such cases Truelove (1959) achieved a good clinical remission in 14 out of 22 cases with hydrocortisone suppositories.

Phenylbutazone is known to possess several actions, such as anti-inflammatory (Wilhelmi, 1949; Belart, 1949), reduction of capillary permeability (Wilhelmi, 1949, 1950), and antihistaminic (Domenjoz, 1952). Its local effect is also proved (Heilmeyer *et al.*, 1953) and we have previously used it with success for the local treatment of ulcerative colitis. The drug gets into the deeper layers of the mucosa, too, as was demonstrated by Hawkins and Fawns (1959), who investigated its absorption from the rectum. In our above-mentioned observations we pointed out that the direct contact of the drug with the diseased area is the decisive factor influencing its effectiveness. Our present observations also support this view.

The severity of the inflammatory process does not seem to determine the success of treatment. The decisive factor is the localization of the process. We could achieve success even with a lesion reaching the sigmoid colon if the enemata described above were given for some days before suppository treatment.

Phenylbutazone, by reducing inflammation and capillary permeability, as well as by its antihistamine effect, is beneficial to the inflamed mucosa. Phenylbutazone and prednisolone used in combination seem to potentiate each other's effect (Wilhelmi and Domenjoz, 1951; Kuipers, 1959; Châtel, 1960). They may have a different mechanism of action; this is supported by the fact that in some cases only the one drug, in other cases only the other, is effective.

We have never encountered the ulcerogenic side-effects of phenylbutazone either in suppository form or in enemata. On the contrary, its use in cases of ulcerative colitis and proctitis has resulted in rapid improvement of ulcers and in stopping bleeding.

It should be noted that all treatments of this kind must be preceded by thorough-going proctological examinations to establish the diagnosis and to exclude lesions such as carcinoma.

Summary

Phenylbutazone is well known to be an anti-inflammatory agent, and this property applies to its local use.

Suppositories containing 200 mg. of phenylbutazone have been found to produce clinical remission and sigmoidoscopic improvement in a large proportion of patients with proctitis, either primary non-specific or secondary. In the case of secondary proctitis, the primary disease was given appropriate treatment before employing suppositories for the proctitis.

Even better results were obtained with "combined" suppositories in which prednisolone and (in some cases) "protargol" were also included. Such "combined" suppositories brought about improvement in some patients who failed to improve with suppositories containing phenylbutazone alone.

I am grateful to the "Köbányai Gyógyszerárugyár," Budapest, for supplying the pure phenylbutazone as well as prednisolone.

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ACUTE ARSENICAL POISONING DUE TO ACETARSOL PESSARIES

BY

D. A. L. BOWEN, M.B., M.R.C.P.Ed., D.Path.

*Demonstrator, Department of Forensic Medicine,
St. George's Hospital, London*

T. L. T. LEWIS, M.B., F.R.C.S., M.R.C.O.G.

*Obstetric Surgeon, Guy's Hospital; Surgeon, Queen
Charlotte's and Chelsea Hospitals, London*

AND

W. R. EDWARDS, M.B., B.S.

*Resident Medical Officer, Chelsea Hospital for Women,
London*

Packing the vagina with acetarsol pessaries is sometimes recommended for resistant cases of trichomonal vaginitis. The danger of this method is illustrated by the following case (reported briefly in the *British Medical Journal* of July 16, 1960, p. 242).

A healthy married woman of 28 complained of vaginal discharge due to infection with *Trichomonas vaginalis*. She had not been pregnant, nor had she any serious illness. In January and February, 1958, she was treated for eight weeks with acetarsol 4-gr. (0.26-g.) pessaries, one night and morning for four weeks and then two each night for four weeks. Because the infection persisted and she complained of some local irritation, "penotrane" and then nystatin pessaries were given with lactic-acid douches. Nine months later (April, 1959) she returned to hospital and was treated with penotrane pessaries for a month and acetarsol 4-gr. (0.26-g.) pessaries two nightly for four months. In January, 1960, she was again treated, with "pruvagol" pessaries, but without improvement.

