treatment by compression difficult. In our view, all cases in which local symptoms and signs persist at ground-level, with or without a drop in blood-pressure, should be compressed. This we feel is justified by the dramatic symptomatic relief produced alone. In addition, if the full picture of post-decompression shock is allowed to develop, then compression is much less likely to be effective although it may still be a valuable adjunct to therapy.

The pressure depth to which these cases should be compressed should, in our opinion, be the minimum which produces relief of symptoms in order to avoid the risk of further hazards during subsequent decompression. Sixty-five feet (19.8 m.) of water appears to be the optimum depth initially. At this depth the pressure is 12 times that at which bubble formation presumably occurred. Even the most severe symptoms in divers yield to much lower relative pressure increases than this. After recovery, times for subsequent decompression must be somewhat empirical until there is more evidence on which decompression schedules can be designed.

Post-decompression collapse is undoubtedly rare. The introduction of the pressurized cabin, however, has not entirely eliminated decompression sickness in flight, and cases like those above still occur in decompression chambers. Like decompression sickness in divers, it is of general interest because cases with a prolonged latent interval between flight and development of symptoms could be seen by virtually any doctor in the country.

Summary

Four cases of the post-decompression collapse syndrome are described in aviators who have been exposed to a simulated altitude of 37,000 feet (11,277 m.) in a decompression chamber. The factors which predispose to the development of this condition are discussed. In all four cases compression to pressures greater than atmospheric produced immediate relief, and theories of the aetiology of post-decompression collapse are discussed in relation to this effect.

The success of compression in these four cases and in two cases treated elsewhere by this method suggests that this form of treatment should be generally adopted for these cases, and a scheme of treatment is outlined.

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Clinical and Biochemical Features of a Case of Hartnup Disease

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A disease characterized by "pellagra-like skin rash, with temporary cerebellar ataxia, constant renal amino-aciduria, and other bizarre biochemical features," was first described by Baron, Dent, Harris, Hart, and Jepson (1956). This disorder, now known as Hartnup disease, is transmitted as a recessive autosomal trait and at the time of writing we were able to find reports of 13 known cases of this syndrome in nine families. One of the most striking features of the disorder is the renal amino-aciduria without evidence of any other tubular dysfunction. Because of the associated pellagra-like rash, Baron *et al.*

(1956) postulated that the immediate biochemical lesion was an abnormality of nicotinic acid metabolism. On the basis of their investigations in two Hartnup cases, Milne, Crawford, Girao, and Loughridge (1960) have suggested that Hartnup disease is primarily a disorder of amino-acid transport—across both the mucous membrane of the jejunum and the renal tubule. In addition, a defective conversion of tryptophan to nicotinic acid has also been postulated. The latter defect, it is claimed, fully explained the pellagra-like rash.

The clinical features and the results of investigations on a subject with Hartnup disease and his asymptomatic sister are reported here. The clinical manifestations are identical with the reported cases, but results of biochemical investigations seem

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to be different from what has been reported by Milne *et al.* (1960).

Case Report

The patient (Y), a boy aged 7 years, was the third child of a family of four born to healthy parents who were first cousins. He was a full-term baby successfully breast-fed for one year and then started on supplementary diets containing rice, dhal, vegetables, and cow's milk. Until his fifth year he was healthy, but he developed episodes of gastroenteritis, oedema of the feet, and slight tremors of the hands. His gait was unsteady, and he had a marked tendency to fall to one side. He had signs of protein-calorie malnutrition, xerosis of the conjunctivae, and angular stomatitis. A pellagra-like rash was present on his hands. The liver was palpable 1 in. (2.5 cm.) below the costal margin, soft, and not tender. Mild tremors of the hand, an ataxic gait, and exaggerated deep jerks were observed. On the basis of the history of dietary deprivation, diarrhoea, oedema, and hypoalbuminaemia, a diagnosis of protein-calorie malnutrition was made and nutritional rehabilitation instituted. The oedema, signs of avitaminosis, skin rash, and diarrhoea responded to treatment rapidly, but the neurological manifestations took five to six weeks to disappear. The deep jerks were still brisk. He was discharged after six weeks in hospital.

There were no events of note during the next year. He then developed fever, which subsided with treatment; but subsequently

metrical dermatitis characteristic of pellagra on the forearms, hands, legs, and face (Figs. 1 and 2). Ataxia, tremors, and exaggerated deep reflexes were present. There were no signs of mental retardation. Haemoglobin was 9.7 g./100 ml., total serum protein 6.9 g./100 ml., and albumin 3.7 g./100 ml. Urine showed no sugar or albumin. Stools did not show anything abnormal.

FIG. 1.—Photograph showing bilateral symmetrical dermatitis.

FIG. 2.—Photograph showing dermatitis on hands and forearms.

Investigations.—Total nitrogen and amino-nitrogen were determined in 24-hour urine samples obtained from the patient and his elder sister (R). Two-dimensional paper chromatograms for urinary amino-acid were obtained from the patient, his two sisters, and the father (see Family Tree).

