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# The Carcinogenic Action of Aristolochic Acid in Rats*

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**Abstract.** Male and female Wistar rats treated orally with 0.1, 1.0 or 10.0 mg/kg/day aristolochic acid as its sodium salt (AA) developed a high incidence of tumours dependent on dose and time. After 3 months' treatment 1.0 and 10.0 mg/kg AA led to severe papillomatosis of the forestomach with occasional signs of malignancy. Three to 6 months later without further treatment the rats developed squamous cell carcinomas in the forestomach with formation of metastases. At the same time anaplasia of the tubular epithelium and mainly adenomas appeared in the renal cortex. The transitional epithelium of the renal pelvis and the urinary bladder showed hyperplasia, papillomas or carcinomas. For the low dose (0.1 mg/kg) the treatment with AA varied between 3 and 12 months. No tumours were observed in the first 6 months of the study. After 12 and 16 months, however, papillomas or squamous cell carcinomas also occurred in the forestomach. In addition, hyperplasia of the transitional epithelium of the renal pelvis was found while the renal cortex and the urinary bladder remained normal.

**Key words:** Aristolochic acid – Toxicology – Chronic toxicity – Carcinogenicity – Rat

## Introduction

Aristolochic acid (AA) can be isolated from the roots of Aristolochia clematitis L., which has been known as a medical plant since antiquity (Hahn 1979). Chemically it is a mixture of AA I and AA II, which differs from AA I by

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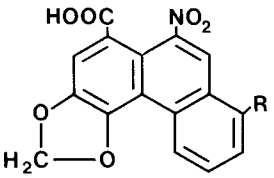
absence of a methoxy group. Both acids are characterized by a methylenedioxy group and an aromatic nitro group.




AA I: R = $-O-CH_3$
3,4-methylenedioxy-8-methoxy-10-nitrophenanthrene-1-carboxylic acid
$C_{17}H_{11}NO_7$ (m.w. 341.276)

AA II: R = $-H$
3,4-methylenedioxy-10-nitrophenanthrene-1-carboxylic acid
$C_{16}H_9NO_6$ (m.w. 311.250)

The pharmacological action of AA is well known, consisting in stimulation of various host defence mechanisms (Möse 1963; Möse 1967; Möse and Lukas 1961; Möse and Porta 1974; Bartfeld 1977).

Very much less information has been published on the toxicological profile of AA. A few reports show that high doses of AA lead to kidney damage in animals (Martincic 1956; Méhes et al. 1958; Hedwall 1961; Peters and Hedwall 1963) and in human beings (Jackson et al. 1964; Thiele et al. 1967). Further cytostatic (Kupchan and Doskotsch 1962; Kupchan and Doskotch 1962; Kupchan and Merianos 1968; Möse 1975; Schvartzman et al. 1977; Moretti et al. 1979) and antifertility effects (Pakrashi and Chakrabarty 1978; Pakrashi et al. 1980) are known from several experimental studies.

The present paper shows the results of an experiment, which was primarily planned as a routine chronic toxicity study in rats. But the development of papillomas in the forestomach after 3 months' treatment prompted us to change the trial design in order to follow up these neoplastic changes.

## Material and Methods

*Animals and Environment.* The animals used in this study were 10 weeks old male and female Wistar rats (Mus Rattus, Brunnthal, FRG) weighing about 250 g at the beginning of the experiment. They were kept in groups of three males or three females in polypropylene cages with stainless steel lids in fully airconditioned animal rooms with a natural outside light-dark cycle. The temperature was maintained at 23 ± 1° C with a relative humidity of 55 ± 5%. Standardized food pellets (ssniff $R^{(R)}$, Versuchstier-Diäten GmbH, Soest, FRG) and tap water from plastic bottles with steel nipples were available ad libitum. The animals were used after a 14-day acclimatization period.

*Compound and Treatment.* AA as its sodium salt (77.24% AA I, 21.18% AA II, Dr. Madaus & Co., Cologne, FRG) was given orally to 30 males and 30 females per group at dose levels of 0.1, 1.0 or 10.0 mg/kg on 7 days a week. Administration through a gastric tube was preferred to addition to the diet because AA has an unpleasant taste. AA was dissolved in distilled water. The control rats received the solvent in an equivalent volume of 4 ml/kg. The period of treatment lasted 3, 6 or 12 months in the low dose group and 3 months in the middle and high dose groups. Body weights were recorded once a week so as to ascertain the exact individual dose for each rat.

