism are, however, not always papular in character. The case of Mendes da Costa & Van der Valk (1919) showed a vesicular dystrophy of the skin, and that of Clouston (1929) pustular bullae on the soles of the feet. Furthermore, several writers have noted a similarity between psoriasis vulgaris pustulosa and impetigo herpetiformis. Danbolt's (1937) patient was suffering from impetigo herpetiformis, but seven years later from psoriasis vulgaris complicated by the plaques becoming surrounded by vesicles and pustules, thus turning into a case of psoriasis pustulosa, the clinical course of which was

closely similar to, if not identical with, that of the first eruption.

Schardorn's (1921) two cases of impetigo herpetiformis were associated with tetany resulting from strumectomy. He quotes the various theories concerning the aetiology of this eruption: Hebra who was the first to describe it in 1872, and who incriminated changes due to toxins originating in the uterus during pregnancy as the responsible factor; Dubreuilh who thought that the condition is connected with a predisposition which may remain dormant, but becomes manifest should an occasion arise, such as arises most frequently during pregnancy; du Mesnil who, not being enlightened by the results of microscopical examination, assumed that the dermatosis may be due to a disturbance of the nervous system, since several signs and symptoms accompanying it point in this direction; Dauber who held that some kind of toxæmia is the cause; Tomassoli who, whilst rejecting the mycotic theory as a convenient refuge for many dermatological conditions, believed that we are dealing with a manifestation of a metabolic disturbance, and attributed 'this strange and very rare dermatosis to a peculiar and mysterious form of intoxication which is derived partly from the gastro-intestinal tract, and partly, namely to a larger extent, from the entire body totius substantiae';* Scheuer who expressed the opinion that the noxon, wherever it may come from, produces the features of eclampsia† as well as those of impetigo herpetiformis; and finally Ziemann who stated that 'this is the case of a congenital or acquired debility of some inner-secretory organ which cannot cope with the increased function imposed by the pregnancy. It fails, and causes signs of deficiency or signs of hyperfunction of the antagonistic glands, in any case a disturbance of the endocrine equilibrium', but 'we do not know which organs or which organ is the starting point of the disturbance'.* In Schardorn's (1921) view, the impetigo herpetiformis is an autointoxication caused by a deficiency in the parathyroid function. He quotes Breier who noted an attack of eclampsia† in impetigo herpetiformis.

Walter's (1922, 1927) case of impetigo herpetiformis was associated with osteomalacia. It will be remembered that osteomalacia has been shown by Erdheim (1911) to have occurred in some of his parathyroidectomized rats. Leszczynski (1928) considers impetigo herpetiformis to be an intoxication dermatosis, the result of an endocrinopathy caused in particular by a dysfunction of the parathyroids, and Brill (1928) believes that the condition is intimately connected with a disturbance of the calcium metabolism. Lutz (1928) has brought

about a remission, by the administration of parathyroid, in a case of impetigo herpetiformis complicating tetany which followed strumectomy. Rapp (1931), too, records a similar case, and considers it to be a toxicodermia. Since, amongst other areas, the intertriginous regions were affected, the lesion was first thought to be of mycotic origin, although no fungus could be detected. In Tenlén's (1937) case of impetigo herpetiformis which recurred during three consecutive pregnancies, Chvostek's sign, at first negative, became positive as the condition of the skin grew worse. The child born on the interruption of the first pregnancy died from convulsions two days after birth. In the mother, the pustules disappeared, the impetigo herpetiformis was replaced by exfoliative dermatitis, there was paronychia, and the hair of the scalp, the axillae and the pubic region fell out entirely. A complete regeneration of the skin, nails and hair took place a few weeks later. The attack of impetigo herpetiformis during the third pregnancy was cured by injections of parathyroid extract and calcium, in addition to a gonadotropic hormone from the anterior lobe of the hypophysis, and a healthy child was born at full term. Lachmann (1941) observed impetigo herpetiformis complicating 'idiopathic' hypoparathyroidism.

