Post-mortem Findings

Death was found to be due to mitral endocarditis with embolic lesions in the kidneys and spleen. The left ventricle was slightly hypertrophied, with mitral stenosis and fusion of the cusps. The anterior cusp and part of the posterior cusp were covered by friable vegetations resting on dense fibrous tissue, in which was some calcareous deposit. Cultures from the vegetations were overgrown by a post-mortem invader, but bacilli showing the usual *Brucella* morphology were found in large numbers in sections of the vegetations. These were mostly in aggregates of varying size up to 30 to 40 microns in diameter, parts of the vegetations being apparently largely composed of these masses of organisms. No Gram-positive cocci were seen.

The spleen contained three white infarcts and was not enlarged. In the cortices of both kidneys were large numbers of small red infarcts, and thrombosed vessels were readily found in sections, which also showed small focal collections of polymorphs and lymphocytes. No marked change was found in any of the other organs, there being no enlargement of the lymph glands or liver.

Discussion

This case presents several points of special interest. The calcified area in the mitral valve suggests the probability of previous valvular disease, and the vegetations produced by *B. abortus* may therefore have commenced at the site of an old lesion. To the frequency of such a sequence in other infections attention has been drawn by Cowan and Rennie.⁶ That the earlier damage must have been slight is clear from the history and from the physical findings on admission to hospital. Moreover, there was no evidence of any active infection other than that due to *B. abortus*. The blood cultures gave no other pathogenic organisms nor were any demonstrated in the vegetations post mortem. There seems little doubt, therefore, that all the recent lesions and the fatal outcome were due to *B. abortus*.

The upper abdominal pain so frequently complained of by the patient is difficult to explain, even with the post-mortem results before us. The damage to the liver and spleen seems insufficient to account for it, and similar pain in endocarditis with renal involvement is a most unusual feature. Nor could the pain be related to the diarrhoea. Post mortem, nothing was found to account for this diarrhoea and for the intestinal haemorrhage. This is in line with the findings of Cooper and Marsteller⁷ in a fatal case of undulant fever without endocarditis. In their case, too, haemorrhage occurred on one occasion only, and post mortem no lesion could be discovered.

Summary

1. A fatal case of malignant endocarditis of the mitral valve due to *B. abortus* is recorded.

2. Only one similar case, confirmed by post-mortem examination, has been found in the literature.

We are indebted to Dr. Buckell, who found a titre of 1 in 9,896 for *B. abortus* and 1 in 3,766 for *B. melitensis* in the blood, and isolated *B. abortus* from the urine.

REFERENCES

- ¹ Hughes: *Mediterranean, Malta or Undulant Fever*, 1897.
- ² Casanova and d'Ignazio: *Minerva Medica*, August, 1933, p. 209.
- ³ Kristensen: *Ugeskrift for Laeger*, 1927, lxxxix, 1123.
- ⁴ Scott and Saphir: *Amer. Journ. Med. Sci.*, 1928, clxxv, 66.
- ⁵ Attinger: *Schweiz. med. Woch.*, 1932, No. 3.
- ⁶ Cowan and Rennie: *Lancet*, 1923, i, 223.
- ⁷ Cooper and Marsteller: *U.S. Naval and Military Bull.*, 1931, xxix, 660.

BELLADONNA POISONING BY LIQUID EXTRACT OF LIVER

BY

N. F. WINDER, M.B., CH.B.

AND

C. H. MANLEY, M.A. Oxon, F.I.C.

LEEDS CITY ANALYST

The following details of a case of belladonna poisoning present some serious questions for consideration.

On Sunday, September 15th, 1935, a woman aged 46, who had been suffering from pernicious anaemia, and had taken without harm six 15 oz. bottles of liquid extract of liver (1 fl. oz. = 1/2 lb. liver), all supplied direct by the same firm of manufacturing pharmacists, within half an hour of taking 1/2 oz. from a seventh bottle from the firm showed symptoms of belladonna poisoning, there being dryness of the mouth, flushing of the skin, impairment of vision, numbness of the extremities, and mild delirium. Medical aid was not summoned on this occasion, and no further dose was taken until Tuesday the 17th, when 2 drachms only of the extract were taken. Within half an hour there was a recrudescence of all the original symptoms, with complete dilatation of the eye pupils, the patient having to be walked about the room to prevent her from falling asleep. One of us (N. F. W.) was called in; recovery followed the administration of morphine, strychnine, and hot coffee.