*Sacrifice and Postmortem Examinations.* Some of the rats were killed in batches by ether overdose after 3, 6, 9 and 12 months and the remainder after 16 months. After external inspection each animal was autopsied and all macroscopic lesions were registered. Organ weights (brain, thymus, lungs, heart, liver, spleen, kidneys, adrenals and gonads) were determined from all rats which were killed after 3 months. Thyroid, thymus, lungs, heart, liver, pancreas, spleen, stomach, small and large intestine, kidneys, adrenals, urinary bladder, gonads, prostate, uterus and all tissues with abnormal appearance were excised and fixed in formalin for histological examination. Frozen and paraffin sections were prepared and stained with haematoxylin and eosin. If necessary special staining methods were used. This procedure was also carried out in rats who died intercurrently or were killed in extremis. In some cases with advanced autolysis no readable tissue sections could be obtained, so that only the macroscopic findings were taken into consideration. All neoplastic lesions were classified and the tumour incidence in each group was determined.

*Haematology, Clinical Chemistry and Urinanalyses.* As the experiment was first planned as a routine chronic toxicity study, blood samples from the orbital venous plexus and 16-h samples of urine were taken from each rat before the study and at intervals of about 4 weeks up to 3 months. Full haematological and biochemical investigations were performed, but these results will not be reported here in detail.

*Observations.* All rats were inspected daily for clinical signs and for gross external macroscopical changes.

## Results

### *Clinical Signs*

The clinical state of the rats was remarkably good during the experiment, although many rats, especially in the high dose group, developed a high incidence of tumours. Severe cachexia was noted only in those rats which died, and only a few days before their deaths.

### *Mortality Rates*

A high treatment-related mortality rate was observed in the group receiving 10 mg/kg AA. Tumours of the forestomach with formation of metastases led to death in 11 males and nine females within 9 months. In the group receiving 1.0 mg/kg AA death occurred in one male after 6 months with the same findings and in the low dose group one female died after 16 months with a tumour of the mammary glands. One female rat in the control group died at 12 months.

### *Biochemical Studies and Organ Weights*

Full analyses of blood, plasma and urine during the first 3 months and the organ weights gave no indications to toxic effects of AA. The data are not reported here.

### *Morphological Findings*

All neoplastic findings are shown numerically in Tables 1–3. In 6 cases it was not possible to perform histological examination because of advanced autolysis or

**Table 1.** Incidence of tumours in male and female rats after 3 months' treatment with 0.1, 1.0 or 10.0 mg/kg/day AA

| Dosage (mg/kg) | Time of sacrifice after beginning of the study | | | | | |
|---|---|---|---|---|---|---|
| | 3 months | 6 months | 9 months | 12 months | 16 months | Total |
| 0 ♂ | 0/9 | 0/10 | | 0/6 | 0/5 | 0/30[a] |
| ♀ | 0/9 | 0/10 | | 1/7 | 0/4 | 1/30 |
| 0.1 ♂ | 0/9 | 0/10[b] | | 4/7 | 4/4[c] | 8/30 |
| ♀ | 0/9 | 0/10[b] | | 2/6 | 5/5[c] | 7/30 |
| 1.0 ♂ | 7/9 | 9/11 | 9/9 | | | 25/29 |
| ♀ | 8/9 | 7/10 | 10/11 | | | 25/30 |
| 10.0 ♂ | 10/10 | 18/18 | | | | 28/28 |
| ♀ | 10/10 | 13/13 | 4/4 | | | 27/27 |

[a] Number of rats with one or more tumours / total number
[b] Half the rats were treated for 6 months
[c] All rats were treated for 12 months

cannibalism, but macroscopically all these rats had nodular lesions of the forestomach.

After 3 months' treatment with 10 mg/kg AA the male and female rats macroscopically showed papillomatosis of the entire forestomach with branched papillomas up to 6 mm high. Ulceration occurred occasionally (Fig. 1). Histologically, hyperplasia and papillomas of the squamous epithelium with occasional signs of malignancy were observed (Fig. 2). The other organs showed no visible abnormalities but microscopically there were some pathological changes in the urinary tract. The tubular epithelium of the renal cortex often showed atypical cells with gigantic nuclei and enlarged basophilic nucleoli. In addition, multifocal dedifferentiation of the renal tubular epithelium and hyperplasia of the transitional epithelium of the renal pelvis and urinary bladder was found.