It is now known (Bruhns, 1924; Bloch, 1926) that impetigo herpetiformis is not limited to pregnancy alone, and that it may affect non-pregnant women and even men as well. Whilst there can be no doubt that each one of the mentioned theories concerning its aetiology is based on very reliable and painstaking observation, it seems reasonable, in view of the recorded additional information available, to suggest that it is the sum of these theories, now further extended by our recent knowledge of the action of fluorine, which appears fully to explain all the aspects of the disease. The target of attack by this highly potent noxon has been thus far clinically traced back to the vegetative nervous system, whose fibres supplying the parathyroid glands seem to be affected so as to produce hypoparathyroidism and reduction of the calcium content of the body. Under normal conditions, and whilst the available calcium supply is sufficient to replace the calcium depot which is being depleted through the action of fluorine, no serious ill-effects will ensue. If, however, the fluorine is permitted continually to enter the body, with the result that the calcium content remains constantly below the normal level, and more especially, if pregnancy supervenes, during which the mother parts with some of her own, already deficient, calcium content so as to share it with the foetus, the chance of impetigo herpetiformis developing in a woman who, moreover, may be particularly susceptible, is just as great as is that of the other ectodermal signs of tetany arising, for

* Translated from the German text.

† Vide supra, p. 96, footnote on eclampsia.

instance brittleness of the nails, loss of hair, etc., which are frequent features even in normal pregnancy (Scherber, 1909).

The similarity between impetigo herpetiformis and pustular psoriasis (a similarity to which Scheuermann (1938) adds certain forms of dysidrosis) assumes significance by the clinical evidence which indicates that both dermatoses are caused by a hypofunction of the parathyroid glands. According to Leszczynski (1928, 1929b, 1931, 1936) psoriasis vulgaris is of endocrine origin. He was the first to draw attention to the fact that it is in many cases associated with a positive Chvostek's sign, which in his series occurred nearly three times as often in patients suffering from psoriasis as in non-psoriatics, thus indicating that the parathyroids are frequently involved; and he stated that the exudative and pustular component complicating the picture is brought about by a superadded damage to the parathyroids. He reports that peroral administration of calcium and injections of parathyroid extract were, in some cases, followed by a remarkable improvement of both the latent tetany and the co-existent impetigo herpetiformis as well as pustular psoriasis. The same result was obtained by Scherber (1938) by appropriate antitetanic treatment.

This similarity is further strengthened by the fact that impetigo herpetiformis may be associated with severe polyarthritis in a manner characteristic of psoriasis arthropathica. Wohlstein (1931) describes a case of impetigo herpetiformis which was complicated by severe arthritis deformans with onychodystrophies and other changes, such as are encountered in endocrine dysfunction. A co-existence of impetigo herpetiformis with severe arthritis deformans, with onycholysis, and with alopecia has also been reported by Buschke & Boss (1931) who state that the similarity of the arthritic changes in impetigo herpetiformis to those of psoriasis arthropathica permits the assumption of a certain aetiological equality in the sense of an endocrine dysfunction which can be ascribed to both these diseases.

In Vohwinkel's (1929) case of psoriasis arthropathica, severe arthritis deformans was accompanied by considerable decalcification of the bones, by total alopecia, and by deformed, brittle and longitudinally striated nails. The sudden and complete loss of hair led him to believe that all these dystrophies may be produced in a manner closely similar to that produced by thallium, that is to say, through the vegetative nervous system and the parathyroid glands. He recalls an observation by Baer (1907) of a rapid and complete cure obtained by intravenous and intramuscular injections of calcium in a case of severe psoriatic arthritis. It should be remembered that Spira (1946), too, showed that

clinically signs and symptoms of chronic fluorine poisoning appear to be identical with those of chronic thallium poisoning, both being traced back to a mode of action through the same channels.

Pruritus and acute and chronic urticaria are well-established signs of fluorosis. Under the name of 'heat-spots' or 'heat-bumps' derived from the popular belief that they are caused by an 'over-heated' blood, urticaria constitutes a frequent complaint amongst the population of this country. Lévy-Franckel & Juster (1926) attribute urticaria to a disturbance of the endocrine and sympathetic nervous systems. Csillag (1930) reports that a case of pruritus which persisted for 15 years showed signs of definite improvement after charcoal was given for not more than 7 days.

From the larger group of urticaria a dermatosis was detached under the name of lichen urticatus (papular urticaria) by Bateman as long ago as 1813, but its aetiology remained obscure until it was observed that the eruption is frequently accompanied by signs and symptoms of a systemic condition. Funk & Grundzach (1894) found it always associated with rickets and digestive disturbances, and in particular with flatulence and severe constipation. Barber (1914) considers this very common disease of childhood to be a manifestation of a 'scrophulous diathesis', in the same way as seborrhoeic eczema is a manifestation of the 'seborrhoeic diathesis'. He believes that the exudative diathesis is perhaps dependent on abnormalities in the ductless glands, and that the association of papular urticaria with a pathological condition of the lymphoid structures, such as adenoids, enlarged tonsils, etc., and also with gastro-intestinal disorder, is too frequent to be coincidental.

