ACETANILID POISONING FROM THE USE OF PROPRIETARY HEADACHE POWDERS.*

A. E. AUSTIN, M.D., AND
R. C. LARRABEE, M.D.
BOSTON.

The use of "patent medicines" by the laity has grown to such proportions that it has come to be looked on by physicians as a necessary evil. Many such medicines are inert, in which case their deleterious influence is exerted chiefly on the pocket of the purchaser. Unfortunately, patent medicines containing potent drugs are often sold without the slightest warning concerning excessive doses, and the experienced physician who has not seen injurious effects from them is either hopelessly blind or hopelessly prejudiced. Warnings against overdoses are rarely seen on the labels of such remedies, for the reason that the public would take alarm and the sale be diminished.

No class of remedies is subject to more abuse than the so-called headache cures. In no class is caution more needed, for the chief ingredient is almost always acetanilid. The reason for the wide use of this drug is easily seen when it is noted that the remedy used in the two cases herewith reported costs 25 cents for a box of ten powders, each containing about four grains of acetanilid, or about four grains of acetanilid and about a grain of camphor. Acetanilid may be bought by any one for 40 cents a pound and camphor is high at \$1.25 a pound.

The symptoms of acetanilid poisoning need not be given in detail here, but we may say in brief that cases fall into two classes. In acute cases due to single doses the chief phenomena noted are those of collapse and circulatory depression, coldness of the skin, sweating, palpitations, disturbances of the pulse, superficial breathing, cyanosis, dullness of intellect or total unconsciousness, followed in case of recovery by persistent muscular weakness. In cases in which doses too small to produce these effects are taken for a considerable period of time, susceptible persons may show extreme cyanosis, with very little evidence of injury to the circulatory apparatus. In both forms, particularly in the more chronic ones characterized by severe cyanosis, there is a most disastrous effect on the red corpuscles. Their hemoglobin is in part converted into methemoglobin and thus rendered incapable of performing its function of carrying oxygen. The destruction of red corpuscles may result in an anemia of a most severe type.

It is a common practice to "guard" the action of acetanilid in headache powders by the addition of substances like camphor or caffeine designed to act as cardiac stimulants. It is conceivable that they might have some effect in preventing the acute collapse, but it is difficult to see how they could have the slightest effect in preventing the conversion of hemoglobin to methemoglobin.

Our attention was called to this subject by two cases, in both of which the popular remedy "Nervease" had been taken for the cure of headache, and which are reported in full as follows. The first occurred in the service of Dr. Larrabee:

CASE 1.—A married woman of 43 was seen in the out-patient department of the Boston City Hospital. She gave a long history of aural sepsis, beginning at the age of 6 years. She had suffered from occipital headaches as long as she could remember. In 1901 these became much worse and in 1903 she came to the hospital complaining of this symptom and of vomiting and constipation. Notes made at the time record a palpable enlargement of the spleen and enlargements of the lymph nodes in the neck and left axilla. There was a mod-

erate leucocytosis and the hemoglobin was 60 per cent. The glands afterward suppurated. They were probably the result of the aural disease. Shortly after, Dr. G. A. Leland operated for mastoid necrosis. Though the operation was successful and recovery was prompt the headaches were not wholly relieved.

In January, 1905, two years later, she returned to the hospital. For years she had been taking a proprietary headache powder sold under the name of "Nervease"—often as many as six powders a day, and sometimes even a whole box of ten. At first these gave relief to the pain, but for three weeks the headache had been unusually severe and there had been some nausea. The urine had been red in color and there was slight dyspnea—not enough to be at all disabling. She knew she was blue, but the fact had not appealed to her as indicating anything out of the way. Her appearance on the cold day when she first presented herself for treatment was most astonishing. The color was a deep, dusky blue. The lips and nails were at times almost black. In spite of this her general condition was perfectly good and there was no evidence of dyspnea or suffering. The pulse and respirations were not increased in rapidity. Apart from an easily palpable spleen, nothing further was found on physical examination. Dr. Leland examined her ears and reported that no active disease was present.