Three and 6 months later, without further treatment, the rats of both sexes developed carcinomas with a diameter up to 7 cm in the forestomach. The tumours had penetrated the stomach wall and the friable white surface often showed ulceration. Histologically, the tumours were identified as keratinized squamous cell carcinomas with epithelial pearl formation (Figs. 3–4). In some cases the carcinoma invaded the glandular stomach. Metastases were present in the regional lymph nodes, in the intestinal mesentery, in the small intestine and the diaphragm. In some cases formation of metastases was observed in the thoracic, axillary, cervical and inguinal lymph nodes. Histologically, they appeared as squamous cell carcinomas or adenocarcinomas. The tumours of the forestomach and their abdominal metastases sometimes showed adhesion to the spleen, liver or small intestine with penetration into these organs. In the renal cortex there were small white tumours which histologically appeared mainly as adenomas though sometimes as adenocarcinomas (Fig. 5). In the renal pelvis and in the urinary bladder formation of papilloma like tumours was observed.

**Table 2.** Number of lesions in male rats treated for 3 months with 0.1, 1.0 or 10.0 mg/kg/day AA

| | Time of sacrifice after beginning of the study | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 3 months | | | | 6 months | | | | 9 months | 12 months | | 16 months | |
| | Dosage (mg/kg) | | | | | | | | | | | | |
| | 0 | 0.1 | 1.0 | 10.0 | 0 | 0.1[a] | 1.0 | 10.0 | 1.0 | 0 | 0.1 | 0 | 0.1[b] |
| Forestomach | | | | | | | | | | | | | |
| Hyperplasia | | | 2 | | | | 2 | | | | 3 | | |
| Papilloma | | | 7 | 10 | | | 6 | 5 | 3 | | 2 | | |
| Microcarcinoma | | | | | | | 1 | 5 | 4 | | 1 | | |
| Carcinoma | | | | | | | 2 | 8 | 2 | | 1 | | 4 |
| Kidneys | | | | | | | | | | | | | |
| Anaplasia[c] | | | | 1 | | | | 5 | | | | | |
| Adenoma | | | | | | | | 5 | 1 | | | | |
| Carcinoma | | | | | | | | | | | | | |
| Renal pelvis | | | | | | | | | | | | | |
| Hyperplasia | | | | 5 | | | 1 | 2 | 3 | | 1 | | |
| Carcinoma | | | | | | | | 8 | | | | | |
| Urinary bladder | | | | | | | | | | | | | |
| Hyperplasia | | | 2 | 9 | | | 2 | 9 | | | | | |
| Papilloma | | | | | | | | 3 | | | | | |
| Carcinoma | | | | | | | | 3 | | | | | |
| Metastases[d] | | | | | | | 2 | 8 | | | | | 1 |
| N | (9)[e] | (9) | (9) | (10) | (10) | (10) | (11) | (18) | (9) | (6) | (7) | (5) | (4) |

[a] Treatment period 6 months
[b] Treatment period 12 months
[c] Anaplasia means dedifferentiation of the normal tubular epithelium of the renal cortex
[d] Present in the regional and peripheral lymph nodes, in the intestinal mesentery, in the small intestine and in the diaphragm
[e] Number of rats (in brackets) which were examined histologically

