TABLE IV

No. of Times Prescribed	Name of Drug
Under 60	Calcium
.. 50	Iron with folic acid, or liver, or hog's stomach
.. 40	Anthelmintics
.. 30	{ Phenytoin
	{ "Methedrine" and nikethamide
	{ Cold vaccines
.. 20	{ Other vaccines
	{ Mersalyl
	{ Ergot
	{ Ergotamine tartrate
	{ "Diparcol" and "trasentin"
7	{ "Pernivit"
3	{ "Priscol"
2	{ Thiouracil
	{ Stannoxyl
1	{ Antimalarial
	{ "Tridione"
	{ "Myocrisin"

prescribed more than 50 times, and that vaccines for the prevention of the common cold, for the use of which there can be little scientific justification, do not seem to have been popular.

Mersalyl is a valuable drug which was prescribed fewer than 20 times. It is, however, an example of a drug which the doctor often administers from his own stores. Nevertheless the number of times it appeared on these forms seems surprisingly low.

It also seems quite remarkable that *thiouracil* was prescribed only twice out of 17,301 prescriptions. In spite of the fact that it is often used under hospital supervision, it is generally the practitioner who writes the prescription for maintenance treatment. If this practice is general it can only be supposed that the conservative treatment of thyrotoxicosis with *thiouracil* is less common in England than might have been expected.

Conclusions

The study of a large number of prescriptions provokes certain reflections on the teaching of pharmacology and practical therapeutics in our medical schools. In some schools pharmacology is taught along with physiology as a preclinical subject. In others it is taught in the first clinical year, when the student has seen only a limited number of the disorders the treatment of which is discussed. Thereafter instruction in treatment is often limited to the last ten minutes of a medical clinic, and during the fifth and sixth years of his course the undergraduate often forgets the actions and uses of the drugs which he heard about while studying pharmacology. In consequence many young graduates go into practice with a very inadequate knowledge of applied pharmacology, and tend to rely more and more on the ingenious (sometimes very good, but sometimes very misleading) advertisements of the drug firms which cover his breakfast table. In the days when there were few potent or specific drugs this ignorance of applied pharmacology was of less importance. Nowadays when we are Jove-like in the therapeutic thunderbolts we can hurl—drugs potent for evil as well as for good—it is of paramount importance for us to be thoroughly conversant with the pharmacological tools of our trade. It is suggested, therefore, that a series of simple lectures in therapeutics by a practical physician interested in pharmacology should be given in the last clinical year of the medical course. It is a subject which lends itself to systematic lecturing, and is of more importance than the study of some of the more recondite specialties which at present overload the curriculum.

Courses in pharmacology in medical schools are now usually, and very properly, undertaken by academic scientific pharmacologists, who have revolted against the old-fashioned instruction in *materia medica* and in the compounding of elaborate prescriptions elegantly flavoured, meticulously bottled, and exquisitely labelled. They have realized that there are few occasions in practical therapeutics which demand the prescription of more than one drug in a bottle, tablet, or powder, plus the vehicle and flavouring agent. Perhaps, however, the pendulum has swung too far in the other direction and that inadequate instruction is now being given in the principles of correct simple prescribing. At a recent oral examination for one of the higher clinical diplomas five consecutive candidates were quite unable to write out a correct prescription for a simple laxative pill containing cascara and belladonna, though they were ready and eager to discuss the most abstruse and recondite clinical syndromes.

It has been the object of this survey to present modern trends in prescribing in an objective and uncontroversial manner. While it is the aim of us all to give our patients the best treatment possible it is also our duty to consider the means at the country's disposal. Good prescribing is often economical prescribing, and it is not improbable that the rewards of thoughtfulness in this respect will be enjoyed by both patient and doctor.

A CASE OF ACUTE BERIBERI COMPLICATING POLYSEROSITIS IN BRITAIN

BY

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Several cases of beriberi developing in Britain have been reported, and the subject has been reviewed by Jones and Bramwell (1939). Most of the cases have been secondary to chronic alcoholism, as in two cases described by Konstam and Sinclair (1940). Similarly vitamin-B₁ deficiency may be found in the absence of alcoholism if the diet has been subnormal over a long period, as in cases described by Yudkin (1938) and Bates (1941).

Apart from deficient food intake, vitamin-B₁ deficiency may arise from either one or more of the following factors (Harris, 1938): (1) imperfect absorption, as in chronic dysentery; (2) imperfect utilization, as in hepatic cirrhosis; (3) increased demand, as in pregnancy.