The theory of an association of lichen urticatus with a dysfunction of the endocrine apparatus was strengthened by Cornbleet (1929) who was the first to report that subcutaneous injections of parathyroid extract in conjunction with peroral administration of calcium lactate in massive doses were followed, even without any local treatment, by a prompt relief of the pruritus and subsequent disappearance of the papular urticaria. Pillsbury & Sternberg (1937), too, obtained excellent results in their patients with lichen urticatus treated by hypodermic injections of parathyroid extract and peroral administration of calcium lactate or gluconate, in addition to local treatment.

Lichen urticatus has been found by several investigators to occur mostly during the summer months, and Hallam (1927, 1932) includes the disease in the allergic group with hay fever, asthma and infantile eczema. He draws attention to the fact that change of environment has sometimes a remarkable effect on the course of both papular

urticaria and asthma. Kinnear (1933), Gordon (1933) and Tate (1935) reported that the eruption cleared immediately on confining the patient to a hospital, or even on change of residence, whether any therapy was instituted or not, with a rapid recurrence of the lesions on the patient's return home. Gordon (1933) assumed that some cases of lichen urticatus are dermatological neuroses. It would, however, be interesting to investigate whether the pronounced seasonal incidence of the disease is not due to taking, during the summer months, larger quantities of fluids which may have contained toxic amounts of fluorine, and whether the disappearance of the eruption following the removal of the patient to a different environment was not due to a supply of pure and wholesome drinking water in the new locality. Bray (1933) observed that the condition is frequently associated with enuresis, migraine and asthma. The fact that these latter disorders are known to be due to sympathetic-parasympathetic imbalance may perhaps give further support to this new conception of the aetiology of lichen urticatus.

Eczema was observed to accompany the syndrome of ectodermal dystrophies by Montgomery (1916), Pulay (1926), Jacobsen (1928), Bowen (1932), Hill (1933), Lord & Wolfe (1938), Friedman (1940) and Tomasi (1940). Lachmann (1941) records the case of a patient suffering from post-operative hypoparathyroidism, who *sub finem* exhibited a violent eczematous skin lesion. Hutton (1939) states that infantile eczema is probably most often complicated by thyroid and parathyroid insufficiency, with a consequent disturbance of the calcium metabolism. Spira (1933) reported the case of children suffering from infantile eczema which resisted every conceivable method of external therapy for several years, but yielded promptly within 10 weeks to internal treatment aimed at avoiding the chemical irritants contained in the drinking water and aluminium cooking utensils, and eliminating the amount of poison accumulated in the body. This was at a time when fluorine was not yet known to be one of the irritants. He later (1942c) described a case of infantile eczema in a boy who was suffering from asthma as well, and who exhibited both mottled teeth and onychodystrophies as signs of hypoparathyroidism.

Rhagadae at the corners of the mouth (*perlèche*) were noted by MacKee & Andrews (1924), Leszczynski (1928), Weech (1929), Falconer (1929), Broekema (1933) and Schwarz (1935); and paronychia was a prominent feature in the cases of Nicolle & Halipré (1895), White (1896), Murray (1921), Fraser (1927), Thompson (1928), Weech (1929), Hill (1933), Hardwick (1939) and Spira (1943a).

There was extensive lichen pilaris in the patient of Ziegler (1897), and keratosis pilaris with a dis-

turbance of the endocrine and vegetative nervous system in those of Oliver & Gilbert (1926), Gordon & Jamieson (1931), Whittle (1944) and Spira (1947).

Atrophia cutis was an outstanding feature in the cases of Jones & Atkins (1875), Tendlau (1902), Kraus (1903), Christ (1913) and Strandberg (1919). Singer (1921) elicited Chvostek's sign in one of his patients who exhibited atrophy of the skin in association with ectodermal dystrophies, and found a cataract in another, thus establishing the presence of parathyroid insufficiency in both cases.