She was admitted to hospital, and on April 6 her vagina was packed, under general anaesthesia, with 18 acetarsol pessaries (total dose 72 gr.—4.67 g.). The next day she complained of nausea and vomited several times. As this was thought to be due to the anaesthetic she was given chlorpromazine hydrochloride ("largactil") 25 mg. On April 8 12 acetarsol pessaries (48 gr.—3.1 g.) were inserted into the vagina without anaesthesia. Nausea persisted and her temperature was 99° F. (37.2° C.). On April 9 she was restless and at midday had a generalized epileptiform fit, after which she was drowsy and disorientated. She appeared dehydrated; her pulse was 116 a minute, blood-pressure 110/70 mm. Hg. and temperature 100° F. (37.8° C.). There were no abnormal physical signs in the central nervous system: she was able to move all her limbs, the pupils reacted to light, and the fundi appeared normal; her jerks

were present and plantar reflexes were flexor. Her vagina was washed out, but it was empty. Ten hours after the first fit a second occurred, and so she was transferred to another hospital. On arrival there she was unconscious but responded to painful stimuli. The cerebrospinal fluid was clear and under normal pressure; it contained 24 lymphocytes per c.mm., a few red cells, and 75 mg. of protein per 100 ml. Blood investigations were as follows: haemoglobin, 14 g./100 ml.; white cells, 11,000/c.mm.; P.C.V., 36%; electrolytes: Na 132, K 4.5, and Cl 94 mEq/l.; alkali reserve, 9 mEq/l.; blood urea, 181 mg./100 ml.

A third fit occurred at 3.45 a.m. on April 10, 16 hours after the first one. She was given 10 ml. of paraldehyde by intramuscular injection and 4 ml. of dimercaprol in the next 14 hours. Later an intravenous drip infusion of 4.3% dextrose and 1/5 N saline was given. At 10.30 a.m. several more fits occurred, her coma gradually deepened, and she died at 6 p.m.

Post-mortem Examination (48 Hours After Death)

The deceased was of average build and adequately nourished. There was no evidence of any purpuric or erythematous rash and no evidence of haemorrhage. All the organs were congested and the brain substance showed moistness with some dilatation of the small vessels, but no evidence, macroscopically or histologically, of haemorrhagic encephalitis.

The stomach contained some bile-stained mucus, its lining was pale, and the smaller vessels were prominent. There was no visible inflammation anywhere in the intestines, and the large intestine contained some partly fluid faeces only.

Both kidneys showed a pale moist swollen cortex, the bladder was empty, the uterus and adnexae were entirely normal in size and appearance, and the cervix was healthy. There was no evidence of any ulceration or inflammatory change in the vagina, the mucosa appearing quite intact, but an acute vulvitis was present.

Microscopically the kidneys showed evidence of widespread tubular damage not localized to any particular area, with fresh blood casts in the tubules. The liver showed no evidence of necrosis, being healthy.

Analysis (Forensic Laboratories, Scotland Yard).—The liver was found to contain arsenic amounting to 0.3 gr. (20 mg.) (16 parts/million) as arsenious oxide, and it was calculated that this would indicate the equivalent of about 6 tablets of acetarsol, 4-gr. size, present in the whole body.

(To exclude acute porphyria as a cause of death in this case porphyrin estimation was carried out by Professor Rimington. The intestinal contents contained 43.8 μ g./g. dried weight of coproporphyrin and 29.7 μ g./g. dried weight of protoporphyrin. This result suggests a relatively small increase in coproporphyrin. It is known, however, that in cases of poisoning, among which arsenic is an example, the level of porphyrin may be slightly raised.)

Discussion

Acetarsol in the form of "stovarsol" or "S.V.C." pessaries is a recognized form of treatment in primary and resistant cases of trichomonal infection of the vagina. In the hospital concerned it has been carried out on numerous occasions without producing any serious untoward effects.

Serious skin reactions of any kind have rarely been reported to follow the widespread use of acetarsol for trichomonal infection, although minor reactions are well recognized (Campbell, 1937; Long, 1937; Kesten, 1938; Prosser-Thomas, 1948; Doyle, 1952; Peck, 1954).

