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Fatal Liver Damage After Barium Enemas Containing Tannic Acid

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ABSTRACT

Tannic acid contained in the barium enema was found to have been the sole known potential hepatotoxin in four of the five cases of fulminating fatal liver failure that occurred in a 213-bed hospital over a period of 27 months. In the other case halothane anesthesia had also been administered. Autopsies (performed on four of the cases) did not suggest viral hepatitis but showed substantially identical hepatic changes, not unlike those reported in the past following tannic acid exposure. Proof is not claimed that tannic acid was the cause of these deaths, but further investigation regarding the safety of its administration in barium enemas is advocated.

IN October 1962 a 9-year-old boy (J.M.) died at the Chedoke General and Children's Hospital, Hamilton, Ontario, from acute liver failure. There was no known contact with cases of infective hepatitis and no history of recent infection, or of exposure to hepatotoxic agents. The patient had received a barium enema two days before death, but the possible etiological role of its tannic acid content was not immediately appreciated. Autopsy was refused and death was ascribed to viral hepatitis.

Five months later, on the occasion of a second acute liver death, that of a 2-year-old girl (J.S.), the possible role of the tannic acid content of the barium enema was considered.* Three other deaths from fulminating liver failure, since the opening of the Chedoke General and Children's Hospital, in December 1960, were then recalled and perusal of the records revealed that each of these patients had received a barium enema containing tannic acid one to six days before death.

In April 1963 the summary of a forthcoming article by McAlister *et al.*[6] and an editorial by Thomas[8] became available, each discussing the possibility of liver damage resulting from the use of barium enemas containing tannic acid. This prompted the authors to re-examine the five fatal cases of liver failure referred to above, from the point of view of their deaths being related to tannic acid exposure. This is a report of our observations.

The barium enema technique employed at the Hamilton Health Association Hospitals has been similar to that in use at most x-ray departments: preparation consisted of purgation late on the day preceding the barium enema, with no breakfast on the day of the enema. The barium sulfate (Wander) suspension was prepared to contain 2% tannic acid.

From March 1962 on, a Clysodrast* cleansing enema containing 0.25% tannic acid and administered early on the morning of examination was added to the routine preparation of adults. This was not given to patients under the age of 16 years. Consequently, only two of the five patients received a Clysodrast enema before the barium enema.

Details of the five cases are presented in Table I, which shows that the course of events following the barium enema was similar in three patients (Cases 1, 3 and 5). Having received the enema in mid-morning, they were well until late the same day or early the next morning when their terminal illness set in, with vomiting and abdominal pain.

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*Acknowledgment is due to Dr. A. B. MacMillan for having brought to our attention the possible association between the deaths of the two children and their barium enemas.

*Clysodrast (Barnes-Hind Barium Products Company) contains 1.5 mg. of 4,4'-(diacetoxydiphenyl)-(pyridyl-2) methane and 2.5 g. of tannic acid U.S.P., per package, to be dissolved in 1 litre of water.

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TABLE I.

Patients	*1. D.T., female, 18 yrs.*	*2. A.F., male, 79 yrs.*	*3. J.M., male, 9 yrs.*	*4. R.N., female, 24 yrs.*	*5. J.S., female, 2 yrs.*
Complaint or diagnosis on admission	Irritable colon syndrome	Meteorism, peptic ulcer?	Abdominal pain	Abdominal pain	Constipation
Day of barium enema	October 5, 1961: no Clysodrast; a.m. barium enema; later abdominal pain, swelling of face	March 30, 1962: a.m. Clysodrast and barium enema; nausea, vomiting in afternoon	December 12, 1962: no Clysodrast; a.m. barium enema; vomited in early aftn., later abdominal pain	December 11, 1962: a.m. Clysodrast and barium enema; abdominal pain and nausea in afternoon	March 19, 1963: no Clysodrast; a.m. barium enema; well all day but refused supper
1st day after	Abdominal pain, vomited once	Drowsy and weak; not eating; became confused and died in aftn.	Vomited from early morn. on; abdominal pain	Laparotomy under halothane anesthesia	Vomited breakfast; irritable and later very drowsy
2nd day after	Repeated vomiting; abdominal pain, drowsy, later comatose and in shock		Drowsy and faint later in day.	Not taking fluids well; slept for long periods; urine appeared concentrated	Voided dark urine, later jaundiced; drowsy; vomiting "coffee-grounds"; coma
3rd day after	Vomiting brown fluid; conscious off and on		Morn. vomiting; later semi-comatose, restless and vomiting again; jaundiced later in day	Very drowsy, sleeping most of day	Died in early morn.
4th day after	Restless, semicomatose, facial edema; jaundice, coma		Died in early morn.	Incontinent of urine; jaundiced; lethargic, pulse 120/min.; noisy, restless; coma; petechiae noted	
5th day after	Died in evening			Increasing jaundice, comatose	
6th day after				Died in early morn.	
Liver weight	1250 g.	1100 g.	——	920 g.	515 (normal: 395 g.)
Remarks	——	——	No autopsy	——	——

