SEVERE AND FATAL PHENOBARBITONE ERUPTIONS

BY

I. B. SNEDDON, M.B., Ch.B., M.R.C.P.

Consultant Dermatologist, United Sheffield Hospitals

AND

A. W. D. LEISHMAN, M.A., D.M., F.R.C.P.

Consultant Physician, United Sheffield Hospitals

With the world-wide increasing consumption of phenobarbitone it is comforting, though perhaps surprising, that reports of dangerous reaction to this drug have been so few. Nevertheless it has been estimated that between 1 and 3% of patients taking phenobarbitone develop skin reactions. Recently it has been brought home to us that such skin reactions, far from being innocent, may unexpectedly lead to a dangerous illness and death. We are therefore prompted to report our experience, since we do not believe we have been alone in underestimating the consequences of a phenobarbitone eruption.

In the past 18 months we have seen, at one hospital, four severe cases of phenobarbitone eruption; two of these ended fatally, and a third, equally severe, was saved only by the use of A.C.T.H. Though few similar cases have been reported, this experience suggests that the condition is not a rarity, and it may well be that on a number of occasions the association of this severe illness with phenobarbitone has escaped notice. Since the first report by Chavany and Vannier (1929) of a fatality from skin eruption due to phenobarbitone, 14 fatal cases have been published by Brunsting (1932), Millard (1933), Poole and Wehger (1934), Heckmann (1935), Scarlett and MacNab (1935), Sweitzer and Laymon (1937), Wile and Benson (1940), Winer and Baer (1941), and Sexton *et al.* (1941), and one severe but non-fatal case by Winton (1946). In general the clinical description of these cases has conformed closely to our own.

Case 1

A housewife aged 73 was first seen by one of us (I. B. S.) on April 20, 1950. Six weeks previously she had complained of retrosternal pain and dyspnoea, which had been diagnosed by her doctor as due to a coronary occlusion. He had been unable to find any objective physical signs to support the diagnosis, but as a precaution had kept her in bed and prescribed phenobarbitone, $\frac{1}{2}$ gr. (32 mg.) thrice daily. On April 16 she developed a generalized erythematous maculo-papular eruption. The phenobarbitone was stopped and mepyrmine hydrogen maleate ("anthisan"), 100 mg. thrice daily, was given. The skin eruption continued to spread, and her doctor sought further advice. When examined on April 20 she did not appear seriously ill or distressed, but the face, limbs, and trunk were covered with a profuse bluish-red morbilliform eruption which in places was becoming confluent. Her mucous membranes were unaffected, and there was no enlargement of lymph nodes, liver, or spleen. Heart sounds were normal and B.P. was 140/90. It was considered that the eruption was due to an allergic response to the phenobarbitone, and a good prognosis was given in the belief that the drug would soon be eliminated. On April 27, her condition having deteriorated, she was admitted to hospital.

On admission it was apparent that she was gravely ill. She was drowsy, febrile, incontinent, and collapsed. Her B.P. was 90/70, temperature 104° F. (40° C.), and her lips and tongue were dry and cracked. The skin eruption was confluent over the whole body and had become purpuric, and

in some areas it was desquamating. Her appearance was that of severe toxæmia with peripheral circulatory failure.

The white blood cells numbered 24,000 (metamyelocytes 4%, polymorphs 75%, lymphocytes 10%, monocytes 8%, eosinophils 3%). Blood non-protein nitrogen was 160 mg./100 ml.; plasma chlorides, 620 mg./100 ml. The cerebrospinal fluid showed no abnormality, and pressure was not raised. The urine contained a cloud of albumin; microscopic examination was negative. An electrocardiogram showed no evidence of infarction. Despite active measures to combat the uræmia, she lapsed into coma and died on May 2.

Necropsy showed passive congestion and oedema of the brain and lower lobes of the lungs. The left ventricle of the heart was hypertrophied and the myocardium infiltrated with fat. Diffuse atheromatous changes were present in the aorta and cerebral and coronary arteries; there was no evidence of coronary thrombosis. The liver was enlarged and showed fatty infiltration. The kidneys were smaller than normal, contracted, and firm, with rough granular surface and narrow cortex. The suprarenals were normal. Microscopical examination of the organs did not add anything of significance to the above findings.

Case 2

An assistant cashier aged 53 was first seen by one of us (A. W. D. L.) on March 29, 1951. His previous history was uneventful; he had had no illnesses of note and had never experienced chest pain on exertion. Some four weeks previously he had been seized with a constricting pain across the upper chest which lasted for approximately two hours; this did not radiate to either arm and was not repeated. It was accompanied by some dyspnoea but no palpitations. His doctor thought it highly probable that he had had a cardiac infarct, and kept him in bed and treated him accordingly. The cardiac condition gave no cause for disquiet, but the patient's increasing anxiety and agitation demanded the prescription of phenobarbitone in a dosage of $\frac{1}{2}$ gr. (32 mg.) four times daily.

