Cardiovascular Lesions and Various Tumors Found in Rats Given T-2 Toxin, a Trichothecene Metabolite of Fusarium

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ABSTRACT

White rats given intragastrically 3α-hydroxy-4β,15-diacetoxy-8α-(3-methylbutyryloxy)-12,13-epoxy-trichothec-9-en (T-2 toxin), a trichothecene metabolite of several Fusarium species, developed various acute and chronic, topical and systemic lesions. The rats that survived 12 to 27.5 months after the first of three to eight doses of T-2 toxin (0.2 to 4 mg/kg body weight) alone or in conjunction with nicotinamide given i.p. (200 to 250 mg/kg body weight) developed cardiovascular lesions of various degrees of severity and/or tumors, benign and malignant, of the digestive tract and of the brain.

T-2 toxin is known occasionally to contaminate cereals and other agricultural products, harvested or stored under damp and cold conditions. T-2 toxin was responsible for an often fatal disease in humans, known in the U.S.S.R. as “alimentary toxic aleukia,” and also for outbreaks of hemorrhagic mycotoxicoses in livestock in various countries. T-2 toxin and other Fusarium mycotoxins may be involved in the etiology of cardiovascular lesions and of certain tumors considered as “spontaneous” in animals and humans.

INTRODUCTION

We have described (28, 29) some of the acute and more chronic lesions that develop in rodents treated with crude alcoholic extracts from cultures of Fusarium poae and Fusarium sporotrichioides, the authentic species, which have been responsible for the often fatal disorder known as ATA (9) but also in various outbreaks of lethal mycotoxicoses in livestock (7, 17, 34, 38). The acute and some of the more chronic effects of T-2 toxin in rats, mice, trout, cats, and chicken have been reported (2, 11, 13, 14, 16, 28, 31, 41). In the present paper, we describe the long-term experiments, during which severe cardiovascular lesions and various tumors, benign and malignant, were found in white rats given several i.g. doses of T-2 toxin alone or in conjunction with i.p. treatment with nicotinamide. The lesions and tumors were similar to those found among rats that survived for corresponding times the treatment with crude alcoholic extracts from cultures of F. poae and F. sporotrichioides (28, 29). Abstracts of preliminary reports of some of the results have been published (29, 30).

MATERIALS AND METHODS

Strain. White, weanling male rats and one lactating female with her litter were used. The rats, derived from the Wistar-Porton strain, were obtained from the MRC Laboratory Animal Centre, Carshalton, Surrey, United Kingdom, where they were bred under pathogen-free conditions. The rats separated by sex were kept in plastic or metal cages, not exceeding 6 rats/cage, and given the commercial pelleted diet (Dixon’s Diet for Scientific Research; Dixon and Sons, Ware, England) and tap water ad libitum.

Appropriate quantities of crystalline colorless T-2 toxin (43) were dissolved before dosing in a few drops of ethanol and diluted with distilled water to the required volume; the final concentration of ethanol did not exceed 10%. The solutions (or slight suspensions) containing 1 to 4 mg/ml were given to the rats by stomach tube in doses corresponding to 0.2 to 4.0 mg/kg body weight.

Some of the rats were additionally pretreated with nicotinamide (obtained from British Drug House Ltd). Solutions in distilled water, containing 100 mg/ml, were injected i.p., 200 to 250 mg/kg body weight, 10 min before and approximately 2 hr after each p.o. dosing with T-2 toxin (18). Control rats were given the nicotinamide treatment or were left untreated.

The animals that died or that were killed by gassing when they appeared ill were autopsied, and their organs, including the brain, the pituitary, and any tissue that appeared abnormal, were fixed in ethanolic formol and processed in the usual manner. Sections 5 to 6 μm thick were stained routinely with hematoxylin and eosin for microscopic examination. Other strains were used if required.