There are even fewer reports of serious systemic reactions. Crosswell (1951) described the case of a patient developing rigors, facial oedema, a widespread morbilliform rash, and subsequently jaundice within a week of commencing treatment with acetarsol pessaries;

dimercaprol was almost immediately effective. Liver-function tests indicated an obstructive lesion. Crosswell suggested that in the absence of liver-cell damage the bile becomes plugged in the capillaries due to an exudative reaction in adjacent tissues. Thompson and Marshall (1958) had a similar case of a woman who used two acetarsol pessaries at the twenty-second week of her third pregnancy; four weeks later she inserted six more pessaries—two each night for three nights. She developed rigors, prostration, gross oedema of the hands and face, and urticarial weals on the trunk. A week later she was deeply jaundiced; and tests showed that the lesion was obstructive. Antihistamine drugs and prednisone were given and she recovered, but the foetus died *in utero* and was born macerated. White (1956) reported the case of a woman who was admitted to hospital in a state of general collapse and mental confusion complaining of severe abdominal pain and a generalized erythematous rash. For three weeks before admission she had been treating a vaginal discharge with acetarsol, two 4-gr. (0.26-g.) pessaries night and morning. She was treated with cortisone, adrenaline, and intravenous fluids and recovered. In Worms's (1939) case encephalitis ensued when treatment with only one pessary was recommenced three months after the original course.

Brouardel (1902) mentions a man who murdered three women with inorganic arsenic (arsenious acid), introducing it into the vagina, in "boulettes de farine." From the evidence available on the absorption of pentavalent arsenicals from the intestinal tract there is no reason why it should not be absorbed from any mucous membrane if given in suitable quantities, and especially if the mucous membrane was inflamed or abraded; but in the case reported here, there was no evidence at necropsy of any vaginal mucosal abnormality. We are now investigating the arsenical content of blood, hair, and nails in patients who are being treated with acetarsol pessaries given daily.

The quantity of arsenic in the liver of this case, while not very great, is consistent with death from acute poisoning. By comparison, amounts found in the liver in well-known cases (as reported by Willcox, 1922) of arsenical poisoning are as follows: Maybrick, 0.3 gr. (20 mg.); the three Bingham's, 1.1, 0.5, and 1 gr. (71, 32, and 65 mg.) respectively; Seddon, 0.17 gr. (11 mg.); Greenwood, 0.13 gr. (8 mg.). Larger amounts were found in the case of Radford, 2.75 gr. (178 mg.), and of Roberts, 1.75 gr. (113 mg.). In Egypt, where arsenical poisoning is commonplace, 3–5 parts per million are regarded as normal amounts. One must bear in mind that pentavalent arsenic (acetarsol) was administered in the present case, as experimentally it has been shown that excretion after intravenous injection in rats was most rapid in the case of the pentavalent compounds and slower with the trivalent group: also the toxicity of the trivalent arsenicals was greater than that of the pentavalent ones (Voegtlin and Thompson, 1922); so it may be that the toxicity of arsenicals is determined by the rate of excretion. After injection the pentavalent forms are to a large extent excreted before becoming fixed in tissues, and it is also probable that the pentavalent forms are reduced to the trivalent forms before exerting a marked toxic effect. Little work has been done on the absorption and excretion of acetarsol itself.

Reasonable proof that death was due in this case to arsenical poisoning appears to be present: first, there is

the known administration of arsenic (32 gr.—2.079 g.) ; second, symptoms known to be caused by arsenic were observed before death ; and, finally, enough arsenic was found in the liver to account for death. In this connexion it is important to differentiate between examples of arsenical encephalitis following acetarsol administration and acute arsenical poisoning as described here. Although clinically there may be few distinguishing features, post-mortem findings, and in particular toxicological analysis, will readily provide the answer. Encephalitis may result from very small amounts of organic arsenical—for example, intravenous arsphenamine—but acute poisoning must be related to the amount ingested and may have medico-legal significance.

Summary and Conclusions

A fatal case of acute arsenical poisoning due to acetarsol vaginal pessaries is reported.