The patients of Tobias (1925) and Wende (1926) with ectodermal dysplasias were affected by epidermolysis bullosa, and Hesse (1930) and Pinter (1930) reported that their patients suffering from epidermolysis bullosa exhibited onychodystrophies. In Drosdek's (1930) case there was an association of epidermolysis bullosa with palmar and plantar hyperkeratosis. Kerl (1930) recorded a case of this dermatosis complicated by onychodystrophies (pitting, onychorrhexis, Beau's lines, onychatrophy); administration of calcium prevented further development of bullae. Schwartz & Levin (1923) obtained a distinct improvement in a child suffering from epidermolysis bullosa by giving calcium lactate and parathyroid extract.

Sellei (1931, 1932) obtained good results in the treatment of chronic alimentary urticaria, Quincke's angioneurotic oedema, dysidrosis (eczema dysidroticum) and eczema intertrigo by means of hypodermic injections of parathyroid extract and peroral administration of calcium. He recalls that calcium has a sedative action on the vegetative nervous system, and that the improvement which follows the calcium therapy, in addition to a fungicide applied locally in those cases in which a fungus can be detected, is due to the fact that the nature of the soil which was fertile for the growth of the fungus has thereby been changed into one on which it cannot thrive so easily.

Like Sellei (1931, 1932), Richter & Herzfeld (1932) succeeded by means of parathyroid hormone in effecting a cure in cases of chronic urticaria which had resisted every method of treatment for a long time. They obtained good results also in some cases of chronic eczema which was caused by a disturbance of the vegetative nervous system, and a case of acne rosacea responded promptly to the administration of parathyroid extract.

The controversy concerning the question of whether a dermatosis is to be regarded as an affection of the skin *per se*, in the same way as a disorder of any other organ is regarded, or whether it should be looked upon as an external manifestation of a pathological condition within the body, continues unabated. So far the progress towards a better understanding of the pathogenesis of skin

diseases has been insignificant. Nor has Pirquet's conception of 'allergy', originally understood to denote nothing but an abnormal reaction to a foreign protein, but now extended in many directions to replace and to include the old conception of 'sensitiveness', 'susceptibility' or 'idiosyncrasy', helped to solve the difficult problem. The knowledge of sensitiveness to certain substances introduced into the body through the gastro-intestinal tract, such as drugs, some articles of food, etc., dates from time immemorial. It was, however, only when American investigators established the fact that the protracted ingestion of small amounts of fluorine, the element which alone amongst the group of the halogens succeeded in escaping the attention of scientific research, is capable of producing considerable damage, that hope was revived of finding the aetiology of certain morbid processes. Since, in particular, the skin and its appendages were the first tissues found to be affected by the action of fluorine, it may be justifiable to claim for dermatology that, being now itself relieved to some extent of the onerous task of bringing light into darkness, it will be able to help other branches of medicine better to understand the pathogenesis of various conditions within the body. The presence of certain dermatoses and of dystrophies of other organs of ectodermal origin indicates at a glance that the calcium metabolism of the body is disturbed. This fact alone should be able clinically to determine, as no ancillary method of examination can, that any co-existent disorder may be caused by the same factor. There can be no doubt that, on affecting the surface of the body through the nerve

distribution and the blood circulation, fluorine may affect internal organs as well, thus pointing to the close relationship which may exist between any co-existent morbid states. Moreover, in view of the fact that some skin lesions have already been clinically ascertained to be aetiological closely related to a disturbance of the vegetative nervous system and the parathyroid glands, it seems reasonable to suggest that other dermatoses may also be produced in the same way. In addition, since lesions caused by fluorine seem to bear a striking similarity to those produced by other noxa of a chemical nature, namely, arsenic, thallium, bromine and iodine, the probability should be kept in mind that there may be some more chemical substances which are capable of causing damage in a like manner.

The opinion of Reede (1918) is, above all, here worth recalling: 'I believe that oftentimes within reach of the dermatologist lies the key which may unlock the secret of an illness which is much more extensive than the skin lesion, and that it is the duty of the dermatologist always to endeavour to find the underlying causes of skin diseases.'

Note: Since the completion of this paper, Dowling, G. B., Thomas, E. W. P. & Wallace, H. J. (*Proc. Roy. Soc. Med.* 1946, **39**, 225) and Dowling, G. B. & Thomas, E. W. P. (*Lancet*, 1946, **1**, 919) have reported favourable results obtained in long-standing cases of Lupus vulgaris by the method of M. J. Charpy (*Ann. Derm. Syph., Paris*, 1943, **3**, 331 and 1944, **4**, 110, 331), which is based on the administration of large doses of calciferol.

