occurred, it is suggested that all cases should be immobilized in a short plaster-of-Paris collar for one month, as the type 1 injury will recur if the neck is forcibly extended (see Case 13).

Laminectomy is contraindicated unless spinal block is shown on lumbar puncture or myelography.

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# PELLAGRA CAUSED BY ISONIAZID

BY

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In 1913 pellagra occurring in Britain was the subject of articles appearing in the *British Medical Journal* (Box, 1913; Mott, F. W., 1913; Sambon, 1913; Hammond, 1913); and the *Lancet* (Blandy, 1913). At that time Thomas (1913) suggested that certain sedative drugs such as trional and sulphonal, then in common use in mental asylums, might produce pellagra by "intoxication."

The concept of secondary pellagra, as distinct from the endemic disease, was reviewed by Bean, Spies, and Blankenhorn (1944), who listed a large number of abnormal conditions and diseases which rendered the body susceptible to this deficiency syndrome. On the other hand, pellagra was mentioned only rarely as a sequel to the use of chemical compounds.

An observation that isoniazid seemed to be of benefit in disseminated sclerosis (Kurtzke and Berlin, 1954) led to further trials of this drug.

Dr. D. B. Handley gave isoniazid in combination with pyridoxine to a number of patients with disseminated sclerosis. One of these patients, who had been existing on an inadequate diet, developed a typical pellagrous dermatitis. Three weeks after stopping the drug, while still taking the same poor diet, her symptoms persisted. There was a rapid response to nicotinamide therapy.

### Case History

A spinster aged 45 had suffered from disseminated sclerosis for twenty years. Her first symptoms occurred at the age of 25, with paraesthesiae in the legs and hands. There was a constant sensation of pins-and-needles in both legs up to the groins and in the hands and fingers up to the wrists. She also noticed that she could not appreciate hot water as acutely as before, but nevertheless never burnt herself because of this. Pin-prick, too, did not feel quite so sharp as formerly. There was no weakness of the legs, but she often felt as though she was walking on air.

After eighteen months these sensations passed off, and were later followed by pains in the legs, chiefly in the knees and calves, which were present day and night throughout the year. Then came some weakness and stiffness of the legs, especially on going upstairs. However, she could still walk long distances if she wished. On direct questioning she said that she had never had any visual or auditory symptoms, no double vision, and her speech had always been normal. There was no dyspepsia, her bowels were opened regularly, and she had never had difficulty with, or precipitancy of, micturition, or any urinary incontinence.

In 1950 she had been investigated in a neurological centre, and a diagnosis of disseminated sclerosis had been made.

*History.*—Her appetite had always been poor. She would have only a cup of tea and a biscuit for her breakfast, and the same again at noon. She would take a very light lunch, with little meat and fish. At tea-time she would again have tea and biscuits, and nothing further until next morning. There was no family history of fits, faints, or neurological or mental disease. Her two brothers were both well. Her father died at the age of 60 (carcinoma); her mother died aged 70 (following a stroke). At school she was reasonably intelligent, and reached the senior class. Later she worked for ten years as a bookbinder. However, for the last few years she had been doing light work in a chemist's shop, chiefly dispatching and bottling medicines. She smokes little, and drinks no alcohol.

*Development of Pellagrous Dermatitis.*—In May, 1955, 300 mg. of isoniazid was given daily, together with 20 mg. of pyridoxine three times a day. She took her usual inadequate meals, as her appetite did not improve. She pursued her normal activities, and did not expose herself unduly to the strong sunlight, but it was an exceptionally fine summer. During July she experienced burning sensations in the hands and feet, and the typical symmetrical pellagrous dermatitis developed on the hands and feet.

On examination her intelligence was not high; she was quite co-operative, but did not give a very good history. She was a thin woman, height 5 ft. 2 in. (157.5 cm.), weight 8 st. 2 lb. (51.7 kg.). *Special Senses.*—No anosmia. Visual acuity, good; visual fields, full to confrontation; fundi, disks normal; retinal vessels, normal; no haemorrhages or exudates. Hearing normal. Taste, normal. *C.N.S.*—Cranial nerves, normal. Motor system: nutrition of limbs—rather thin, but no wasting; no fasciculation; slight hypotonia of arms; slightly increased tone in the legs, no clonus. Power in arms, normal; both legs could be raised from the bed simultaneously. Other movements within normal range except for moderate weakness of dorsiflexion of the right ankle. *Co-ordination.*—Finger–nose test performed well, but on each side some clumsiness, especially on the left when performing repetitive movements; finger flexion normal. The impression was of slight ataxia on the left. Co-ordination of legs within normal limits. *Reflexes.*—Arm reflexes brisk and equal; abdominals sluggish; knee- and ankle-jerks brisk and equal; plantar responses extensor—the responses being obtained from the foot only. *Sensations.*—Pin-prick and cotton-wool were normally appreciated. Two-point discrimination, within normal limits. Postural sensibility, normal. Projection of one limb towards another with eyes closed was well performed. Vibration sense, normal. No rombergism.