RESULTS

The results in this paper are based on observations made on certain other agricultural products (2, 7, 15, 34, 36–38, 42). T-2 toxin has been implicated not only in the human disorder (ATA) (9) but also in various outbreaks of lethal mycotoxicoses in livestock (7, 17, 34, 38). The acute and some of the more chronic effects of T-2 toxin in rats, mice, trout, cats, and chicken have been reported (2, 11, 13, 14, 16, 28, 31, 41). In the present paper, we describe the long-term experiments, during which severe cardiovascular lesions and various tumors, benign and malignant, were found in white rats given several i.g. doses of T-2 toxin alone or in conjunction with i.p. treatment with nicotinamide. The lesions and tumors were similar to those found among rats that survived for corresponding times the treatment with crude alcoholic extracts from cultures of F. poae and F. sporotrichioides (28, 29). Abstracts of preliminary reports of some of the results have been published (29, 30).
Lesions were almost invariably present in the gastrointestinal tract and consisted of hyperkeratosis and hyperplasia of the squamous epithelium of the stomach and esophagus, especially at the margo plicata, ulceration, and submucosal edema (Fig. 7). The lesions of the squamous part of the stomach were similar to those described in rats treated with the crude extracts from cultures of *F. poae* and *F. sporotrichioides* (28). Atypical glandular elements were often present in the glandular part of the stomach and in the duodenum. There were irregularities of the crypt and duct epithelium and foci of calcification of muscularis, infiltration of the crypts, and thick-walled arteries.

The kidneys were often enlarged, granular, with many casts and foci of infection, cellular infiltration, and sometimes calcification; large calculi surrounded by calcified, in places hyperplastic epithelium were present in the distended pelvis (Fig. 8). Some rats in which calcification of organs was striking had enlarged hyperplastic parathyroids. The liver usually did not show significant specific lesions. Hyperplastic and neoplastic lesions were frequently present in the gastrointestinal tract and included malignant tumors (Figs. 9 and 10). One was an adenocarcinoma of the glandular part of the stomach, which penetrated the muscle layer and showed extensive fibrosis (Figs. 9 and 11). Another adenocarcinoma formed large nodules and extensive areas of infection in the greatly distended duodenum (Fig. 10). The site of penetration of the muscularis is shown in Fig. 12.

In the brain, distension of blood vessels, foci of necrosis with macrophage infiltration, and fibroid thickening of arterial walls were present. Tumors included a neuroblastoma (Figs. 13 and 14) in a rat that died 12 months after the first of 8 doses of T-2 toxin given in conjunction with nicotinamide treatment. An astrocytic glioma was present in the same rat that had the adenocarcinoma of the stomach. Brain tumors were also found among rats treated with crude extracts from cultures of *F. poae* and *F. sporotrichioides*.

In the pancreas, hyperplastic and neoplastic lesions were frequent; these ranged from small budding islets (Fig. 6) to large islet cell adenomas (Fig. 15) and from microscopic adenomas to large multiple pink nodules of the exocrine pancreas, up to 6 mm in diameter, which were grossly visible in the peritoneal cavity (Fig. 16). In one series, all of the 6 rats that survived longer than 16 months after the first of 8 doses of T-2 toxin (including those that also had the nicotinamide treatment) had neoplasias of the exocrine pancreas (2 of these rats had in addition islet cell adenomas). Degenerative and reparative lesions were often present in the pancreatic ducts, the stromal vessels, and the connective tissue.

Heart lesions (Figs. 17 and 18) and pancreatic neoplasias, of both the endocrine and the exocrine type (Figs. 19 and 20), were also found among the rats that survived for long periods the treatment with crude extracts from cultures of *F. poae* and *F. sporotrichioides*. A striking example is shown in the Figs. 17 to 20.

Pituitary adenomas were frequently seen; adenoscarcinomas with many mitotic figures and giant nuclei were also present; one penetrated deeply into the brain.

Several animals had multiple tumors of various cell types in several organs (Table 1).

Of the control rats, run parallel to the experimental ones, 3

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T-2 Toxin: R¹ = H; R² = CH₂CO; R³ = (CH₃)₂CHCH₂CO

Chart 1. The structure of T-2 toxin.

mg/kg body weight i.g.) at approximately monthly or irregular intervals. Thirty of these rats were given in addition i.p. injections of nicotinamide. Ten other rats that were given the nicotinamide treatment only (but no T-2 toxin) and 10 untreated rats served as parallel controls.

About two-thirds of the experimental rats died within a few days after the first or after one of the subsequent treatments with T-2 toxin, alone or in conjunction with nicotinamide. These rats usually developed a hunched posture, soiled underbelly from diarrhea, and bleeding from body orifices; some were found in coma. At autopsy, the stomach and the small intestines were greatly distended with soft, often blood-stained content, hemorrhagic petechiae, and erosions in the stomach; the lymph glands and the spleen appeared enlarged, the thymus appeared small, the lungs were congested, the heart was engorged, and the blood vessels were congested, particularly conspicuously in the brain.