**Table 3.** Number of lesions in female rats treated for 3 months with 0.1, 1.0 or 10.0 mg/kg/day AA

| | Time of sacrifice after beginning of the study | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 3 months | | | | 6 months | | | | 9 months | | 12 months | | 16 months | |
| | Dosage (mg/kg) | | | | | | | | | | | | | |
| | 0 | 0.1 | 1.0 | 10.0 | 0 | 0.1[a] | 1.0 | 10.0 | 1.0 | 10.0 | 0 | 0.1 | 0 | 0.1[b] |
| Forestomach | | | | | | | | | | | | | | |
| Hyperplasia | | | 1 | | | | 1 | | 2 | | | 1 | | 1 |
| Papilloma | | | 8 | 10 | | | 7 | 5 | 7 | | | 2 | | 3 |
| Microcarcinoma | | | | | | | | 5 | | 1 | | | | |
| Carcinoma | | | | | | | | 3 | 2 | 3 | | | | 1 |
| Kidneys | | | | | | | | | | | | | | |
| Anaplasia[c] | | | | | | | | 2 | 1 | | | | | |
| Adenoma | | | | | | | | | | 4 | | | | |
| Carcinoma | | | | | | | | 2 | | | | | | |
| Renal pelvis | | | | | | | | | | | | | | |
| Hyperplasia | | | | 4 | | | | 2 | 2 | 2 | | 3 | | 1 |
| Carcinoma | | | | | | | | | | | | | | |
| Urinary bladder | | | | | | | | | | | | | | |
| Hyperplasia | | | 1 | 9 | | | 2 | 7 | | 3 | | | | |
| Papilloma | | | | | | | | 1 | | 1 | | | | |
| Carcinoma | | | | | | | | 1 | | | | | | |
| Pituitary | | | | | | | | | | | | | | |
| Adenoma | | | | | | | | | 1 | | | | | |
| Breast | | | | | | | | | | | | | | |
| Carcinoma | | | | | | | | | | | | | | 1 |
| Uterus | | | | | | | | | | | | | | |
| Polyp | | | | | | | | | 2 | | 1 | | | 1 |
| Metastases[d] | | | | | | | | 5 | | 3 | | | | |
| N | (9)[e] | (9) | (9) | (10) | (10) | (10) | (10) | (13) | (11) | (4) | (7) | (6) | (4) | (5) |

[a] Treatment period 6 months
[b] Treatment period 12 months
[c] Anaplasia means dedifferentiation of the normal tubular epithelium of the renal cortex
[d] Present in the regional and peripheral lymph nodes, in the intestinal mesentery, in the small intestine and in the diaphragm
[e] Number of rats (in brackets) which were examined histologically

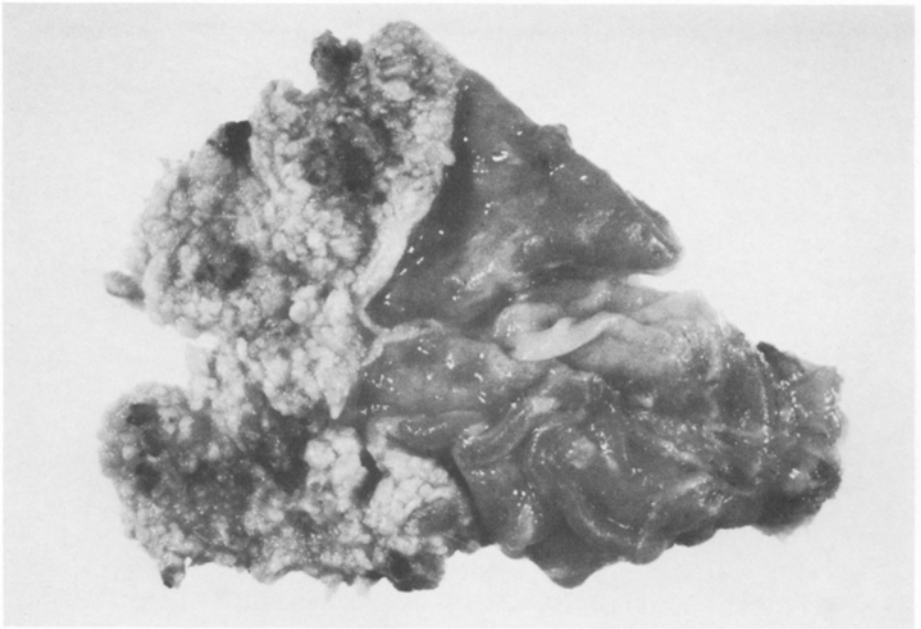


**Fig. 1.** Forestomach after 3 months (10 mg/kg AA): multiple papillomas, up to 6 mm in height, often exhibit ulceration and replace the limiting ridge