The blood was almost black as it flowed from the ear, and when spread on the filter paper the color was such that the hemoglobin could not be estimated by the Tallquist method. The specific gravity by the method of Hammerschlag was 1052 corresponding to a hemoglobin percentage of 70. Red corpuscles, 3,168,000. White corpuscles, 6,400. A differential count of 500 white corpuscles resulted as follows:

	Per cent.
Polymorphonuclear neutrophiles	75.6
Small mononuclear basophiles (lymphocytes)	19.0
Large basophiles (large mononuclear and transitionals) ..	4.8
Eosinophiles	0
Mast cells	0.4
Myelocytes	0.2

During this count one nucleated red was seen, a normoblast. There was slight polychromatophilia and rare basic stippling. The reds varied much in size and shape. Many were broken and distorted. There was moderate achromia and the hemoglobin appeared unusually irregular in its distribution within the cells. There were no parasites. No abnormalities were noted in the platelets.

Spectroscopic examination of the blood showed methemoglobin.

The urine was normal except for an excess of urobilin; it contained no hemoglobin, methemoglobin nor hematoporphyrin.

She was directed to stop taking the powders and potassium bromid was given instead. She was also given a capsule containing five grains of mass of ferrous carbonate and one-sixth of a grain of extract of nux vomica, three times daily. Also ten grains of potassium iodid three times daily. Three weeks later there was little or no cyanosis or headache. The color of the blood was normal.

Nearly a year later she returned to the clinic, stating that for several months the headaches had again become severe and that she had had pain and swelling in the left ear. For a fortnight she had been using "Nervease" again, never more than two powders daily. The cyanosis had promptly returned, but, save for slight dyspnea, no other unfavorable symptom had accompanied it. The ear was examined by Dr. Leland, who found no active disease. The skin showed the same blue color as before, but to a much slighter degree. The spleen was enlarged.

The hemoglobin could not be estimated by the older colorimetric methods for the same reason as before. By the Sahli test there was no difficulty, the percentage being 81. Red corpuscles, 3,808,000. White corpuscles, 10,500. A differential count of 500 white corpuscles resulted as follows:

	Per cent.
Polymorphonuclear neutrophiles	72.6
Small mononuclear basophiles (lymphocytes)	22.0
Large basophiles (large mononuclears and transitionals) ..	4.0
Eosinophiles	0
Mast cells	1.4

There were no nucleated reds. The qualitative changes were

* From the Medical Chemistry Laboratory of Tufts College.

about the same as before, but decidedly less severe. The spectroscope again showed methemoglobinemia.

The second case occurred in the practice of Dr. John Warren Achorn:

CASE 2.—The patient, a female, unmarried, dressmaker, complained of headache on the top of her head for which she had been taking six "Nervease" powders daily. She complained of loss of energy and nausea, though she had not vomited. She also said that the night before coming under observation she had taken the contents of one box or ten powders. The patient was livid with dark blue nails. The pulse was tense and hard. The blood contained methemoglobin. The red blood corpuscles amounted to 3,991,000, the whites to 9,855. Hemoglobin could not be estimated by the common color tests on account of the peculiar chocolate shade of the blood. A differential count of 200 leucocytes showed:

	Per cent.
Polymorphonuclear neutrophils	62.5
Small mononuclear basophiles	19.0
Large basophiles	15.0
Eosinophiles	3.5
Mast cells	0
Myelocytes	0

A very few granular red corpuscles were found.

The use of the powders was stopped and the patient rapidly regained her health.

As the symptoms of both these cases were plainly attributable to the "Nervease," our next efforts were directed to the determination of the character of the deleterious ingredients in the remedy. Samples from two boxes were analyzed, the first bought Jan. 14, 1905, the second Jan. 31, 1906. The powders weigh approximately 0.5 gram; the substance is pink in color with small glistening granules scattered through it, and has a pungent taste. It is but slightly soluble in water. This description applies only to the powders purchased in January, 1905; those bought in January, 1906, have camphor added, which is discernible not only by odor but by chemical tests. On heating with hydrochloric acid and the subsequent addition of phenol and hypochlorite of calcium, both samples gave a red color, which subsequently changed to blue on the addition of ammonia. This is a positive test for acetanilid. A powder of each was then extracted with water acidulated with hydrochloric acid, which separated it from the camphor in the second box, and the solution extracted with chloroform, which was then evaporated and the residue weighed. It was absolutely colorless and showed nothing but glistening crystals.