The manufacturers were forthwith advised that they must cancel all further supplies of the batch of liver extract of which the contents of this bottle were a part, and recall any stock held by retailers. The remainder of the contents of the bottle in question was then submitted to the second-named author for examination for belladonna alkaloids. From the final chloroform extract from ammoniacal solution was obtained a residue which, after drying at 40°-50° C., gave typical alkaloidal precipitates with Wagner's and Mayer's reagents, and yielded a positive Vitali reaction (red-violet with freshly prepared 10 per cent. alcoholic caustic potash after evaporating with concentrated nitric acid and cooling). A control experiment on a liquid extract of liver obtained from an entirely different source furnished negative results when similarly tested.

In a quantitative determination 5 mg. of alkaloid were obtained from 2 fl. oz. of extract, corresponding to a maximum of 1/25 grain per fl. oz., or 1/50 grain in the Sunday dose, and 1/100 grain in the Tuesday dose. Biological tests carried out for us by Dr. W. A. Bain in the Pharmacological Laboratory at the Leeds School of Medicine showed the active principle to belong to the belladonna group of alkaloids (see addendum). It was therefore concluded that atropine and/or other belladonna alkaloid was present in the liver extract, and since 1 fl. oz. of liver extract is equivalent to 1/2 lb. of liver the indication is that the original alkaloid content of the liver was about 1/12 grain per lb.

Although a 2 drachm dose does not contain more than 1/100 grain of alkaloid (the therapeutic dose being 1/240 to 1/60 grain), it should be remembered that adults tend to show less tolerance for the drug than do children, and that the total alkaloids of belladonna (which consist of hyoscyamine and atropine) possess a greater physiological activity than atropine alone. Moreover, in a case in which belladonna treatment is not indicated, it is possible that the effect would be more pronounced than in one in which there were symptoms calling for such treatment.

Sources of the Alkaloids

There appeared to be two possible sources of the alkaloids. The possibility of contamination of the bottle through its having originally contained an atropine salt solution or a belladonna preparation was strongly denied by the manufacturers. It was ruled out later by the fact that, shortly after the present case had been brought to our notice, symptoms of belladonna poisoning occurred in another patient who had been taking from another

bottle some of the same batch of liver extract. Further, an eighth bottle, which was incorrectly believed to represent a separate batch of liver extract, on being used for the first patient, also produced symptoms of belladonna poisoning. Analysis indicated the presence of belladonna alkaloid in amount approximating that in the seventh bottle. In this case, however, no confirmatory biological tests were carried out.

The second possibility was that belladonna leaves and fruit had been eaten, probably with impunity, by the animals from whose livers the extract was manufactured. (The *B.P.*, 1932, directs that ox and sheep liver should be used for the preparation of the extract.) According to W. E. Dixon (*Pharmacology*, p. 82) herbivorous animals are very insusceptible to belladonna poisoning, it being stated that rabbits, for instance, can feed on the leaves without injury. Firth and Bentley (*Lancet*, 1921, ii, 901) quote a case in which a man, two women, a cat, and a dog displayed symptoms of belladonna poisoning after eating half of a rabbit which had fed unharmed on the plant; from the other half of its body belladonna was isolated. Further, Lander (*Veterinary Toxicology*, p. 246) states that while cats, dogs, and birds are sensitive to belladonna, horses and oxen are less so, while pigs, goats, sheep, and rabbits cannot be poisoned either by the plant above ground or by the root.

It therefore seems highly suggestive that in the present instance the most likely source of the alkaloid is to be found in the livers used for the manufacture of the liquid extract. Since, moreover, atropine is rapidly eliminated in the urine, the animals concerned most probably fed on *Atropa belladonna* shortly before being slaughtered. The manufacturers state that, to the best of their suppliers'

knowledge, the lot of liver in question was ox and of Argentine origin, this being exceptional, as the usual source of supply was Canada.