The case described showed signs similar to those of beriberi secondary to a severe illness, with prompt relief following the intramuscular administration of vitamin B₁.

Case Report

On the night of March 2, 1950, a 12-year-old girl, an only child, complained of headache and pain in the mid-sternal region. She did not sleep that night, and the next day was off her food and vomited at intervals. On the following day her own doctor diagnosed pneumonia, and a course of

sulphonamide was begun. As there was no improvement she was admitted to hospital on March 7. She did not complain of cough or of sputum, had not previously been breathless, and showed no cyanosis. During the previous two months her mother had noticed that she had not wanted to play and that she had been inclined to sweat at night. There had been no loss of appetite, but there was some constipation. She did not complain of sore tongue, and oedema had not been noticed.

She had had whooping-cough complicated by pneumonia at the age of 3, diphtheria thereafter, and then measles with pulmonary congestion at the age of 7. Her mother and father were both alive and well and there was no history or sign of tuberculosis in the family. Her diet prior to admission was quite normal in quality and amount, including meat, liver, bacon and eggs, much milk, vegetables in moderation, and a great deal of fruit. Her mother re-

On March 10 Mantoux 1:1,000 was positive and E.S.R. was 29 mm. in the first hour (micro-method; normal 10 mm.). Pericardial tap was carried out and 20 ml. straw-coloured fluid withdrawn, containing a large number of polymorphonuclear cells and 5.75 g. of protein %. No micro-organisms could be demonstrated in the fluid and microscopical examination for acid-fast bacilli was negative. On March 14 the liver was enlarged to 2½ in. (6.3 cm.) below the costal margin and was tender on pressure. Neck veins were engorged but no ascites was present. On the 17th she began to show some clinical improvement, with decrease in liver size and in the volume of the effusion.

An x-ray film of the chest on March 27 showed that the pericardial effusion continued to diminish, but there was a pleural effusion on the right side extending up to the eighth rib. Next day she complained of pains in her elbows, which were red and slightly tender. On the 29th she complained of pain in the left side of the neck, and the left side of the face became oedematous. There was no sign of glandular enlargement of the neck.

On March 30 the left side of the chest was oedematous anteriorly, and dullness to percussion became marked on the right side. The temperature was 100.8° F. (38.2° C.); the pulse rate had risen to 156 and respiration rate to 54. Puncture of the right pleural cavity yielded 9 oz. (255 ml.) of blood-stained fluid which contained 2.5 g. of protein per 100 ml., with lymphocytes and a few polymorphs. A large pleural effusion then became evident on the left side of the chest. Streptomycin, 0.5 g. twice daily, was given intramuscularly from March 31 to May 4.

During the next few days the facial oedema became less and the temperature, pulse, and respiratory rate settled, and E.S.R. on April 4 was only 5 mm. in the first hour. Despite this she became more dyspnoeic and cyanosed. On April 3 pericardial tap was attempted, but no fluid was obtained. Aspiration of the left pleural cavity carried out on April 4 produced 30 oz. (850 ml.) of straw-coloured but not blood-stained fluid. This fluid contained red blood cells and mononuclear cells.

From this time, four weeks after admission, she was given a salt-free diet and her fluid intake was restricted to 30 oz. (850 ml.) a day on account of increasing breathlessness and cyanosis. "Digoxin" was begun by mouth and pushed to the limits of tolerance; this was continued in a dosage of 0.25 mg. twice a day until April 11, when it was reduced to 0.25 mg. once daily until May 8. During this period she was extremely ill, requiring continuous oxygen to relieve cyanosis and paraldehyde four-hourly for her restlessness. There was oedema of the legs and sacral region as well as of her left arm and left side of face.

Mersalyl, 1 ml., given intramuscularly on April 9 and 11, on each occasion produced a copious diuresis for one day, as shown in the Chart. By April 10 the respiratory rate, temperature, and pulse rate were more settled, but were 35, 98.2° F. (36.8° C.), and 110 respectively. On April 14 the legs were still very oedematous and the skin of the legs and upper arms was noted to be scaly. Mersalyl, 1 ml., was repeated on the 17th with similar result, but she remained oedematous and the liver was enlarged below the umbilicus. An x-ray film of the chest on the 17th showed the persistence of a bilateral pleural effusion, which obscured the heart outline.

The fluid-balance chart illustrates the low output in comparison with the intake between the times on which mersalyl was given, despite digoxin and a salt-free diet. Up to this

Chart showing fluid balance

marked that the girl appeared to have grown very tall during the previous year and "was going dark under the eyes."