Her legs were held stiffly, especially the right. Although she was a little unsteady on turning, there was no marked ataxia. The skull was normal, no bruits. Spine: no scoliosis or kyphosis; full range of movements. Heart normal in size; sounds normal, no murmurs; pulse regular; blood pressure, 105/75. The respiratory system and abdomen were normal.

*Skin Manifestations.*—There was a typical pellagrous dermatitis, chiefly affecting the dorsal surfaces of the hands and dorsa of the feet. Around the mouth was a fine branny desquamation. The neck was not affected. The hands and feet showed a reddish-brown colour with coarse scaling, the upper boundary of the involved skin was sharply demarcated from the normal, as in the classical case (Figs. 1 and 2). The tongue was normal but angular stomatitis was marked. There was some fine scaling of the lips. Although the drugs were stopped her symptoms persisted; there was no change in her appetite or diet.

Three weeks after the drugs were discontinued she was given 1,000 mg. of nicotinamide daily. The burning sensations in her limbs rapidly lessened; her dermatitis also quickly improved, and within eighteen days the skin appeared normal.

*Investigations.*—Blood count, normal. Plasma protein, normal. Fractional test meal, normal. Serum cholesterol, 159 mg. per 100 ml. Urine, no porphyrins. An E.E.G., taken on August 22 by Dr. J. A. Irwin, showed that the dominant activity in the post-central areas was an 8–9 c/s alpha rhythm which was blocked by eye-opening. On these occasions a lower-amplitude 11–12 c/s rhythm was visible. Traces of low amplitude 4–5 c/s activity were mixed with the alpha rhythm and blocked by it. Overbreathing increased the amount of slow activity, and a small amount of low-amplitude 3 c/s activity was seen in the posterior temporal regions. This record is abnormal, containing an excess of theta activity and an unstable hyperventilation response.

## Discussion

Although our patient's intake of food was poor it was sufficient for her ordinary needs; at least, it did not lead to a recognizable vitamin deficiency. She continued with this diet while taking isoniazid and developed pellagra. Since the symptoms appeared during the isoniazid administration there would seem to be a causal relationship, and her improvement after nicotinamide treatment would be proof that she had been deficient.

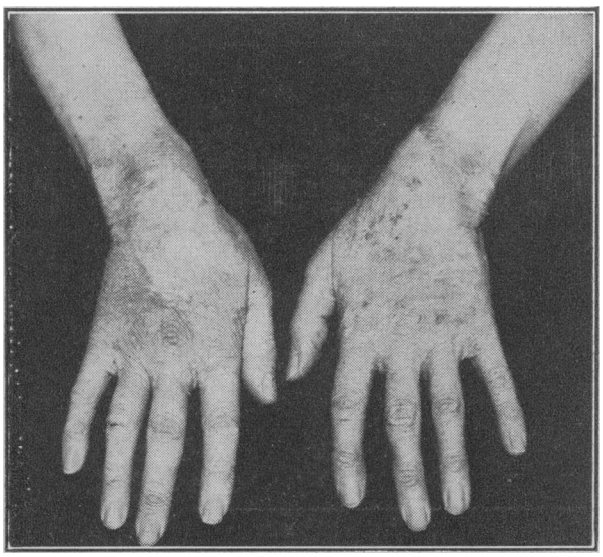

FIG. 1.—Showing typical pellagrous dermatitis affecting the hands.