A matter of such serious import as we have here recorded at once raises the question whether stricter control will not have to be exercised in future over the manufacture of liver extract. While it may be difficult, if not impossible, to ensure in every instance that the sheep and oxen, the livers of which are subsequently to be used for the manufacture of liver extract, are prevented from feeding on poisonous plants, the desirability of submitting each batch of liver extract to a test for alkaloids before placing it on the market seems deserving of careful consideration.

Addendum

By W. A. BAIN, Reader in Pharmacology, University of Leeds

Pharmacological tests, with a neutralized solution of the alkaloidal hydrochloride obtained by C. H. Manley from the first sample of liquid extract of liver dealt with in the above paper, were carried out by me at the School of Medicine, Leeds. It was found: (1) that addition of the alkaloid to fluid perfusing through a frog's isolated heart rendered the heart completely insensitive to the action of acetylcholine; and (2) that application of a few drops of the alkaloidal solution to the left eye of a cat caused maximal dilatation of the pupil and abolition of the light reflex, the pupil of the right side being unaffected.

From such observations it was concluded that the test solution contained atropine and/or other alkaloids of the belladonna group.

Clinical Memoranda

An Unusual Case of Colitis

The following case of colitis seems to me to be sufficiently out of the ordinary to warrant its being reported.

CASE HISTORY

Mrs. A., aged 46, was first seen by me in July, 1934, and gave me the following history.

In 1918 she underwent an emergency operation for a duodenal ulcer. The symptoms of this ulcer so far as can be remembered were fairly typical, and after gastro-enterostomy her recovery was uneventful and all symptoms of her dyspepsia disappeared. She was quite well until early in 1933, when she started to pass blood and mucus in her stools. Her bowels acted three or four times a day, and she had vague abdominal pains, which were referred to the left colon. Her bowel actions became more frequent and were accompanied by tenesmus. She lost weight, and by this time presented the appearance of having a severe mucous colitis. Treatment by dieting, chalk, and salol and other drugs produced only intermittent relief.

CLINICAL INVESTIGATION

Early in 1934 microscopical examination of a stool was carried out and showed a heavy infection with dysentery bacilli. However, as the patient had never been abroad and now lived in the country in a modern house with proper sanitation and water systems, this finding was unexplained and even doubted. The patient was seen in consultation with Dr. Charles of Bristol, who suggested the possibility of there being diverticula and advised a barium enema. This was carried out, but beyond a rather large sigmoid loop there was no evidence of any abnormality to be seen in the large bowel. Further treatment with intestinal disinfectants and albargin washouts failed to produce any relief.

Soon after she came under my care she started to have severe attacks of pain in the region of her splenic flexure. The pain would reach a crescendo with a feeling of

something swelling and bursting, which was followed by the relief of pain with the passage of a stool in about an hour. In the stool were obvious blood and mucus, the blood in the form of clots, which were bright red, and with darker blood mixed with the solid matter of the stool. Two further examinations of the stools failed to show any dysentery bacilli.

At this stage an appendicostomy for lavage purposes was suggested, but the patient was unwilling to submit to any operative procedure as she was now getting more periods of comparative relief, when she might only pass two stools a day. In August, however, she started to have very severe pains again, but this time they were in the middle of the upper abdomen, and several attacks needed large doses of morphine for their control. These pains were of a boring nature.

DIFFERENTIAL DIAGNOSIS

The new complication of these severe pains drew one's attention to the following possibilities: further duodenal ulcer activity with possibly pancreatic adhesions or the formation of a jejunal ulcer with adhesions. Even a leaking ulcer or fistula formation was a remote possibility. Gallstones were considered, but the type of the pain and the absence of jaundice were against this diagnosis, though at times the gall-bladder was tender but not enlarged.

On August 27th operation was again advised, and was carried out by Mr. Richard Warren and myself.

OPERATION

Laparotomy revealed the following state of affairs. The gall-bladder was found to be slightly thickened and adherent to the transverse colon with local perihepatitis. There were no stones in the gall-bladder or the ducts, whilst the bile appeared normal in colour. A cholecystectomy was carried out after the colonic adhesion had been severed. The duodenum was inspected and showed no signs of any ulceration; the anastomosis admitted nearly two fingers, and the edges were regular with no signs of ulceration. The appendix showed some old scarring at its middle and was removed. An examination of the large bowel was next carried out. There was some hyperaemia of the transverse colon, but no thickening or other evidence of ulceration or growth was made out.