Microscopically, the stomach mucosa is usually denuded; there is glandular atrophy, cellular infiltration, and striking submucosal edema in the stomach and duodenum. The pancreas shows interlobular edema; there is depletion of the lymphoid elements in the hemorrhagic spleen and lymph glands; the thymus shows involution and foci of necrosis; the lungs are often edematous. Necrotic changes are present in the gonads.

In animals that die within a few days after treatment, having survived one or more preceding doses, the acute lesions are superimposed on some of the more chronic ones and resemble those that have been described after the treatment of rats with crude extracts from cultures of *F. poae* and *F. sporotrichioides*.

The main lesions and tumors found in the rats that survived 12 to 27.5 months (mean, 22 months) after the first and several weeks or months after the last of several doses of T-2 toxin (1 to 3 mg/kg body weight alone or in conjunction with nicotinamide) are summarized in Table 1. Some of the rats had striking cardiovascular lesions, which included partly organized thrombi in the left auricle and ventricle of the heart. The heart showed various degrees of myocardial degeneration with foci or cellular infiltration and fibrosis (Fig. 1). Two rats had the coronary artery enormously distended and almost occluded by fibrinoid swelling of the collagen (Fig. 2). Degenerative and inflammatory changes and partial or total occlusion of arteries often affected many organs; striking examples are shown in the kidneys (Fig. 3), testis (Fig. 4), and pancreas (Fig. 5). The pancreatic lesions included arteritis, proliferation of the islets (Fig. 6), hyperplasia of the ducts, tumors, benign and malignant, of the exocrine pancreas, and those of the islet cell type (see below).

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8 R. Schoental and A. Z. Joffe, unpublished results.
### Table 1

Main lesions, degenerative or vascular and neoplastic, in rats that survived 12 to 27.5 months after the first of 3 to 8 doses of T-2 toxin given i.g. alone or in conjunction with i.p. injections of nicotinamide

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* D, found dead; NA, nicotinamide; K, killed; C, foci of calcification.

** • • •, thrombus; *, moderate; +, hyperplastic; **, severe; ++, neoplastic; ++++, malignant.
died at 21.5 to 23 months (from bronchopneumonia); the remaining 17 rats were killed at the age of 26 to 28 months. No significant differences were seen between rats that were given nicotinamide and the untreated controls. Most of these rats had slight to moderate thickening of arterial walls, myocardial lesions, and various degrees of nephrotic kidney changes. Four rats had pituitary adenomas. No thrombi were seen in the heart, nor was there coronary artery distension such as in some of the experimental rats.

DISCUSSION

The lesions found in the experimental rats indicate that T-2 toxin has local and systemic effects, both acute and chronic. The acute effects which lead to death within a few days after T-2 toxin include oliguria, hematuria, general congestion of blood vessels, and hemorrhages. T-2 toxin is known to produce hematological abnormalities, such as leukocytopenia and thrombocytopenia, and hemorrhages in several species of animals. Cats appear to be singularly susceptible to the hematological changes, and they show striking alterations in the morphology of the neutrophiles. If the animals do not die, the hematological changes appear to be reversible (13).

T-2 toxin has striking cytotoxic action in tissue cultures, which it shares with some of the other trichothecenes, including diacetoxyscirpenol (35, 37). The cytotoxic effects manifest themselves at the site of application in vivo, whether the skin or the digestive tract. From our results, it appears that when T-2 toxin is circulating in the blood stream after absorption from the stomach it can damage the vascular endothelium, cause extravasation of the blood, and cause hemorrhages in remote organs, including the brain. If the animal survives, the arterial endothelium undergoes reparative processes, giving rise to thickening of the arterial wall and the striking chronic cardiovascular lesions found in our rats. Various degrees of arteritis have been observed to occur occasionally in aging rats, and they have been considered as 'spontaneous' (3, 39, 40). We are inclined to interpret such spontaneous lesions as the result of occasional ingestion of food contaminated with Fusarium mycotoxins.