Two weeks later a rash developed, and temporarily the barbiturate dosage was reduced. On return, however, to full dosage the rash increased and became generalized. Examination at this time showed him to be depressed and tremulous. The skin was covered with a typical drug rash of maculo-papular type; there was no exfoliation. His general condition was fairly good; the heart appeared slightly enlarged, but sounds were of good quality, with regular rhythm, rate 90; there were no murmurs; B.P. 120/74. There was no indication of cardiac insufficiency. The lungs were clear, the abdomen was normal, and there was no oedema. Examination of C.N.S. was normal apart from a possible extensor plantar response on the right side. Opinion at this time agreed with the diagnosis of a previous small cardiac infarct and a drug eruption due to phenobarbitone. No alarm was felt. It was advised that barbiturates be stopped altogether and promethazine hydrochloride ("phenegan"), 25 mg., be given thrice daily.

During the following week, despite these measures, his condition greatly deteriorated and he was admitted to hospital on April 4. He was extremely ill, being disorientated and incontinent; his temperature ranged between 102 and 104° F. (38.9 and 40° C.). The skin was covered with an exfoliating rash; the mouth and tongue were dry and foul. Venous pressure in the neck was not increased; the heart size was unaltered; there was regular tachycardia (120 to the minute); heart sounds were clear and without murmurs; and the blood pressure was 120/90. There was a small area of consolidation in the axillary segment of the right lung. The abdomen was normal. There were no objective neurological signs other than doubtful bilateral extensor plantar responses.

Examination of the blood showed: haemoglobin, 104%; red cells, 5,100,000; colour index, 1; white cells, 14,000 (band cells 5%, polymorphs 65%, eosinophils 2%, lympho-

cytes 12%, monocytes 16%); sedimentation rate, 24 mm. in one hour. Serum potassium, 20.4 mg./100 ml.; serum sodium, 344 mg./100 ml.; blood urea, 68 mg./100 ml.; serum chlorides, 585 mg./100 ml. An electrocardiogram showed sinus tachycardia, generalized low-voltage curves, a flat or biphasic T wave in lead I and an inverted T wave in the fifth and sixth chest leads. There were no significant Q waves. These changes were compatible with coronary ischaemia, but were by no means typical of a previous cardiac infarction.

The dose of phenegan was increased to 100 mg. twice daily without any improvement in the patient's condition, and on the day after his admission he was given 300 mg. of cortisone intramuscularly, followed by daily injections of 100 mg. There was no improvement in his condition: he became delirious and finally comatose, and died on April 7.

Post-mortem examination of the internal organs revealed few striking changes, but the brain was moderately enlarged and very oedematous, and all blood vessels of the meninges and brain were engorged. The lungs showed confluent patches of recent bronchopneumonia; the trachea and bronchi contained much mucous exudate, and the mucosae were congested and oedematous. The heart was of normal size, the myocardium was flabby, and the aortic valves were calcified. The coronary arteries were not atheromatous, and there was no evidence of coronary thrombosis. Both liver and spleen were enlarged. Microscopical examination of sections from the skin and muscle and numerous organs showed no specific changes.

Case 3

A housewife aged 66 consulted her doctor in July, 1951, because of an attack of giddiness and a feeling of tiredness. No abnormal physical signs were discovered and she was given phenobarbitone, $\frac{1}{2}$ gr. (32 mg.) thrice daily, with improvement in her symptoms. At the end of August she noticed a burning of the skin all over her body, and a bright-red rash appeared. Her doctor stopped the phenobarbitone and gave her anthesisan, 100 mg. thrice daily. She then went away to the seaside for two weeks' holiday. While she was there her face became more swollen after exposure to sunlight and she began to feel weak and nauseated, and also complained of dry cough and a pain in the chest on coughing. On her return home on September 15 she was admitted to hospital.

On admission she had a temperature of 104° F. (40° C.) and a pulse of 110, and the skin was covered with a morbilliform erythematous rash, which on the abdomen showed "iris" type lesions. In places the erythema was confluent. Her face and the V of her neck showed considerable oedema of the skin and in places exudation and crusting. Ulceration of the oral mucosa and lips was present. There were no other abnormal physical findings; her B.P. was 148/76.