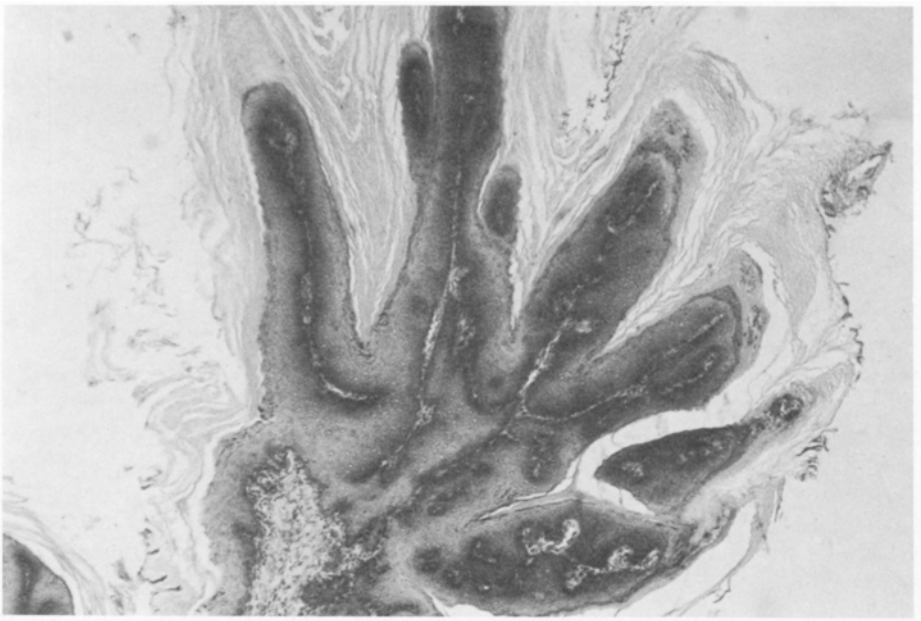


**Fig. 2.** Branched papilloma of the squamous epithelium of the forestomach with hyperkeratosis after 3 months (10 mg/kg AA). Magnification: 50 ×, H.E.

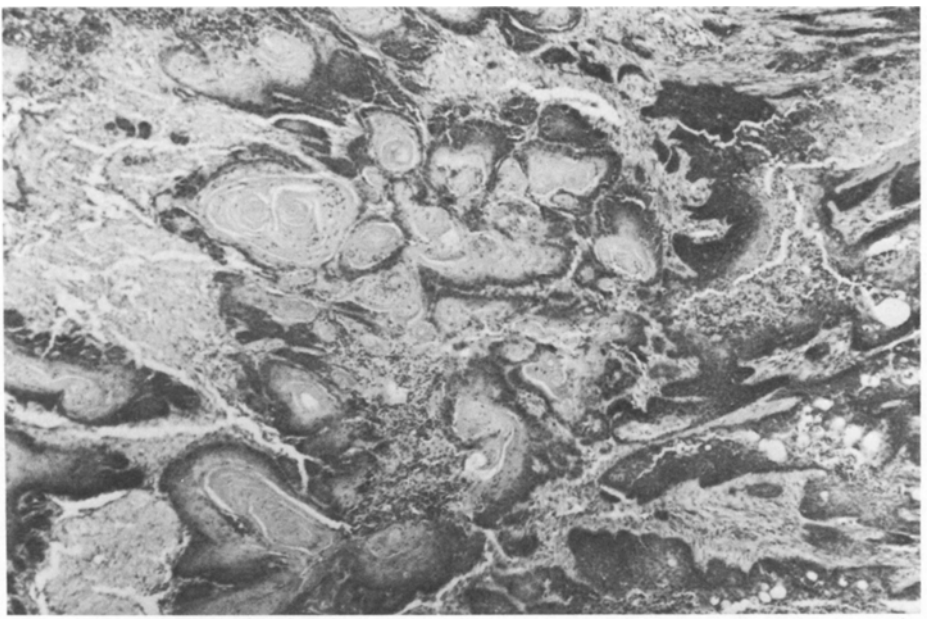


**Fig. 3.** Well-differentiated squamous cell carcinoma with epithelial pearl formation of the forestomach after 6 months (10 mg/kg AA). Magnification: 50 ×, H.E.