The treatment of vaginitis due to infection with *Trichomonas vaginalis* is often satisfactorily and safely carried out with acetarsol (stovarsol or S.V.C.) pessaries. Nevertheless, there is a very small risk of a mild skin reaction, and if treatment is continued the reaction may be severe and generalized. Such reactions may occur in the course of prolonged treatment or they may arise when treatment is recommended after a previous sensitizing dose. Jaundice or haemorrhagic encephalitis may also occur as a sensitivity response to organic arsenicals.

There is evidence that arsenic was absorbed from the vagina in the present case, and in theory either acute arsenical poisoning or haemorrhagic encephalitis could have followed. The distinction is important because the mechanism of production is quite different. Arsenical encephalopathy is not necessarily related to the amount of arsenic present, while acute arsenical poisoning is directly dependent on the amount of the drug that is absorbed. In fact, no such encephalitis was found, and there was enough arsenic in the liver to show that death was due to direct arsenical poisoning. This occurred as the result of packing the vagina on two out of three days with a total of 30 acetarsol pessaries. Such intensive treatment is sometimes recommended for resistant cases, but the presence of a vaginitis almost certainly increases the absorption, and in our opinion the method should be abandoned.

Our thanks are due to Dr. Dudley Hart, who took over the medical treatment of the patient when she was transferred, and to Dr. G. Thurston, H.M. Coroner for West London, for the post-mortem report.

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MYOGLOBINURIA AND SEA-SNAKE-BITE POISONING*

BY

H. A. REID, M.D., F.R.C.P.Ed., D.T.M.&H.

Consultant Physician, General Hospital, Penang, Malaya

The clinical paradox of trismus yet paresis elsewhere originally stimulated investigations of sea-snake-bite poisoning (Reid, 1956a). Experimentally, sea-snake venom is feebly haemolytic: theoretically, a dose of venom sufficient to cause haemolysis should inevitably be fatal. Yet patients survived despite apparent haemoglobinuria. In these survivors, moreover, there was no evidence of excessive haemolysis. These anomalies were resolved in 1957 when it was realized that the urinary pigment was myoglobin, not haemoglobin. The purpose of this paper is to present case records and clinical investigations of patients selected as elucidating the pathogenesis of sea-snake-bite toxæmia.

Material

During 1957–9 38 patients with sea-snake-bite were personally observed in hospitals. The sea-snake was reliably recognized in 25 cases (23 were in fishing folk) ; in four subjects—all bathers—typical toxæmia followed ; and the remaining nine patients (“probable cases”) were bitten in the sea, felt no local pain after the incident (thereby excluding fish-stings), and had bite-marks compatible with those of a sea-snake. In this selected series of 38 victims serious poisoning followed in only nine cases (five fatal, three severe, one moderate). Trivial toxæmia resulted in two instances and no poisoning followed 27 bites (18 unequivocal, 9 “probable” as defined above). The following case records and investigations are representative of the minority developing poisoning.

Case 1

An Englishman aged 32 was bitten in the left calf while bathing at 4 p.m. on September 2, 1957. The first symptom was slight giddiness at 4.25 p.m. On reaching hospital at 4.30 p.m. the back of his neck felt stiff and ached, particularly on moving his head. At 4.35 his tongue felt stiff and was slightly swollen, there was some pain on swallowing, and all four limbs were stiff on moving “as if I had taken a lot of exercise.” At this time the admission doctor found the B.P. 140/92. Dr. C. P. Cheah, who had examined the patient for life insurance on September 8, 1955, kindly informed me subsequently that the B.P. was then 125/68. At 6.30 p.m. the B.P. was 120/100, and on the left calf were multiple pin-point marks which could only have been made by at least two bites.

His pupils were equal, not unduly dilated, and reacted briskly to light. Abdominal reflexes were present, plantar responses flexor. He was unable to look to the left, otherwise eye movement was normal. He could clench his jaws strongly and open them 35 mm. (between teeth edges). Showing his teeth or grinning was difficult owing to stiffness of his face, but there was no asymmetry of movement. Palate movement and coughing appeared normal, but the latter caused pain in the abdomen and lower ribs. Swallowing of fluids was painful although not otherwise difficult. Hearing a watch and appreciation of light touch, pinprick, joint movement, and vibration were normal. There was no nystagmus. He could lift his head off the bed against strong pressure, but turning it to either side was painful. He could

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