The average of two determinations of the acetanilid in this manner gave 0.281 gram, the difference between the samples purchased in 1905 and in 1906 being inconsiderable. As the dose is given as from 0.2 to 0.8 gram, with the maximum for twenty-four hours 1.3 grams, we can plainly see that the second patient, according to this, was taking 1.686 grams daily, and in one night had taken 2.81 grams of this substance. Yet in the circular accompanying the box we read: "Contains no opiate and is perfectly harmless." The camphor in the second sample was extracted from the residue from which the acetanilid had been removed with alcohol and found to amount to 0.075 gram. The ordinary dose of camphor is from 0.13 to 0.65 gram, with a maximum daily amount of 1.3 gram, so that the danger from camphor is not great.

The lesson is that drugs of this dangerous character should not be dispensed except on a physician's prescription, and their sale should be as strictly guarded as is that of strychnia or aconite. The use of a danger label would throw the responsibility of an overdose wholly on the patient. The German government limits the character of the ingredients which may enter a headache powder openly sold to the public to harmless substances, like

bicarbonate of soda and caffeine, and it seems that the time has arrived when this country should do likewise. The least that can be demanded of manufacturers of nostrums is that they state plainly on the label the ingredients of their preparation and the amount of each. Surely they should not be permitted to label "perfectly harmless" a box of powders containing a drug so powerful for harm as acetanilid.

A SIMPLIFICATION OF THE USUAL TECHNIC OF SKIN GRAFTING.*

JOHN EGERTON CANNADAY, M.D.

PAINT CREEK, W. VA.

In several forms of minor surgical work considerable satisfaction is obtainable even when comparatively careless methods are pursued. However, in the particular field of this subject a minutely planned and carefully carried out technic is essential to a successful issue.

The need for repairs to the epithelial covering may arise from the following causes: deep burns, lacerated wounds, the sloughing of flaps, gangrene from frost bite and other causes, varicose and other ulcers, the correction of deformities and the excision of malignant growths. Bared areas can only cover themselves by the reproduction of epithelium around the edges. After a varying length of time, dependent somewhat on the individual case, this border-line epithelium becomes apparently entirely exhausted and ceases to reproduce itself further. Then Nature must be assisted. Indeed, it is not usually best to wait until she has thrown up the sponge.

Unless the denuded area is quite large, it is usually most convenient to take the grafts from the individual needing them. Inasmuch as molecular life persists for some time after somatic death, one can often get about a hospital a suitable material from amputations and other operations. The skin and underlying tissue can be kept in warm normal saline solution for several hours until needed. The skin of the white when grafted on to the negro in time assumes the coloring of its host, and the reverse obtains when the skin of the black is transplanted to the white. Frogs, chickens and pigs have loaned their integument to man with very good grace. Once I grafted skin from a common water lizard on the foot of an Italian with a fair measure of success. The skin of the anterior portion of the arm or thigh is of suitable character for this work and from its location is very accessible. Especially when the defect to be covered is on a limb it is usually advantageous to take the grafts from a nearby location.

Among the many methods in vogue for securing a clean granulating site I have found the bi-daily wet dressing of gauze (wet with chloral hydrate, grs. ii to the ounce of water) kept covered with oiled silk to be satisfactory.

In my work I use the Thiersch graft. I have the part from which the shavings are to be taken carefully cleansed with liquid antiseptic soap, gauze pad, warm sterile water and alcohol. The granulations are irrigated with hot saline solution and the surface is freshened by a very gentle rubbing with an ordinary sterile nail brush. This freshens the granulations without destroying them. Some time since I abandoned the curette for this purpose. With it smooth and even freshening is an impossibility. It tears off the granulations *in toto* and leaves an irregular surface having an

* Read before the Kanawha Medical Society, Charleston, W. Va., Feb. 20, 1906.