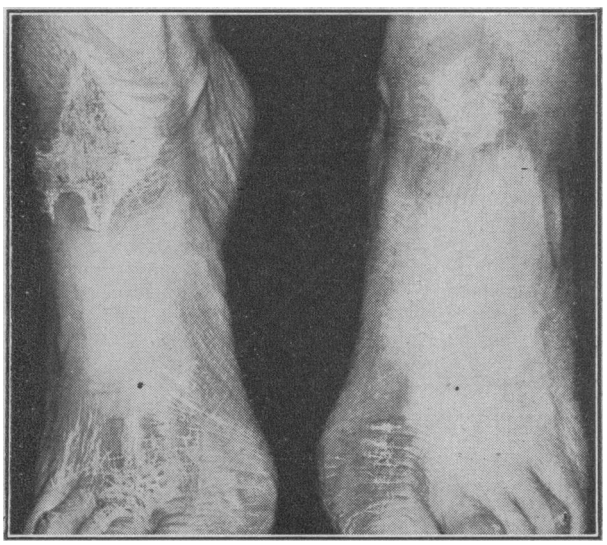

FIG. 2.—The involved skin of the feet is seen to be sharply demarcated from the normal.

That isoniazid may lead to the development of pellagra in poorly nourished patients was also observed by Wood (1955). Bantu out-patients with pulmonary tuberculosis receiving isoniazid developed pellagra within a few weeks and required admission to hospital. Wood also found that patients who had both pulmonary tuberculosis and pellagra could not be treated satisfactorily on a good diet, even with vitamin supplements, if isoniazid were given concurrently; in fact, clinical deterioration occurred in some cases.

In this country McConnell and Cheetham (1952) observed the occurrence of pellagra in a patient receiving isoniazid for abdominal tuberculosis, a condition known to predispose to secondary pellagra.

In our case pyridoxine was given together with isoniazid, as previous studies (Biehl and Vilter, 1954) suggested that peripheral neuritis, a common complication of isoniazid therapy when large doses are given, was due to an effect on pyridoxine metabolism.

Our patient was given the standard dose of isoniazid (5 mg. per kg. body weight). The development of pellagra suggested a nicotinamide deficiency, which raises the question of a metabolic antagonism between isoniazid and nicotinamide.

Reports of an antagonistic action between nicotinic acid and sulphonamide drugs led Bean *et al.* (1944) to use pyridone-3-sulphonic acid, related to nicotinic acid as sulphanilamide is to *para*-aminobenzoic acid, in three patients with subclinical pellagra on a vitamin-B-free diet for a two-weeks period. Under these circumstances pellagra did not occur, but those workers thought that larger doses for longer periods were necessary before conclusions could be drawn.

Nicotinamide is an integral component of the pyridine nucleotides (P.N.) and the co-enzymes diphosphopyridine nucleotide (D.P.N.) and triphosphopyridine nucleotide (T.P.N.), which play an important part in cellular metabolism. McConnell and Cheetham suggest that the pellagra-producing effect of isoniazid depends on the patient's original nicotinamide level being low; the amount of isoniazid which would compete successfully with nicotinamide in the formation of co-enzyme depending, by the law of mass equilibrium, on their relative concentrations and their relative affinity for the co-enzyme residue.

However, the mechanism of the biological activity of isoniazid is not yet known; the highly specific action against *Mycobacterium* tuberculosis suggests interference with an essential metabolite. It is established that there is a high concentration of nicotinic acid in the tubercle bacillus (Pope and Smith, 1946; Bird, 1947).

The structural similarity of isoniazid to both pyridoxal and the pyridine nucleotides has suggested that it may act by competing with structurally similar essential co-enzymes in the organism.

Zatman *et al.* (1953) observed that certain D.P.N. nucleotidases cause an exchange of isoniazid for the nicotinamide portion of D.P.N. Their preliminary experiments indicated that the acetylpyridine analogue of D.P.N. can be synthesized in the whole animal, and especially in tumour tissue, with the administration of acetylpyridine, which is closely related to nicotinamide. They thought it possible that the synthesis of the analogue in the intact animal might be a factor in the toxicity of the compound, which could lead to symptoms resembling nicotinamide deficiency (Kaplan *et al.*, 1954).

However, to date Kaplan and his co-workers (1955, personal communication) have not been able to show any direct relationship between nicotinamide and isoniazid in animals.

Also with regard to pyridoxal, A. Albert (1955, personal communication) states that the biological antagonism between isoniazid and pyridoxal would seem to be due to the

ordinary chemical reaction (hydrazone formation) between a substituted hydrazine and an aldehyde, which occurs readily at room temperature in dilute aqueous solution; this would be sufficient explanation for pyridoxal deprivation.