On examination on March 7 respirations were rapid and she was pale. The tongue was dry and coated, but there was no evidence of glossitis and the fauces were clear. The pulse rate was 110, regular in time and force; temperature 99.8° F. (37.7° C.), respirations 24. The apex beat was palpable just inside the nipple line, in the fourth left interspace 3 in. (7.5 cm.) from the mid-sternal line. There were no murmurs. The chest moved evenly with respirations and the trachea was central. The percussion note was impaired over the right lung anteriorly and there were inspiratory crepitations in the right mid-zone anteriorly. Breath sounds were bronchovesicular. Vocal resonance and fremitus were normal. Thorough examination of the abdomen and central nervous system revealed no abnormality. Blood white cell count was 24,600 per c.mm.

Treatment was begun with penicillin and sulphadimidine. This produced no improvement, and an x-ray film of the chest one day after admission showed the presence of a large pericardial effusion and normal lung fields. At that time she had orthopnoea and a short irritating cough. Re-examination of the heart clinically showed extension of deep cardiac dullness up to the third left rib and muffling of the heart sounds at all areas except the apex.

time the urine had contained albumin to the amount of 0.5 g. per litre per 24 hours, but there was no microscopical abnormality. On April 24 plasma albumin was 3.4 g.% and globulin 2.85 g.%.

Because of the unusual distribution of the oedema, its lack of response to treatment, and the presence of tenderness of the calves, 25 mg. of vitamin B₁ was given intramuscularly on alternate days, beginning on April 26. There was a rapid and dramatic improvement in the girl's condition. The diuresis, which had begun with an intramuscular injection of 1 ml. of mersalyl on April 26, continued for 13 days. Within 48 hours the oedema of the left arm had disappeared and that of the left leg was much less. On April 29 venous congestion in the neck was much less marked. By May 10 there was no oedema of the face, arms, legs, or sacral region. The calves were no longer tender and the liver was now only one fingerbreadth below the costal margin.

More remarkable than the diuresis, however, was the change in the patient's facies. Within 24 hours of beginning vitamin-B₁ therapy her appearance changed from one of distress to one of convalescence, and she obviously felt much better and much happier. Her appetite improved rapidly and her dyspnoea at rest disappeared. Vitamin-B₁ therapy was stopped on May 19, by which time the fluid intake and output approximated to one another, while an x-ray film of the chest showed a normal cardiac outline and the left pleural effusion clearing well, but with only slight improvement on the right side.

She was allowed up for a short while on June 28. A few days later she noticed that her hair was falling out in considerable quantity. The dermatologist (Dr. G. W. Senter) described the alopecia as of the diffuse type commonly associated with serious illness. This loss of hair did not become excessive and she continued to improve. Her serious condition had prevented her being weighed until June 7, when she was 5 st. 7 lb. (34.9 kg.). Thereafter her weight rose slowly to 5 st. 13½ lb. (37.9 kg.) on July 26.

On September 1 there was no evidence of oedema or signs of vitamin deficiency in the eyes, tongue, lips, or skin. Apart from the persistence of her right pleural effusion, the only findings of note were a network of prominent veins over the upper anterior part of the chest in the absence of congestion of the external jugular veins, and purple striae similar to striae gravidarum over the buttocks, lower thigh, and dorsum of the feet, most marked on the left side.

X-ray films of the chest on June 6 and August 29 had shown a slight increase in the right pleural effusion. Because of this, vitamin B₁, 25 mg., was resumed on September 1, being given intramuscularly on alternate days. On September 7, 30 oz. (850 ml.) of blood-stained fluid was withdrawn from the right pleural cavity. To ensure a more balanced intake of the vitamin-B complex, and in view of the increase of the pleural effusion, treatment was begun on September 15 with one tablet three times a day of "benerva" compound, which contains 1 mg. of aneurin, 1 mg. of riboflavin, and 15 mg. of nicotinic acid amide. There ensued an immediate increase in the fluid output, similar to that obtained from vitamin B₁ alone earlier in the illness. This moderate diuresis continued for the next three to four weeks, but with little change in the amount of fluid in the right pleural cavity. On October 10 the Hb was 95%, the white cell count 8,600, and E.S.R. 12 mm. in the first hour. On discharge to a pleurisy unit on October 27 her general condition was excellent despite the persistence of the right pleural effusion. She was eating well and gaining weight, and had no trace of oedema or respiratory distress. The purple striae on the limbs and prominent superficial veins over the chest still persisted, however.