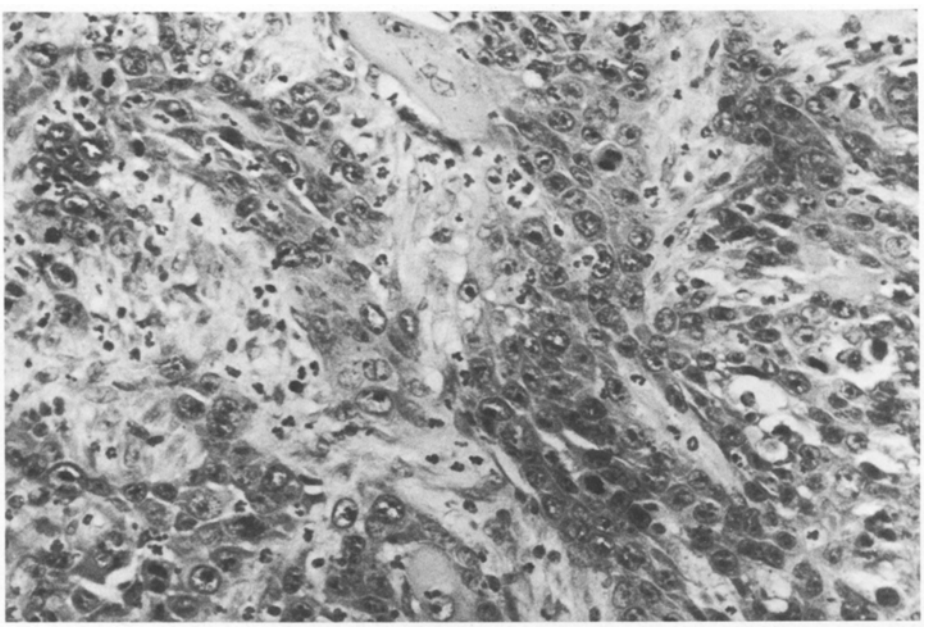


**Fig. 4.** Squamous cell carcinoma of the forestomach after 6 months (10 mg/kg AA). The neoplastic epithelium shows vacuolated cytoplasm, irregular nuclei and numerous mitoses, mainly atypical forms. Magnification: 250 ×, H.E.