During the next 24 hours they became irritable and drowsy. There was a terminal phase of icterus, semi-coma and coma. Survival after onset of symptoms ranged from one to five days.

Case 2, a man aged 79, differed from the rest, mainly by the absence of jaundice and the rapid course of his illness, terminating in death less than 36 hours after the barium enema.

The case of R.N. (Case 4), a 24-year-old woman, presents special problems because she had been exposed to both tannic acid and a laparotomy under halothane (Fluothane) anesthesia, and because her subsequent clinical course differed, in minor details, from that of the other patients in this report. She was admitted after six days of recurrent right-sided abdominal pain. There was tenderness in the right lower quadrant but there was no abdominal rigidity. Onset of menstruation had occurred on the day of admission. No significant physical or laboratory findings were recorded. No liver function tests were performed. Her erythrocyte sedimentation rate (E.S.R.) was 7 mm. in one hour. Barium enema, preceded by a Clysodrast cleansing enema, was administered on her third day in hospital. Exploratory laparotomy on the following day, under halothane anesthesia of one hour's duration, revealed no abnormalities: a normal appendix and an ovarian biopsy (normal) were removed. She was exceptional in both the absence of vomiting and the length of survival.

In all five cases, manifestations such as fever and leukocytosis varied from patient to patient and there was no constant pattern. Likewise, there were no constant significant laboratory findings.

Autopsy findings, with minor variations, were similar in the four cases examined and, in particular, there were no abnormalities that could be related to the complaints which had brought these patients to hospital. Icterus was present except in Case 2, where the interval between enema and death had been shortest. Generalized hemorrhagic manifestations were seen in all four. Liver damage was the single finding of importance in all instances. The livers ranged from moderately swollen and firm (Case 5) to flabby and shrunken (Case 4). No portions of any of these livers were spared by the process. All stages of parenchymal cell death, with fatty change a constant finding, were seen. Although virtually the entire liver lobule was involved, the more advanced degree of destruction around the central vein and the survival of some peripheral cells pointed to a centrilobular type of degeneration and necrosis (Fig. 1). Cellular reaction was minimal, except in Case 4, where there

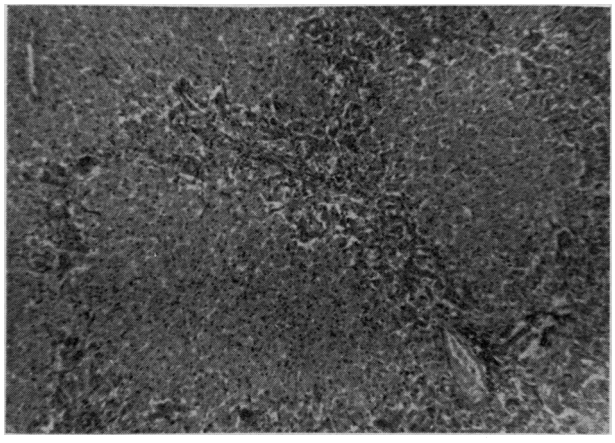

Fig. 1.—Case 5, J.S.—Three liver lobules with large central areas of degeneration and narrow peripheral rims of surviving cells (× 60).

were numerous intralobular and portal neutrophils, mononuclear cells and some eosinophils, as well as a marked proliferation of bile ductules.*

RECENT HISTORY OF THE USE OF TANNIC ACID

Tannic acid has had many topical—dermal as well as mucosal—applications in human medicine, based on its astringent, tanning properties. The *United States Pharmacopoeia* (25th ed., 1957, p. 1380) mentions its use, e.g. in gastric hemorrhage, for diarrhea, and for irrigation in ulcerative colitis (0.2-0.5% solution).