Tryptophan Load Test.—The effects of ingestion of L-tryptophan on the urinary excretion of tryptophan, indican, and indolyl-acetic acid and blood tryptophan levels were determined in both Y and R. Two basal samples of urine were collected at hourly intervals and 70 mg. of L-tryptophan per kg. body weight was administered orally. Urine was collected at hourly intervals during the next seven hours and all the urine voided during the next 17 hours was collected as one sample. Toluene was used as the preservative. Samples of blood were drawn before the administration of tryptophan and two hours after the load. All the faeces passed during the next 24 hours

his mother noticed areas of pigmentation on his forearms, legs, and face, and marked ataxia. He was brought to hospital with these complaints and was admitted for investigation. The diagnosis of Hartnup disease was considered.

He was 7 years old, weighed 13 kg., but was without any gross sign of malnutrition. The skin showed the typical bilateral sym-

FIG. 3.—Urinary amino-acid pattern of patient Y.

FIG. 4.—Urinary amino-acid pattern of R.

FIG. 5.—Urinary amino-acid pattern of patient's younger sister.

were collected for determination of L-tryptophan. For purposes of comparison two normal children aged 8 and 12 years were similarly studied.

Tryptophan in urine and blood was determined without delay by microbiological assay, using *Lactobacillus leichmannii* and indican by the colorimetric method after developing the colour with Obermayer's reagent. Indolyl-acetic acid was determined by the method of Weissbach, King, Sjoerdsma, and Udenfriend (1959). Amino-acids in urine were estimated by the method of Albanese and Irby (1944), and two-dimensional paper chromatograms were obtained with urine containing 250 γ N. Phenol-ammonia water was used in one phase and butanol-acetic acid in the other.

Results

Urinary Amino-acids.—Y excreted 1,608 mg. of amino-nitrogen in 24 hours, which constituted 30% of total nitrogen. R excreted 1,020 mg., which constituted 22% of total nitrogen. The chromatograms showed a pattern characteristic of Hartnup disease, both in the patient and his two asymptomatic siblings, (Figs. 3, 4, and 5), while that of the father appeared normal.

Response to Tryptophan Load.—The results are presented in Figs. 6, 7, and 8 and the Table. The fasting level of indican in the basal urine specimen was higher in both Y and R compared with the normals, but more so in Y. After the tryptophan load Y showed a pronounced elevation by the end of an hour which was still present at two hours but had returned to basal levels by the third hour. There was again a sudden and sharp rise by the sixth hour, followed

Effect of Oral Tryptophan Load on 24-hour Urinary Excretion of Indican, Indole Acids, and Tryptophan

Subject	Urinary Indican		Indole Acids		Tryptophan	
	Absolute	% of Load	Absolute	% of Load	Absolute	% of Load
Normal	12	1.0	13	1.1	13	1.1
..	20	1.3	15	1.0	35	2.3
R: Hartnup—	30	1.8	63	3.9	100	6.0
asymptomatic	62	6.2	10	1.0	240	24.0
Y: Hartnup—						
symptomatic						

L-Tryptophan was given orally, 70 mg. kg. body weight.

by a return to basal level by the seventh hour. In R, however, the increase over the basal level was less marked but was maintained over a longer period (six hours) and then returned to basal levels. In the two normals a small rise was observed which returned to normal levels by the third hour. The total urinary indican excreted during the 24 hours after the tryptophan load was 20 and 12 mg. in the two normals, 30 mg. in R, and 62 mg. in Y.

The levels of excretion of indolyl-acetic acid in the basal urine samples were similar in both the normals and subjects R and Y, but the effects of the tryptophan load were different. Both normals showed a peak increase by the second hour which returned gradually to basal levels by the fifth hour. The changes in Y were somewhat

similar to what was observed in normals, but in R the urinary excretion continued to rise until the fourth hour to a much higher peak, and at seven hours had still not returned to normal. The total 24-hour excretion was 13 and 15 mg. in the two normals, 10 mg. in Y, and 63 mg. in R.

Urinary excretion of tryptophan increased after the load and a peak excretion of 5 mg./hour was reached by five to six hours and gradually returned to basal level in both normals. In R a higher peak was reached—12 mg./hour, and the excretion continued at a higher level for a long period. The most marked excretion was found in Y, reaching a peak of 50 mg./hour at the fourth hour. While in the two normals only 1.1% and 2.3% of the load were excreted, both R and Y excreted much larger proportions—6% by R and 24% by Y.

Blood tryptophan levels under basal conditions were 0.44 and 0.57 mg./100 ml. in the two normals and 1 mg. in Y. Two hours after the load it was 4.4 and 5.8 mg./100 ml. in the two normal subjects and 5.2 mg. in Y.

After the load tryptophan could not be detected in the faeces either by the microbiological assay or by paper chromatography.

Discussion

The pellagra-like rash, cerebellar signs, and renal amino-aciduria in patient Y, and the presence of the renal amino-aciduria in the asymptomatic siblings, leave little doubt that this is a case of Hartnup disease. The response to the tryptophan load, however, showed features which are somewhat different from those reported earlier by Milne *et al.* (1960). The marked rise in urinary indican and the maintenance at this high level over prolonged periods after the tryptophan load reported by

FIG. 7.—Indolyl-acetic acid in urine after tryptophan load

FIG. 6.—Indican in urine after tryptophan load.