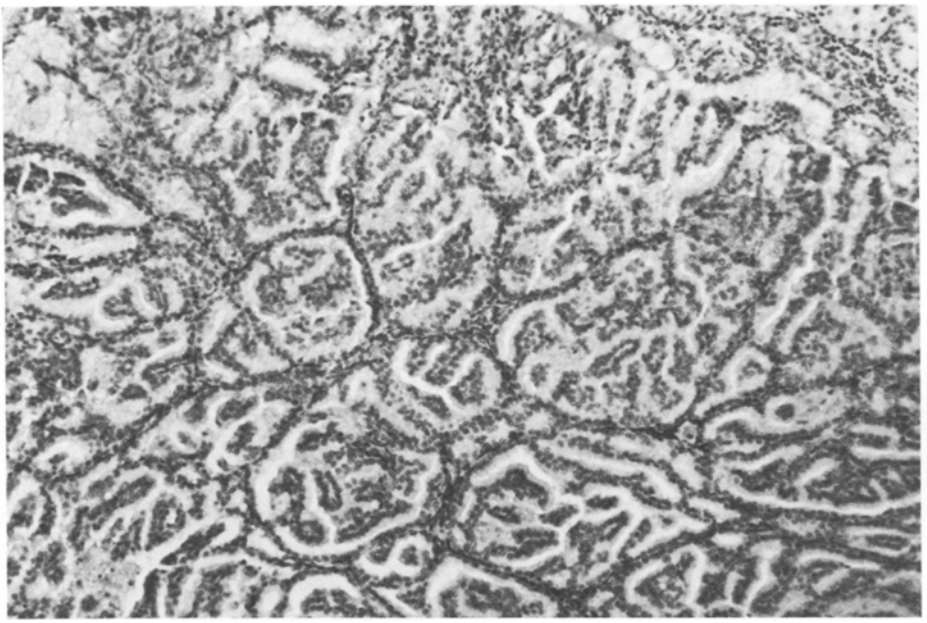


**Fig. 5.** Adenoma of the renal cortex after 6 months (10 mg/kg AA). Magnification: 100 ×, H.E.

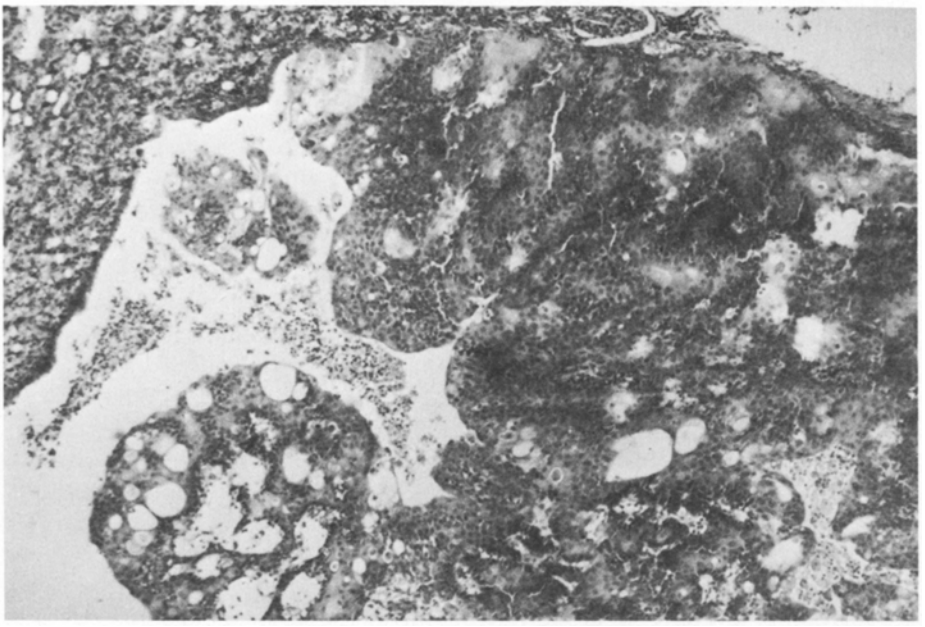


**Fig. 6.** Carcinoma of the renal pelvis after 6 months (10 mg/kg AA). Magnification: 50 ×, H.E.

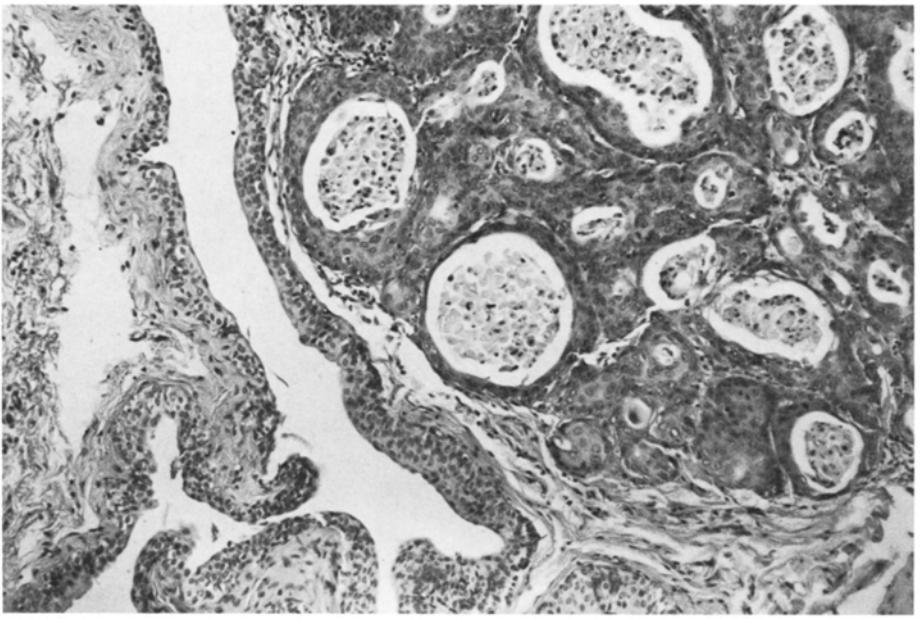


**Fig. 7.** Carcinoma of the urinary bladder after 6 months (10 mg/kg AA). Magnification: 100 ×, H.E.

Microscopically, these tumours could be described as carcinomas of the transitional epithelium of the renal pelvis (Fig. 6), with infiltration of the medullary parenchyma in some cases, and as papillomas or carcinomas of the transitional epithelium of the urinary bladder (Fig. 7).

In the group receiving 1.0 mg/kg AA the tumour incidence was quantitatively lower and qualitatively less severe than in the high dose group after 3 months treatment. Tumours of the forestomach mostly appeared as small nodular papillomas without signs of malignancy. But 3 and 6 months later without further treatment some rats developed squamous cell carcinomas of the forestomach with metastases in some cases. In a few cases there was dedifferentiation of the renal tubular epithelium or hyperplasia of the transitional epithelium of the renal pelvis or urinary bladder. A renal adenoma of the cortex was found in one male rat. In addition, one female rat developed a hypophyseal adenoma and two females had endometrial polyps.