REFERENCES

- BAER, T. (1907). *Arch. Derm. Syph., Wien*, **84**, 15.
 BARBER, H. W. (1914). *Practitioner*, **93**, 820.
 BARBER, H. W. (1921a). *Guy's Hosp. Rep.* **71**, 112.
 BARBER, H. W. (1921b). *Brit. J. Derm.* **33**, 1.
 BARBER, H. W. (1929). *Lancet*, **2**, 363.
 BLAISDELL, R. H. & CUNNINGHAM, A. R. (1917). *Boston Med. Surg. J.* **176**, 210.
 BLOCH, B. (1926). *Schweiz. Med. Wschr.* **7**, 753.
 BLOCH, B. & STAUFFER, H. (1929). *Arch. Derm. Syph., Chicago*, **19**, 22.
 BOWEN, R. (1932). *South. Med. J.* **25**, 481.
 BRAIN, R. T. (1930). *Proc. Roy. Soc. Med.* **23**, 163, 1482.
 BRAY, G. W. (1933). *Brit. J. Child. Dis.* **30**, 180.
 BRILL, E. (1928). *Derm. Z.* **53**, 70.
 BROEKEMA, J. H. (1933). *Acta derm.-venereol., Stockh.*, **14**, 113.
 BRUHNS, C. (1924). *Arch. Derm. Syph., Wien*, **148**, 489.
 BURCKHARDT, W. (1938). *Derm. Wschr., Lpz.*, **106**, 288.
 BUSCHKE, A. (1911). *Arch. Derm. Syph., Wien*, **108**, 27.
 BUSCHKE, A. & BOSS, A. (1931). *Derm. Wschr., Lpz.*, **93**, 1394.
 CHRIST, J. (1913). *Arch. Derm. Syph., Wien*, **116**, 685.
 CLOUSTON, H. R. (1929). *Canad. Med. Ass. J.* **21**, 18.
 COOPER, Z. K. (1930). *Arch. Derm. Syph., Chicago*, **21**, 1007.
 CORNBLEET, T. (1929). *Arch. Derm. Syph., Chicago*, **19**, 281.
 CSILLAG (1930). *Derm. Wschr., Lpz.*, **91**, 1877.
 CUMMING (1876). Quoted by Leszczynski (1929a).
 DANBOLT, N. (1937). *Acta derm.-venereol., Stockh.*, **18**, 150.
 DARIER, J. (1919). *Lancet*, **2**, 578.
 DARIER, J. (1921). See Milian & Périn (1921).
 DE SILVA, P. C. C. (1939). *Quart. J. Med.* **8**, 97.
 DODDS, L. (1935). *Med. J. Aust.* **1**, 715.
 DOWLING, G. B. (1932). *Brit. Med. J.* **1**, 142.
 DOWLING, G. B. (1939). *Brit. J. Derm.* **51**, 1.
 DROSDEK (1930). *Derm. Wschr., Lpz.*, **91**, 1135.
 ERDHEIM, J. (1906). *Mitt. Grenzgeb. Med. Chir.* **16**, 632.
 ERDHEIM, J. (1911). *Frankfurt Z. Path.* **7**, 175, 238, 295.
 FALCONER, A. W. (1929). *Lancet*, **2**, 656.
 FLEISCHMANN, O. (1931a). *Z. Laryng. Rhinol.* **20**, 503.
 FLEISCHMANN, O. (1931b). *Zbl. Haut- u. Geschl.Kr.* **39**, 181.
 FOERSTER, O. H. (1916). *J. Cutan. Dis.* **34**, 1.