Fisher (1954) showed that haemin antagonizes the effect of isoniazid; however, Albert and Rees (1955) and Knox *et al.* (1955) proved that haemin catalyses the oxidative destruction of isoniazid even in the absence of tubercle bacilli.

Recent work by Cymerman-Craig *et al.* (1955) presents experimental evidence that the action of isoniazid appears to include an essential chelation step, but this is not the whole story.


## Summary

Pellagra developed in a woman who was receiving isoniazid for disseminated sclerosis. Her intake of food was poor. The dermatitis appeared during a particularly sunny summer.

Isoniazid was stopped. During the next three weeks her symptoms persisted. She continued to take the same inadequate diet. The burning sensations in both hands and feet were so severe that they caused her great distress. She was unable to sleep at night with her limbs covered. These latter symptoms were quickly relieved when nicotinamide was given. The dermatitis cleared completely in just over two weeks.

As the symptoms of pellagra came while isoniazid was taken, there seemed to be a causal relationship.

Other clinical observations are mentioned which point to isoniazid being a contributory factor in producing pellagra if the patient is in a pre-pellagrous condition.

These clinical findings suggest a possible metabolic antagonism between isoniazid and nicotinamide. Isoniazid bears an undoubted structural similarity to nicotinamide, which is an integral component of an essential oxidation-reduction co-enzyme—that is, D.P.N.

Experimental work has shown that it is possible by enzyme action to cause an exchange of isoniazid for the nicotinamide portion of D.P.N., which points to a mechanism whereby isoniazid might produce nicotinamide deficiency; but in experiments on the whole animal this has not yet been demonstrated. The biological antagonism between isoniazid and pyridoxal is due to a purely chemical reaction.

The suggestion that the pellagra-producing effect of isoniazid depends on the patient's initial level of nicotinamide being low would cover the facts observed in our case.

The interest of these observations is not so much the causation of pellagra as the demonstration of an apparent relationship between isoniazid and a condition which is caused specifically by a nicotinamide deficiency; this would therefore point to an interference by isoniazid in nicotinamide metabolism; as an integral component of D.P.N., nicotinamide has its most important known metabolic function. The question remains whether these observations are a reflection in the human of the mechanism whereby the tubercle bacillus is inhibited by isoniazid.


The photographs were taken by Miss E. Mason, St. James' Hospital


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# CASE OF FETISHISM TREATED BY AVERSION THERAPY


BY

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Fetishism, or more accurately "erotic fetishism," is the tendency to be sexually attracted by some special part or peculiarity of the body or by some inanimate object. Of all the sexual aberrations, fetishism is one of the most intriguing, perplexing, and varied. The literature is rich in detailed case reports and in speculation about theories of causation. I have been able to find, however, only three apparently successful results in established cases; one attributed to a co-operative wife (Hirschfeld, 1939), one to psycho-analysis (Romm, 1949), and the third to temporal lobectomy (Mitchell, Falconer, and Hill, 1954). I have been unable to find any previous record of a fetishist who responded favourably to aversion therapy. The following case is also of interest in that the fears implicit in psycho-analytical theory, and stressed by East and Hubert (1939), of releasing homosexual or sadistic drives, have not so far been confirmed.

## Case Report

The patient, a married man aged 33, was referred in November, 1954, from the out-patient department of a mental hospital for consideration of a prefrontal leucotomy after he had attacked a perambulator. This was the twelfth such attack known to the police, and because of the previous incidents they were taking a serious view of his recent actions in following a woman with a perambulator and smearing it with oil. Since his first involvement with the police his career had been as follows.

*First Charge* (six incidents).—In September, 1948, whilst in the R.A.F., he slashed two empty prams on a railway station before setting them on fire and completely destroying them. He also admitted five other incidents involving cutting or scratching prams, which had been the subject of police investigations over a period of months. He was convicted of causing malicious damage and put on probation to accept medical treatment. He then left the R.A.F. and was in a mental hospital from March to April, 1949, before being transferred to a neurosis unit, where he stayed for a further month. The view was there expressed that he was unsuitable for psychotherapy, was potentially dangerous, and should remain in a mental hospital.

*Seventh and Eighth Incidents.*—He did not remain in a mental hospital, and early in 1950 he smeared some mucus from his handkerchief on to a handbag and also damaged a pram by scratching and cutting it. He was not charged, but was admitted to a mental hospital and stayed there from February, 1950, until June, 1951.