In the low dose group receiving 0.1 mg/kg AA no abnormalities were detected in any organ after 3 and 6 months' treatment. At the next interim kill after 12 months the rats which had been treated for 3 months only showed papilloma and carcinoma formation in the forestomach and occasional hyperplasia of the transitional epithelium of the renal pelvis. The renal cortex and the urinary bladder seemed to be normal and no metastases could be detected.

In another low dose subgroup with 0.1 mg/kg the rats had been treated for 12 months and were killed 4 months later. Papillomas as well as squamous cell carcinomas were found in the forestomach with formation of metastases in one

case. The kidneys and the urinary bladder showed no neoplastic lesions, but there was slight hyperplasia of the transitional epithelium of the renal pelvis. In addition, one female rat developed a mammary adenocarcinoma and another an endometrial polyp in the uterus.

There was only one female in the control group with a spontaneous endometrial polyp in the uterus after 12 months.

Extramedullar haematopoiesis in the spleen was a very frequent finding in the rats with carcinomas of the forestomach, and was found in rats from all treatment groups.

## Discussion

This investigation with AA in rats was originally planned as a chronic toxicity trial, but necropsies carried out at 3 months – the intended conclusion of the trial – revealed papillomatosis of the entire forestomach in the group receiving 10 mg/kg. The same changes were present in the 1.0 mg/kg group, but they were less frequent and less severe. In the rats which had received 0.1 mg/kg the squamous epithelium of the forestomach showed no abnormalities at that time. To allow further observation of the growth of these papillomas the trial was extended as described under *"Material and Methods"*.

During the subsequent observation period the papillomas in the forestomach underwent malignant change with the formation of metastasizing squamous epithelial carcinomas, this change being dependent on dose and time. Carcinomas of the forestomach developed at a later date even among the rats which had received the low dose of 0.1 mg/kg. In this group it made no difference whether treatment with AA was discontinued after 3 months (at which time there were still no lesions of the squamous epithelium detectable by optical microscopy) or whether it was continued for 12 months.

The glandular stomach and the oesophagus were invariably free from tumours. Only in a few instances did the neoplastic growth encroach from the forestomach into the glandular stomach.

The metastases mainly involved the regional lymph nodes. The tumours of the small intestine were obviously not of primary origin. Instead, they gave the impression of having arisen from the mesenteric lymph nodes and having penetrated the bowel wall from outside. There was no microscopic evidence of precancerous changes in the small bowel mucosa, another fact which points to a metastatic origin.

Long-term oral administration of AA in medium and high doses produced neoplasms not only locally but also in distant organs. The neoplastic changes in the renal cortex, renal pelvis and urinary bladder are regarded as primary tumours. The evidence for this view is the fact that they were accompanied by precancerous changes. In the renal cortex there was dedifferentiation of the tubular epithelium progressing to cortical adenoma or occasionally to carcinoma, while in the renal pelvis and urinary bladder there was hyperplasia progressing to papilloma or carcinoma. The neoplastic changes in these sites appeared later than those in the stomach, possibly owing to the lower local concentration of AA.

No urogenital tract tumours were found in the low dose group up to the end of the experiment. Nevertheless, the hyperplasia of the transitional epithelium in the renal pelvis indicates that neoplastic growth might have ensued if the period of observation had been longer.

The uterine fibromas occurring in four female rats from the low and medium dose groups and the control group are regarded as spontaneous tumours, as are the hypophyseal adenoma and the mammary carcinoma each found in one female from the low and medium dose group. Such tumours are commonly observed in our necropsy material from rats of this age group.

Apart from the neoplastic phenomena described above, the present investigation revealed no other toxic effects resulting from 3 months' administration of AA. Impairment of renal function has been reported after single intravenous injections of AA in high doses (Hedwall 1961; Peters and Hedwall 1963), but was not seen after the doses employed in the present study.

It is not yet known whether AA is itself a carcinogen or whether it must first undergo metabolic activation. It is conceivable that the carcinogenic effect is due to the aromatic nitro group or to metabolic activation of the polycyclic phenanthrene ring.

Quantitative assessment of our findings would certainly establish, that AA must be classified as one of the most effective carcinogenic substances yet known, because of the low dose (0.1 mg/kg/day), its short induction period (3 months) and the multiple growth of tumours (forestomach, kidneys, renal pelvis and urinary bladder) with formation of metastases.

In conclusion it may be stated that long-term intragastric administration of AA produces a high incidence of tumours in male and female Wistar rats, the effect being dependent on dose and time. AA is a carcinogen with both local and systemic effects.

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