Davidson, in 1925,[3] recommended the use of tannic acid for the treatment of burns. It remained the standard treatment in many centres throughout the Second World War, although Wells, Humphrey and Coll[9] had demonstrated, in 1942, that the liver necroses often observed at autopsy in fatal burn cases were not due to 'toxemia' but to the absorption of tannic acid through burned skin surfaces.

In 1943, Barnes and Rossiter,[1] at the request of the Burns Subcommittee, War Wound Committee, Medical Research Council, further investigated the claims made by Wells, Humphrey and Coll,[9] by animal experimentation.† The action of tannic acid as a liver toxin was again established and further British reports in the same vein followed.

It was shown that the hemorrhagic central necroses of liver lobules, as described in human patients,[9] could be reproduced in animals by the application of tannic acid to denuded skin, or as subcutaneous, intramuscular or intravenous injections.

The use of tannic acid in the treatment of burns gradually became obsolete, being superseded by treatments aiming at replenishing lost plasma and by the introduction of antibiotics.

Hamilton,[4] in July 1946, published a brief article based on a personal communication from Sackett, both then serving in the United States Army Medical Corps, recommending the addition of a tablespoon of tannic acid to every two quarts of barium enema, in order to improve the definition of the mucosal pattern on x-ray films. A trial of this method did not result in any adverse effects or complaints.

The introduction of this novel use for tannic acid was received with great interest among radiologists,[7] and Thomas,[8] in 1963, estimated that 25% of all barium enemas then given in the U.S.A. contained tannic acid. A further refinement of its application in radiology was the addition of tannic acid to the preparatory enemas, preceding the tannic-acid barium enemas.

In 1951 Korpássy, Horvai and Koltay[5] investigated, by animal experiments, the absorbability of tannic acid from the gastrointestinal tract. After introduction into the stomach in 2.5%, 5% and 10% solutions, it appeared in the plasma within 30 minutes and reached its peak concentration in from two to three hours. The liver of a dog that died on the fourth day showed extensive centrilobular necroses. Korpássy also tried the effect of tea and burgundy on rabbits, both substances known to have a high content of tannic acid. Oral doses of tea resulted in a measurable plasma level of tannic acid, producing about one-quarter of the maximum concentration recorded for oral administration of 10% tannic acid solution. Intake of burgundy failed to produce measurable tannic acid plasma levels. One must assume that most, if not all, of the tannic acid in Korpássay's experiments was absorbed in the small bowel.

A more recent investigation, by McAlister *et al.*,[6] "Lethal Effects of Tannic Acid in the Barium Enema", published in May 1963, was prompted by the death of a 10-year-old boy from acute hepatic failure six days after receiving preparatory enemas and a barium enema, all containing tannic acid in a concentration of 0.75%. The boy's terminal illness began with vomiting on the third day after the barium enema. Tannic acid had been suspected as the cause of liver damage in this case, and at autopsy a positive reaction was obtained with Nessler's reagent applied to unfixed liver tissue. Two earlier deaths from acute liver failure in children are described in this article, occurring 48 hours and 72 hours after barium enemas.

In the first mentioned case, where death occurred six days after exposure to tannic acid, the liver showed pronounced centrilobular atrophy with necrosis and congestion and a diffuse neutrophilic exudate with central and portal lymphocytic accumulations. In the other two children, liver changes chiefly consisted of fatty degeneration accompanied by minor cellular reaction. Animal experiments were then described which demonstrated, for the first time, absorption of tannic acid from the intact colon, producing plasma levels of up to 14.2 mg. % and typical liver degeneration and necrosis, in dogs.

*Dr. J. S. Carruthers, Princess Margaret Hospital, Toronto, was kind enough to study liver sections of the four cases and agreed with these observations.

†Barnes and Rossiter[1] mention Nessler's solution as one of the methods of demonstrating tannic acid in tissues.

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DISCUSSION

In reassessing the five cases recorded in this report, the authors were struck by their similarity: relatively minor gastrointestinal or abdominal complaints led to admission and investigation, which in all five cases failed to reveal any organic cause for their symptoms. All received a tannic-acid barium enema. In no instance did x-ray examination show intestinal abnormalities that could have explained the clinical picture. Their course in hospital, from barium enema examination to death, varied but little. Autopsy findings were very much alike, with minor variations in the hepatic changes, possibly related to the length of survival.