T-2 toxin appears to be a versatile carcinogen for the rat. When administered by i.g. intubation, it can induce tumors of several organs, including the gastrointestinal tract, but not of the liver. Thus, T-2 toxin appears to act as a direct carcinogen, which does not require activation by specific liver enzymes but which is effective for various cell types. The liver, with its high content of thiols and coenzymes, appears resistant to the carcinogenic action of the toxin under the conditions used in our experiments. In its action, T-2 toxin appears to resemble MNUT, which is also an effective carcinogen for the digestive tract but not for the liver (21, 32). Both compounds can cause depigmentation of dark fur of mice on chronic application (31). However, T-2 toxin is about 15 to 25 times more toxic than MNUT; the 50% lethal dose of MNUT for weanling rats is about 50 to 100 mg/kg body weight, while the 50% lethal dose of T-2 toxin is only 3 to 4 mg/kg body weight. The small margin between the lethal and the carcinogenic dose of T-2 toxin leads often to death of the rats before tumors can develop. The latent period before tumors due to T-2 toxin appear is rather long and probably could not be much shortened as the dosage cannot be readily increased. Another mycotoxin, elaiomycin, a secondary metabolite of Streptomyces hepaticus, induced tumors of the digestive tract, of the brain, and also of the liver (22, 23). T-2 toxin has been tested previously by several groups of workers for chronic toxicity in various animal species. The experiments in which T-2 toxin has been incorporated (5 to 15 ppm) in the diet of rats or trout have been terminated after 8 months in the case of rats and after 12 months in the case of trout, probably too soon for tumors to develop (14). Mice given diets containing 10 or 15 ppm T-2 toxin for 12 months showed in the stomach hyperkeratosis, acanthosis, and papillomatosis with inflammatory cell infiltration (16); when T-2 toxin was excluded from the diet during the subsequent 3 months, most of the lesions subsided but one adenocarcinoma was found (16). Hyperkeratosis and acanthosis was also seen in the forestomach of Wistar rats, within 4 weeks after the start of feeding with a diet containing 10 or 15 ppm of T-2 toxin (16). The conclusion drawn from these experiments was that T-2 toxin is not carcinogenic.

Our experiments were devised to simulate the conditions which may obtain among animals and humans, who are likely to be exposed only occasionally to significant amounts of T-2 toxin (and other trichothecenes) when the ingested foodstuffs had been harvested during wet and cold weather and stored inappropriately. Among the rats that survived between 12 and 27.5 months after the first and several months after the last of 3 to 8 doses of T-2 toxin, cardiovascular lesions and various tumors were found. With the increase of the number of doses, the incidence, especially of the pancreatic tumors, increased in both series in which the rats were given T-2 toxin, alone or in conjunction with nicotinamide.

The incidence of spontaneous pancreatic tumors in Wistar rats has been reported to be less than 1% (19) and the incidence of spontaneous brain tumors has been reported to be even smaller (5). However, the incidence of spontaneous tumors is known to show unexplained variations in different laboratories, and even in the same laboratory at different times (20). It is not unlikely that Fusarium mycotoxins may be involved in the variable occurrence of such spontaneous tumors when present in some of the animal diets as a result of occasional fungal growth (26).

The problem remains. Are the lesions and tumors seen in our rats caused by the administered T-2 toxin, or could the latter possibly have acted in conjunction with factors which at times might have contaminated the rats' diet? Although our control rats have been free of pancreatic, gastrointestinal, and brain tumors, some had slight to moderate vascular and myocardial lesions. Moreover, abnormalities in the pituitary can result from the presence of estrogenic agents in the diet, e.g., zeareNONE, a Fusarium metabolite. The fact that administration of T-2 toxin causes acute lesions in the digestive tract and hemorrhagic lesions in the brain and other tissues supports the interpretation that T-2 toxin significantly contributed to the chronic lesions and tumors found in these organs.

As yet, it is very difficult to trace the development of tumors after the acute lesions caused by carcinogenic agents subside. During the latent period, it is not yet possible to predict at which site and from which cell neoplasia might erupt. This general problem requires detailed investigation.