Discussion

This girl's illness may be subdivided into four phases: (1) the prodromal period, culminating in a severe illness with pericarditis and bilateral pleurisy with effusion; (2)

temporary improvement during the third and fourth weeks in hospital, when temperature, pulse, and respiratory rate were settling and the E.S.R. was reduced to 5 mm. in the first hour; (3) recurrence of dyspnoea, with appearance of oedema and considerable hepatic enlargement, death appearing imminent from congestive heart failure; and (4) rapid regression of oedema and dyspnoea at the start of vitamin-B₁ therapy and continued improvement thereafter. Although no organism was isolated from the effusions and several guinea-pig inoculations were negative, it is probable that the polyserositis was due to tuberculosis.

The presence of vitamin-B₁ deficiency at the onset of the illness is considered unlikely in view of the absence of any predisposing factors, such as alcoholism, poor diet, chronic dysentery, malabsorption, or hepatic disease. In addition the acute and febrile onset of the illness and the finding of haemorrhagic serous effusions make it unlikely that vitamin-B₁ deficiency was the cause of the initial disease. According to Bicknell and Prescott (1942) the serous effusions in beriberi are of a clear greenish-yellow colour. The dramatic and immediate response to vitamin B₁ intramuscularly suggests, however, that the severe dyspnoea, oedema, and hepatic enlargement which developed after the acute illness were due to deficiency of vitamin B₁. It will be appreciated that vitamin B₁ possesses diuretic properties, apart from its action as a vitamin (Bicknell and Prescott, 1942). The improvement in the patient's general condition in this case, however, was as dramatic as was the diuresis. Jones and Bramwell (1939) state that vitamin B₁ has no effect on the normal heart or on cardiac failure due to other causes. In this case the lack of response to routine treatment makes it unlikely that the severe cardiac failure was due to a simple toxic myocarditis, and indeed Sweeney (1940) states that myocarditis is quite rare in pulmonary tuberculosis and makes no mention of beriberi as a complicating factor. One case of beriberi developing in a man aged 56 with pulmonary tuberculosis was described by Farber and Miller (1945).

Sumner (1949) describes three cases of pulmonary tuberculosis developing signs of vitamin-B deficiency while on streptomycin therapy, but these were signs mainly of riboflavin and nicotinic acid deficiency, and the patients had been on streptomycin over much longer periods. Weiss and Wilkins (1937) found cardiovascular disturbances due to vitamin-B₁ deficiency in 35 of 5,506 admissions to hospital and consider it commoner than congenital heart disease, adhesive pericarditis, or thyroid heart disease. As in a case of beriberi described by Konstam and Sinclair (1940), there was no enlargement of the heart in our patient with the onset of oedema, and consequently no alteration in the size of the heart following vitamin-B₁ therapy. There was little reduction in the pulse rate from the beginning to the end of the vitamin-B₁ injections.

The vitamin-B₁ deficiency in this patient may have arisen from the increased metabolism associated with a severe infection. Himwich *et al.* (1931) and Hendricks (1933) have shown that vitamin-B complex requirements are proportional to the body metabolism. Contributory factors might be the poor diet taken in the first few weeks of the illness, as the body is unable to store vitamin B₁ for any considerable length of time (Harris, 1938).

We have been unable to trace in the British literature any cases of vitamin-B₁ deficiency secondary to severe infection. This is surprising, as the pyrexial illness in this case did not exceed a period of five weeks. One possible explanation of this, apart from any hypothetical constitutional factor, is that at the time of her illness this girl was pubescent. Ashworth and Sutton (1942) have shown the adverse effect of oestrogen on the utilization of the vitamin-B complex. On admission this girl had a good growth of pubic hair and marked early development of the mammae. It may be that the presumably high level of oestrogen in her circulation at that time impaired her utilization of vitamin B₁ and so contributed to the production of clinical signs.

In addition to the deficiency of vitamin B₁ the temporary presence of hyperkeratosis and of some darkening of the skin suggest some deficiency of vitamin A and of nicotinic acid. Both signs regressed completely after cure of the vitamin-B₁ deficiency and the taking of a normal diet. There were never any signs of riboflavin deficiency.

ADDENDUM.—During 1951 it became obvious that constrictive pericarditis had developed. In consultation with Professor I. G. W. Hill and Mr. M. Fallon it was decided to carry out pericardectomy, which was done on June 5, 1951. The patient made an uneventful recovery, and is now (January, 1952) attending school once more. Vitamin supplements were continued until the time of operation. Tuberculous tissue was found in the parietal pericardium removed at operation.