The blood urea was 52 mg./100 ml. The white cells numbered 12,000 (metamyelocytes 5%, polymorphs 61%, lymphocytes 14%, monocytes 6%, eosinophils 14%). No Hargrave cells were found. An electrocardiogram was normal. A radiograph of chest showed no abnormality. The urine contained no abnormalities. No specific treatment was given. During the next few days the erythema on her trunk and limbs faded and the skin desquamated in a similar fashion to scarlet fever. The skin of her face and V of neck, however, became more crusted and secondarily infected before improvement was shown a week after admission. She continued to have a swinging temperature for 14 days, but this then settled. Her blood urea on September 27 had fallen to 32 mg./100 ml. She was discharged home well three weeks after admission. Two weeks later she developed diffuse alopecia of the scalp hair.

Case 4

A 25-year-old housewife of Italian birth came under our care on September 18, 1951. Some five months previously she had been under investigation in the neurological ward

for minor epileptic fits for two years' duration. These were considered to be due to idiopathic epilepsy, and since then she had been taking phenytoin sodium ("epanutin"), $1\frac{1}{2}$ gr. (0.1 g.), thrice daily and phenobarbitone, $\frac{1}{2}$ gr. (32 mg.), twice daily. On September 1 a rash had started on her face and arms, and had gradually spread over the entire body. (She had been admitted on September 14 to an isolation hospital, where, in the belief that her rash was due to an infection, she was given chloramphenicol, 250 mg. six-hourly.) She had become progressively more drowsy and ill, and lapsed into semi-consciousness shortly before admission to our hospital.

On examination she was stuporous, lying in a general attitude of flexion and resenting any attempt to examine her. She had Cheyne-Stokes respiration. The pulse of 100 was soft and thready and the temperature 104° F. (40° C.). Her whole body was covered with a bright-red erythema, and the skin of her face and neck was swollen and desquamating. No abnormal physical signs were found in her chest, abdomen, or central nervous system. The systolic blood pressure was 70; the diastolic pressure was unobtainable. A lumbar puncture revealed clear fluid under normal pressure, with normal cytology. The blood urea was 56 mg./100 ml. The white blood cells numbered 13,000, with a simple polymorphonuclear leucocytosis. The haematologist reported scattered abnormal lymphocytes of a type seen in drug eruptions.

In view of the history of phenobarbitone and epanutin and her resemblance to the other cases, the diagnosis was clearly that of a toxic drug eruption of a most severe type, and she appeared to be moribund. With difficulty, since her veins were tightly contracted, 50 mg. of A.C.T.H. in 1 litre of 5% dextrose was given intravenously during the night. The next morning her temperature had fallen to normal, the Cheyne-Stokes respiration had ceased, she had regained consciousness, and the erythema of her skin was much paler. On September 19, 30 mg. of A.C.T.H. was given in dextrose, and on the 20th and 21st 20 mg. On September 21 her temperature, which had remained normal, rose again to 104° F. (40° C.). At first this was thought to be due to thrombophlebitis in the vein used for the infusion, but on the next day signs of pneumonia were present at the right base. The A.C.T.H. was therefore stopped. Despite the pneumonia her general condition had improved and her skin was now pale but peeling. A chest radiograph showed consolidation of the right lower lobe and the left upper lobe.

Despite the presence of a penicillin-resistant staphylococcus in her sputum, the pneumonia responded slowly to chloramphenicol, 500 mg. six-hourly, and she was discharged home well on October 25. It was considered too hazardous to let her take epanutin and phenobarbitone again for the control of her epilepsy, and with the consent of the neurologist she was advised to take only bromides. When seen two weeks later she had diffuse alopecia.

Discussion

Drug eruptions due to acquired hypersensitivity have increased in number with the greater use in recent years of complex organic compounds. For example, phenylethylhydantoin ("nirvanol") attained notoriety on account of the almost inevitable drug rash which followed its use. Barbiturates form an important group of chemicals. According to Potter and Whitacre (1944), the long-acting barbiturates, such as phenobarbitone, cause skin reactions more often than the short-acting barbiturates, such as pentobarbital sodium ("nembutal") and sodium propylmethylcarbinylallyl barbiturate (quinalbarbitone, "seconal"). Commonly, the eruptions are harmless and will subside on withdrawal of the offending drug. It is therefore disturbing to find that in some cases of acquired hypersensitivity to phenobarbitone the eruption continues to extend, and that constitutional symptoms may appear some weeks after the drug has been stopped.

The amount of phenobarbitone which has been given before the eruption and illness appear may vary greatly, and in Chavany and Vannier's (1929) first case 1½ gr. (0.1 g.) daily for nine days proved fatal. In our cases the highest daily dosage was 2 gr. (0.13 g.). Our diagnosis was based on the characteristics of the skin eruptions, the history of exposure to phenobarbitone, and the clinical course, which conformed closely to other accounts of phenobarbitone eruptions. In view of the risk involved no attempt was made to establish the diagnosis by deliberate re-exposure to the drug. Tests of this type, according to Sulzberger and Baer (1945), may in any case be misleading, since a patient in a refractory phase will fail to react to the drug which caused the eruption. They also state that skin tests are of no value in drug eruptions of this kind.