Are the effects of T-2 toxin in rats relevant to human disorders? T-2 toxin, being a directly acting toxin, would be ex-
pected to act in a similar way in many animal species. The people in the U.S.S.R. who consumed bread made from moldy, toxic grain became ill and often died from what came to be known as ATA. According to the Russian sources, summarized by Joffe (9), the illness started with a burning sensation in the buccal cavity and the esophagus; there was excessive saliva

... by Joffe (9), the illness started with a burning sensation in the buccal cavity and the esophagus; there was excessive saliva.


Fig. 1. Section of heart showing degeneration of the muscle fibers, cellular infiltration, and fibrosis. Male rat died 24 months after the first and 8 months after the last of 5 doses of T-2 toxin. Phosphotungstic-Mallory, x 125.

Fig. 2. Cross-section of the coronary artery greatly distended and partly occluded by fibrinoid swelling of collagen. Male rat killed 21.5 months after the first and 10.5 months after the last of 7 doses of T-2 toxin. Phosphotungstic-Mallory, x 13.

Fig. 3. Section of a kidney from the same rat as in Fig. 1, showing the thick-walled, almost occluded arteries, degeneration of most of the renal elements, casts, fibrosis, and cellular infiltration. H & E, x 115.

Fig. 4. Section of testis of the same rat as in Figs. 1 and 3, showing thick-walled partly occluded arteries, cellular infiltration, and degeneration. H & E, x 115.
Fig. 5. Section of pancreas of the same rat as in Fig. 2, showing extremely thick-walled arteries and cellular infiltration. H & E, x 40.

Fig. 6. Another field of the pancreas shown in Fig. 5, showing hyperplasia and "budding" of small islets. A thick-walled artery is seen at the right top of the section. Phosphotungstic-Mallory, x 100.

Fig. 7. Cross-section through the esophagus and part of the squamous stomach showing squamous hyperplasia, edema, and extensive ulceration of the stomach. Female rat died 10 months after the first and 3 days after the last of 7 doses of T-2 toxin. H & E, x 14.

Fig. 8. Section of kidney showing its extensive degeneration and distension of pelvis with calcified walls, from which a calculus was removed. Male rat killed 12.5 months after the first and 1 month after the last of 8 doses of T-2 toxin given in conjunction with nicotinamide treatment. H & E, x 4.8.
Fig. 9. Stomach showing a nodule on the glandular part. Male rat killed 24.5 months after the first and 8 months after the last of 5 doses of T-2 toxin. × 1.28.

Fig. 10. Longitudinal section of the duodenum, distended by the presence of an ulcerated papillary adenocarcinoma penetrating the serosa. Female rat killed 21 months after the first and 4 months after the last of 6 doses of T-2 toxin. H & E, × 6.

Fig. 11. Section through the nodule of the stomach in Fig. 9, showing adenocarcinoma penetrating through the muscular layer. H & E, × 15.

Fig. 12. Higher magnification of the adenocarcinoma from Fig. 10, showing the site of its penetration through the muscle layer. H & E, × 60.
Fig. 13. Section of brain with a large tumor in a frontal lobe. Male rat killed 12.5 months after the first and 1 month after the last of 8 doses of T-2 toxin given in conjunction with nicotinamide treatment. H & E, x 5.

Fig. 14. Higher magnification of the neuroblastoma shown in Fig. 13. H & E, x 120.

Fig. 15. Pancreatic islet cell adenoma. Male rat killed 23.5 months after the first and 13 months after the last of 8 doses of T-2 toxin given in conjunction with nicotinamide treatment. H & E, x 70.

Fig. 16. Pancreas with multiple nodules of exocrine adenocarcinoma. Male rat killed 22 months after the first and 11 months after the last of 7 doses of T-2 toxin. H & E, x 10.
Fig. 17. Section of heart showing areas of infection, inflammation, and cellular infiltration surrounded by fibrosis and degeneration of heart muscle. Male rat died 26 months after the first and 6 months after the last of 22 doses of crude alcoholic extract of cultures from F. sporotrichioides. H & E, x 10.

Fig. 18. Higher magnification of area shown on the right in Fig. 17. H & E, x 50.

Fig. 19. Section of pancreas with large nodules of tumors; the ones at the top and at the bottom of the section are of islet cells; the one darkly stained in the middle is of exocrine pancreas; lymph glands are seen in the top left corner. The same rat as in Fig. 17. H & E, x 10.

Fig. 20. Higher magnification of the triple nodule at the bottom of Fig. 19; adenoma of islet cells. H & E, x 48.
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