Summary

A case of multiple vitamin deficiency presenting the clinical picture of acute beriberi is reported in a patient suffering from polyserositis, possibly of tuberculous origin.

It is suggested that the toxic process causing the polyserositis also produced the beriberi symptoms.

No similar case has been discovered in the British literature.

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GRANULOMATOUS ULCER OF THE NOSE TREATED WITH CHLORAMPHENICOL

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Some 35 cases of progressive granulomatous ulcers of the nose, face, and palate of unknown aetiology have been reported since 1896, when McBride first described a case of rapid ulcerative destruction of the nose and face. The literature on the subject has been reviewed by Stewart (1933a), Hoover (1941), Hargrove *et al.* (1946), and Williams (1949). No curative treatment has as yet been discovered; the course of the disease is slowly progressive, ending fatally in most cases. There have been only four reports of recovery. Woods's (1921) second case was healed after implantation of radium needles, and M'Arthur (1925) used x-ray therapy successfully. Schütz (1938) is quoted by Hoover as having reported a spontaneous cure, and Hoover himself

described an atypical case which recovered. Since the advent of antibiotics there have been reports by Hargrove *et al.* (1946) and Williams (1949). In the case described by Hargrove *et al.* penicillin appeared to control the spread of the lesion, but the patient died of pneumonia. In Williams's first case the patient died from exhaustion despite intensive treatment with penicillin, and penicillin-resistant staphylococci were cultured on numerous occasions from the ulcerated area on the nose, and from other lesions which developed on the arms and legs. The other two cases described by Williams (1949) were also fatal, but the cause of death was stated to be a lymphoma in one case and periarteritis nodosa in the other. The following case of this rare condition is considered worthy of record, as a penicillin-resistant staphylococcus was isolated repeatedly from the ulcerated area and treatment with chloramphenicol controlled the infection and resulted in healing of the ulcer, "aureomycin" previously having failed to do so.

Case Report

A married woman aged 35, employed as a part-time assistant nurse at the Sheffield Royal Infirmary, underwent an operation for submucous resection of the nasal septum on June 26, 1950. The operation was successful in relieving her nasal obstruction and she appeared to recover satisfactorily. On August 10, however, she developed a painful pustule in the left nostril, and was treated with penicillin cream locally and procaine penicillin systemically—600,000 units daily for 10 days. By this time an ulcer extending from the floor of the left nostril to the upper lip was present. She was referred to the skin department on September 4. She was not taking drugs.

Examination revealed an ulcer spreading from the floor of the left nostril to the ala nasi and to the upper lip. The ulcer was covered with a leathery black crust, and the spreading edge was raised and showed firm induration extending 1 cm. beyond the visible margin. At the edge of the crust there were small vesicles. The left cheek and lower eyelid were swollen and oedematous. The regional lymph nodes were not enlarged. Though the ulcer was painful she did not complain of constitutional symptoms and was not febrile. The ulcer was presumed pyogenic in origin, but investigations were carried out to exclude diphtheria, syphilis, anthrax, actinomycosis, and the possibility of an underlying foreign body. No foreign body was found in the nose. Blood Wassermann and Kahn reactions were negative. Radiography of the sinuses and bones of the face and teeth showed no abnormality. A blood count gave 5,000 white cells per c.mm. (52% polymorphs, 38% lymphocytes, 5% monocytes, 5% eosinophils).

Culture of aerobic and anaerobic swabs from the nose and ulcer yielded a mixed growth of a haemolytic streptococcus and *Staphylococcus pyogenes*, and a corynebacterium which was later proved non-virulent to guinea-pigs. No anaerobic streptococcus was isolated. The staphylococcus was found to be sensitive to 1,000 units of penicillin per ml., 500 µg. of streptomycin per ml., 6 µg. of chloramphenicol per ml., and 0.375 µg. of aureomycin per ml. In view of the continued spread of the ulceration the patient was admitted to the ward on September 9 and given aureomycin 250 mg. three-hourly, and applications of saline to the ulcer. On September 14 the ulcer had ceased to extend but showed no sign of healing. Repeated cultures from inside the nose and from the ulcer revealed a *Staph. pyogenes* with the same sensitivity to the antibiotics as above. It was at this stage that a diagnosis of so-called malignant granuloma of the nose was first considered. In view of the grave prognosis if this diagnosis was correct and the success of radiotherapy in the past, superficial x-ray therapy, 200 r, was given to the upper lip and the patient was transfused with 2 pints (1.14 litres) of fresh blood.