FIG. 8.—Tryptophan in urine after tryptophan load.

Milne *et al.* was not observed in Y. Though a sharp rise occurred by the first hour and again by the fifth hour and the total excretion over 24 hours was 6.2% of the tryptophan load (normal 1.1%), this pattern is not similar to that reported by Milne *et al.* The marked increase in urinary indican after a tryptophan load in Hartnup cases has been ascribed to bacterial degradation of a greater proportion of tryptophan which reaches the colon consequent on incomplete absorption from the small intestines. In the subject studied here, the rise in urinary indican after the tryptophan load began even by the second or third hour, by which time the tryptophan would still not have reached the colon for bacterial action. Such a trend is evident also from the results of Milne *et al.* The increase at such an early period therefore has to be explained on some other basis. While there was a higher level of the total indican excretion in Y (6.2% against 1 and 1.3% of tryptophan load in normals), in the asymptomatic R the excretion was almost normal—1.8%. The observation that urinary indican levels were not maintained at high levels over a long period is regarded as complementary to the observation that tryptophan could not be detected in the faeces.

The excretion of indole acids in R was abnormally high (3.9%) but almost normal in Y (1%). These observations are dissimilar to the observation of Milne *et al.* (1960), who found that, like indican, indolyl-acetic acid excretion after the load is abnormally elevated and maintained over long periods. The absence of prolonged maintenance of high levels of indican and indole acids in urine, the elevation of blood tryptophan to the levels found in normals after the tryptophan load, and the presence of marked tryptophanuria indicate that in the subjects here studied there was no defect in the absorption of tryptophan from the gut. On the other hand, the marked loss of tryptophan through the kidney at blood levels comparable to that in normals denotes a pronounced failure of tubular reabsorption of the amino-acid. It is possible that the condition studied here is a variant of Hartnup disease. Milne *et al.* (1960) suggested that Hartnup disease is essentially due to a failure of transport of

tryptophan across the cell membrane and that this can explain both the tryptophanuria and the alteration in indican-indole acid metabolism. The absence of marked changes in indican-indole acid metabolism seen in the above case cannot be explained on this basis unless it is postulated that the absorption of tryptophan from the gut and that from the renal tubule are controlled by independent processes. One could then suggest that in Hartnup disease a defect in the absorption from the renal tubule is always present but the defect in absorption from the gut is variable. The latter consideration will then govern the pattern of changes in the metabolism of indole compounds.

A comparison of the results in Y with those in R suggested that the absence of the pellagra-like rash in R may have been due to the relatively less amount of tryptophan lost in her urine.

The presence or absence of tryptophan pyrrolase could not be established in this case as urinary kynurenine levels after tryptophan load were not determined.

Summary

A case of Hartnup disease is described and some biochemical aspects of the disorder are investigated. The clinical manifestations leave little doubt that the subject was suffering from Hartnup disease, but the biochemical data suggested that he might be a genetic variant of the trait.

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Medical Memoranda

Black Urine After "Jectofer" Injections

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Discoloration of the urine has always roused interest, and this has especially been so with black urine. We report here another cause for this in the hope that the knowledge of its occurrence may save anxiety to patients and doctors and avoid unnecessary investigation.

CASE REPORT

A 54-year-old woman was receiving daily intramuscular injections of iron-sorbitol-citric-acid complex ("jectofer"). A 24-hour specimen of her urine had been collected for an unrelated investigation, and on chance inspection some three hours after completion it was noted to be black. The patient was not receiving any other drugs and denied taking any unusual sweets, drinks, or medicaments. She had not previously noted any discoloration of her urine and there was no family history. A previous routine urinalysis had

been negative and culture of a mid-stream specimen of urine gave no growth of organisms.

Laboratory Investigations.—The urine in the bottle was uniformly black throughout. In a test-tube, however, it was more a dark olive colour. On standing for a few hours a dark-grey deposit appeared. The pH of the urine was 8. Tests on this sample and on a fresh specimen for reducing substances, ketones, protein, bilirubin, urobilin, haem pigments, porphyrins, melanogens, and homogentisic acid all gave negative results. Centrifugation of the original urine provided a dark-grey deposit which was readily resuspended on agitation. Addition of 2 N hydrochloric acid to the deposit dissolved it and produced hydrogen sulphide, detected by its effect on lead acetate paper. The solution gave a strong Prussian-blue reaction, indicating the presence of iron.

It was accordingly concluded that the black coloration was due to the formation of a fine precipitate of iron compounds, partly as iron sulphide. The original urine was found to contain 2.5 mg. of iron per 100 ml., presumably as a result of the administration of jectofer.

To see if the phenomenon was peculiar to this patient, single 24-hour specimens of urine were collected from each of 10 other patients receiving jectofer therapeutically and kept in clean but not sterile bottles. The patients presented no evidence of infection of the urinary tract. Urine colours were within the normal range initially, but in five cases the urines turned black within 24 hours.