- FRASER (1927). *Arch. Derm. Syph., Chicago*, **16**, 359.
- FREY, H. & ORZECOWSKI, K. (1920). *Wien. Klin. Wschr.* **33**, 697, 734, 754.
- FRIEDMAN, R. (1940). *Urol. Cutan. Rev.* **44**, 464.
- FRIEDMANN, M. (1921). *Arch. Derm. Syph., Wien*, **135**, 161.
- FUNK & GRUNDZACH (1894). *Mh. prakt. Derm.* **18**, 109.
- GAUL, L. E. (1937). *Arch. Derm. Syph., Chicago*, **36**, 26.
- GORDON, H. (1933). *Lancet*, **2**, 126.
- GORDON, W. H. & JAMIESON, R. C. (1931). *Ann. Intern. Med.* **5**, 358.
- HALLAM, R. (1927). *Brit. J. Derm.* **39**, 95.
- HALLAM, R. (1932). *Brit. J. Derm.* **44**, 117.
- HARDWICK, C. (1939). *Brit. J. Derm.* **51**, 24.
- HESSE (1930). *Derm. Wschr., Lpz.*, **91**, 1578.
- HILL, A. M. (1933). *Arch. Derm. Syph., Chicago*, **28**, 66.
- HUTTON, J. H. (1939). *Urol. Cutan. Rev.* **33**, 439.
- INGRAM, J. T. (1939). *Brit. Med. J.* **2**, 5.
- JACOBSEN, A. W. (1928). *J. Amer. Med. Ass.* **90**, 686.
- JADASSOHN, J. & LEWANDOWSKY, F. (1906). *Ikonogr. Derm.* **1**, 29.
- JANITZKAJA, E. & RJABOW, M. (1928). *Z. klin. Med.* **107**, 381.
- JONES, H. M. & ALKINS, R. (1875). *Dublin J. Med. Sc.* **60**, 200.
- KÉMERI, D. (1929). *Derm. Wschr., Lpz.*, **89**, 1385.
- KÉMERI, D. (1930a). *Derm. Wschr., Lpz.*, **91**, 1587.
- KÉMERI, D. (1930b). *Derm. Wschr., Lpz.*, **91**, 1615.
- KERL (1930). *Derm. Wschr., Lpz.*, **91**, 1315.
- KERLEY, C. G. (1930). *Arch. Pediat.* **47**, 639.
- KINNEAR, J. (1933). *Brit. J. Derm.* **45**, 65.
- KRAUS, A. (1903). *Arch. Derm. Syph., Wien*, **66**, 369.
- LACHMANN, A. (1941). *Acta med. Scand., Stockh., Suppl.* 121.
- LEHMANN, C. F. (1930). *Arch. Derm. Syph., Chicago*, **21**, 449.
- LÉVY-FRANKEL, A. & JUSTER, E. (1923). *Presse méd.* **31**, 660.
- LÉVY-FRANKEL, A. & JUSTER, E. (1926). *Rev. franç. Derm. Vénérol.* **2**, 277, 438.
- LESZCZYNSKI, R. (1928). *Arch. Derm. Syph., Wien*, **156**, 102.
- LESZCZYNSKI, R. (1929a). *Derm. Wschr., Lpz.*, **89**, 1473.
- LESZCZYNSKI, R. (1929b). *Derm. Wschr., Lpz.*, **89**, 1535.
- LESZCZYNSKI, R. (1931). *Derm. Wschr., Lpz.*, **93**, 1774.
- LESZCZYNSKI, R. (1936). *Wien. Med. Wschr.* **86**, 683.
- LORD, L. W. & WOLFE, W. D. (1938). *Arch. Derm. Syph., Chicago*, **38**, 893.
- LOWENBURG, H. & GRIMES, E. L. (1942). *Amer. J. Dis. Child.* **63**, 357.
- LUTZ, W. (1928). *Derm. Z.* **53**, 384.
- MACKEE, G. M. & ANDREWS, G. C. (1924). *Arch. Derm. Syph., Chicago*, **10**, 673.
- MACQUAIDE, D. H. G. (1944). *Lancet*, **2**, 531.
- MARGOLIS, H. M. & KRAUSE, G. (1939). *J. Amer. Med. Ass.* **112**, 1131.
- MENDES DA COSTA, S. & VAN DER VALK, J. W. (1919). *Urol. Cutan. Rev.* **23**, 159.
- MILIAN & PÉRIN (1921). *Bull. Soc. franç. Derm. Syph.* **28**, 438.
- MITCHELL, J. H. (1929). *Arch. Derm. Syph., Chicago*, **19**, 659.
- MONTGOMERY, D. W. (1916). *J. Cutan. Dis.* **34**, 285.
- MURRAY, F. A. (1921). *Brit. J. Derm.* **33**, 409.
- NICOLLE, G. & HALIPRÉ, A. (1895). *Ann. Derm. Syph., Paris*, **6**, 675, 804.