The type of liver damage was much the same as that described by Wells, Humphrey and Coll[9] and by McAlister.[6] Autopsy findings, however, provide nothing specific by which these lesions can be linked to tannic acid. Liver changes are perhaps more indicative of reaction to a toxic agent than of viral hepatitis although the latter may sometimes produce a similar picture.

In our Case 4 the possibility that halothane may have contributed to the liver damage must be considered; the type of centrilobular necrosis described in the cases recently reported by Bunker and Blumenfeld[2] resembles the changes produced by tannic acid.

Demonstration of the presence of tannic acid in the liver tissue of the four autopsied cases was made impossible by the fact that all of the tissues had been fixed in formalin by the time tannic acid became suspected. All formalin-fixed tissues give a strongly positive reaction with Nessler's solution.

In none of our five patients could a history of exposure to viral hepatitis or to a known hepatotoxin be elicited and no patient had received a blood transfusion.

Although proof that these patients died from tannic acid poisoning is lacking, a high degree of suspicion appears justified: five deaths from acute liver failure occurred in a 213-bed hospital during the relatively short span of 27 months. Twenty-three patients, not including the five fatal cases under discussion, were admitted during this period with a diagnosis of infectious hepatitis. In the literature, the combined mortality of subacute and of fulminating viral hepatitis is placed at from two to four per thousand.

Thomas[8] estimated that approximately 600,000 barium enemas containing tannic acid are given annually in the U.S.A. Canadian and U.S.A. radiological practices being virtually identical, one would consequently estimate that, based on the size of the Canadian population, somewhere in the neighbourhood of 67,000 barium enemas containing tannic acid are performed annually in Canada. So far three deaths have been reported from the U.S.A. and none, heretofore, in Canada.

This very low recorded incidence of liver damage after exposure to tannic acid in barium enemas appears to discredit the possibility of a causative relation.

It seems likely, however, that this paucity of reports also reflects the fact that most physicians ordering barium enema examinations, as well as pathologists performing autopsies on persons who died of liver failure, are not aware of the use of tannic acid in radiological practice.

Both for the clinician and for the pathologist, an etiological diagnosis in cases of rapidly fatal liver failure is usually impossible, unless aided by extraneous evidence; there is a tendency for both groups to classify such fatalities as being of viral origin. This, certainly, has been the case in our own experience.

Retrospective investigation, carried out in larger centres, into the circumstances of deaths from acute liver failure might help to clarify the issue of whether the use of tannic acid in barium enemas is a safe procedure.

SUMMARY

Five cases are presented in which death from acute liver failure followed closely on the administration of a barium enema containing tannic acid.

The possible relationship between liver damage and tannic acid is discussed.

REFERENCES

1. BARNES, J. M. AND ROSSITER, R. J.: *Lancet*, **2**: 218, 1943.
2. BUNKER, J. P. AND BLUMENFELD, C. M.: *New Eng. J. Med.*, **268**: 531, 1963.
3. DAVIDSON, E. C.: *Surg. Gynec. Obstet.*, **41**: 202, 1925.
4. HAMILTON, J. B.: *Amer. J. Roentgen.*, **56**: 101, 1946.
5. KORPÁSSY, B., HORVAI, R. AND KOLTAY, M.: *Arch. Int. Pharmacodyn.*, **88**: 368, 1951.
6. MCALISTER, W. H. *et al.*: *Radiology*, **80**: 765, 1963.
7. SINGLETON, A. C.: Radiography of the colon. *In*: Modern trends in diagnostic therapy, 2nd series, edited by J. W. McLaren, Paul B. Hoeber, Inc., New York, 1953, p. 158.
8. THOMAS, S. F.: *Amer. J. Roentgen.*, **89**: 889, 1963.
9. WELLS, D. B., HUMPHREY, H. D. AND COLL, J. J.: *New Eng. J. Med.*, **226**: 629, 1942.

PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

THE RUNNING SUTURE—AND THE BLOODLESS OPERATION

For many years I have been endeavouring to eliminate, as far as possible, the ligature, and with it the knot, from my wounds, believing as I do that the knot is a frequent source of irritation that may lead to suppuration, for I suppose it is a well recognized fact that most wounds contain bacteria when an operation is finished. If, then, one is able to eliminate a mechanical irritation, one should also succeed —with other care—in eliminating, with greater regularity, failure in primary union.

My excuse for bringing such a simple matter before this Association is, that time and again surgeons who have been present at my operations have commented upon the simplicity of the technique, the absence of ligatures and the freedom from haemorrhage.

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