In our fourth case the possibility that epanutin may have caused the eruption cannot be excluded, but the clinical condition and course of the illness was so similar to the other three cases that we are more inclined to incriminate phenobarbitone. The cause of death in these cases is far from obvious.

In the necropsy reports of other fatal cases no specific changes were found, and death was usually ascribed to terminal bronchopneumonia. In the cases described by Millard (1933) and Poole and Wehger (1934) chronic nephritis was also reported, but renal damage has not been a general finding. In our first case there was certainly chronic renal disease, but this was not found in our other fatal case. It is probable that where there is defective excretion phenobarbitone hypersensitivity is more likely to be fatal. Cerebral irritation was a feature of three of our cases, but there was no rise in cerebrospinal-fluid pressure as was found by Jenkins (1949) in a remarkable case of phenobarbitone idiosyncrasy in which the patient twice became unconscious a few hours after a small dose of the drug. Cerebral oedema, however, was found at necropsy in both of our fatal cases. No evidence of disseminated lupus erythematosus or periarteritis nodosa was found in any of the cases, though it is interesting that Rennie *et al.* (1951) describe periarteritis nodosa as a sequela of an exfoliative dermatitis due to phenobarbitone. It can surely only be coincidence that in two of our cases a clinical but unsubstantiated diagnosis of coronary thrombosis had earlier been made, though Winton (1946) has described severe phenobarbitone eruption in a proved case of myocardial infarction.

On the basis of this small experience it would not be fruitful to speculate too far on the nature of this illness. Nevertheless, the absence of specific pathological changes, the fulminant course, and the appearance of these patients in the terminal stages suggest that they died from a biochemical cause. It may be that this conception, nebulous though it be, receives some support from the recovery of our fourth patient, after treatment with A.C.T.H. when in an apparently moribund condition. The response in this case was so remarkable that we have no doubt that this drug must be given further trial in similar cases.

It is not necessarily surprising that cortisone, on the other hand, proved ineffective, for experience with these two drugs in the treatment of disseminated lupus erythematosus and other collagen diseases (Irons *et al.*, 1951) has shown that A.C.T.H. has much the more rapid action; also it must not be forgotten that when given by the intravenous route, as in our case, the potency of A.C.T.H. is greatly enhanced.

Summary

Four cases of severe allergic reactions to phenobarbitone given in therapeutic dosage are described.

It is suggested that the potential dangers of phenobarbitone skin eruptions may not be sufficiently appreciated.

Post-mortem examination in these cases, as in those previously published, has shown no specific pathological changes.

The life-saving effect of intravenous A.C.T.H. in one case and the failure of cortisone to influence another is reported.

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CHOLESTEROL TOLERANCE IN CORONARY THROMBOSIS

BY

IAN WANG, M.B., M.R.C.P.Ed.

Medical Registrar, Victoria Infirmary, Glasgow

This investigation was planned to determine whether the dietary cholesterol content bore any relation to coronary thrombosis, and, in particular, to learn if patients suffering from coronary thrombosis showed intolerance to cholesterol.

The subject of cholesterol and atheroma has received much attention of late, especially in America, and recently has been reviewed by Firstbrook (1951), who pointed out the importance of coronary artery disease as a cause of death and disability, defined the terminology and pathology, and gave seven main lines of evidence suggestive of plasma cholesterol being implicated in the development of atherosclerosis.

It may be stressed here that cholesterol feeding has proved to be the most consistent method of producing atheroma in experimental animals. Dauber and Katz (1942, 1943), using chicks, showed that atheromatous lesions could be produced consistently, even in omnivora, through a high cholesterol diet alone. Dauber (1944) proved that chicks were suitable experimental animals, when used before six months. The failure of high cholesterol feeding to produce atheroma, or even to raise the blood cholesterol, in some omnivora (Duff, 1935), in contrast to the constant success among herbivora, is possibly explained by the difference in cholesterol storage shown by Menschick and Page (1933), who found that in rabbits the distribution of cholesterol was diffuse, while in cats the distribution was confined mainly to the liver. This difference may account for the difficulty in producing hypercholesterolaemia in omnivora. Nevertheless, no other method in the experimental field is as successful as cholesterol feeding in producing lesions morphologically identical to human atherosclerosis.

Among humans, atherosclerosis often occurs in diseases associated with hypercholesterolaemia—for example, in diabetes (Bowen *et al.*, 1939), myxoedema (Bruger and Rosenkrantz, 1942), nephritis (Weinhouse, 1943), and hereditary xanthomatosis (Boas and Aldersberg, 1945). It would therefore appear that even in humans the presence of hypercholesterolaemia predisposes to the production of atherosclerosis, although,