- OLIVER, E. A. & GILBERT, N. C. (1926). *Arch. Derm. Syph., Chicago*, **13**, 359.
- PILLSBURY, D. M. & STERNBERG, T. H. (1937). *Amer. J. Dis. Child.* **53**, 1209.
- PINTER (1930). *Derm. Wschr., Lpz.*, **91**, 1637.
- PULAY, E. (1926). *Dtsch. med. Wschr.* **52**, 195.
- RAPP (1931). *Derm. Wschr., Lpz.*, **93**, 1487.
- REEDE, E. H. (1918). *J. Cutan. Dis.* **36**, 505.
- RICHTER, W. & HERZFELD, E. (1932). *Münch. Med. Wschr.* **79**, 1650.
- ROHOLM, K. (1937). *Fluorine Intoxication*. London.
- SABOURAUD, R. (1921). See Milian & Périn (1921).
- SAYER, A. (1942). *Urol. Cutan. Rev.* **46**, 719.
- SCHARDORN, E. (1921). *Arch. Derm. Syph., Wien*, **132**, 108.
- SCHERBER, G. (1909). *Arch. Derm. Syph., Wien*, **94**, 227.
- SCHERBER, G. (1938). *Derm. Wschr., Lpz.*, **106**, 391.
- SCHUEERMANN, H. (1938). *Derm. Wschr., Lpz.*, **106**, 461, 497.
- SCHWARTZ & LEVIN (1923). *Arch. Derm. Syph., Chicago*, **8**, 152, 289.
- SCHWARZ, E. G. (1935). *South. Med. J.* **28**, 608.
- SELLEI, J. (1931). *Derm. Wschr., Lpz.*, **93**, 1963.
- SELLEI, J. (1932). *Urol. Cutan. Rev.* **36**, 384.
- SINGER, O. (1921). *Arch. Derm. Syph., Wien*, **136**, 198.
- SPIRA, L. (1928). *Franco-Brit. Med. Rev.* **5**, 1, 61.
- SPIRA, L. (1933). *The Clinical Aspect of Chronic Poisoning by Aluminium and its Alloys*. London.
- SPIRA, L. (1942a). *Lancet*, **1**, 649.
- SPIRA, L. (1942b). *Brit. Dent. J.* **73**, 149.
- SPIRA, L. (1942c). *Edinb. Med. J.* **49**, 707.
- SPIRA, L. (1942d). *J. Hyg., Camb.*, **42**, 500.
- SPIRA, L. (1943a). *J. Hyg., Camb.*, **43**, 69.
- SPIRA, L. (1943b). *Edinb. Med. J.* **50**, 237.
- SPIRA, L. (1944a). *J. Hyg., Camb.*, **43**, 400.
- SPIRA, L. (1944b). *J. Hyg., Camb.*, **43**, 402.
- SPIRA, L. (1946). *J. Hyg., Camb.*, **44**, 276.
- SPIRA, L. (1947). In press. *Acta med. Scand. Stockh.*
- STEPHENSON, J. D. (1936). *Penn. Med. J.* **39**, 976.
- STRANDBERG, J. (1919). *J. Amer. Med. Ass.* **73**, 873.
- TATE, B. C. (1935). *Arch. Dis. Child.* **10**, 27.
- TENDLAU, B. (1902). *Virchows Arch.* **167**, 465.
- TENLÉN, S. (1937). *Acta derm.-venereol., Stockh.*, **18**, 165.
- THOMPSON, H. B. (1928). *J. Amer. Med. Ass.* **91**, 1547.
- TOBIAS, N. (1925). *J. Amer. Med. Ass.* **84**, 1586.
- TOMASI, L. (1940). *Brit. J. Derm.* **52**, 1.
- VOHWINKEL, K. H. (1929). *Derm. Wschr., Lpz.*, **89**, 1236.
- WALTER, F. (1922). *Arch. Derm. Syph., Wien*, **140**, 138.
- WALTER, F. (1927). *Zbl. Haut- u. Geschl.Kr.* **22**, 779.
- WEECH, A. A. (1929). *Amer. J. Dis. Child.* **37**, 766.
- WENDE, G. W. (1926). *Arch. Derm. Syph., Chicago*, **13**, 372.
- WHEELON, H. (1925). *Endocrinology*, **9**, 35.
- WHITE, C. J. (1896). *J. Cutan. Dis.* **14**, 220.
- WHITTLE, C. H. (1944). *Proc. Roy. Soc. Med.* **37**, 643.
- WOHLSTEIN, E. (1931). *Derm. Wschr., Lpz.*, **93**, 1888.
- YOUNG, J. M. (1944). *Lancet*, **2**, 612.
- ZIEGLER, P. (1897). *Arch. Derm. Syph., Wien*, **39**, 213.