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TRANSLATION

EFFECT OF LEAD ON GENITAL-CELL CHROMOSOMES IN THE MOUSE

Huang Xupei, Xu Juanhua (Department of Hygienics, Naujing Institute of Medical Science), Wang Xiaoping (Graduate student), Fong Zhiying (Supervising professor), and Qu Weilei (Supervising professor)
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Abstract

Male mice divided into four groups were naturally fed with waters containing 0, 500, 1000, and 2000 ppm of lead acetate for a continuous 50-day period. Their average blood-lead contents were subsequently determined to be 12, 42, 71, and 87 μg/dL, respectively. The rates of chromosome aberration and sister-chromatid exchange of the spermatogonia cells in these mice were examined by the BrdU experimental method. The results obtained indicate that the long-term exposure of a male mouse to a high dose of lead acetate would very possibly induce permanent damage to the genetic substance of its genital cells.

Key words: lead acetate, mouse, spermatogonia, 5-bromodeoxyuridine, chromosome aberration, sister-chromatid exchange

Lead is a common toxic element seen in industrial and environmental pollutants. In recent years, many studies have been conducted on its genetic effects in the human body both at home and abroad. The results of some animal tests have demonstrated that lead can cause stillbirths and/or teratism in Mus musculus, Rattus norvegicus, and Citellus [1,2]. The number of abnormal spermatogonia cells in mice fed food containing 1% lead acetate for 8 weeks was found to be significantly higher than that in mice of a control group [3]. After an extensive epidemiological

survey, Browder et al. reported that the number of premature births and abortions was found to be increased in women who themselves or their husbands were engaged in professions which involve the use of lead; the number of stillbirths was also found to be increased in women who themselves or their husbands were positively identified to be subject to lead poisoning [4]. Although there have been a handful of publications reporting observations of increases in the periphery of the hemolymph micronucleus, chromosome aberration, and sister-chromatid exchange (SCE) rates in humans caused by lead contact and lead poisoning [5,6], as well as one article describing an animal experiment in which the rate of myelochromosome aberration was found to be increased in the mouse, rat, goat and monkey exposed to excess lead [7], there has been no study reported on the effect of lead on genital cell chromosomes. It is common knowledge that once the genetic substance in genital cells is damaged, the effect will be passed on for generations. In this sense, the examination of the genetic toxicology of lead through the determination of its effect on genital cell chromosomes appears to be very important. In our present study, mice divided into several groups were fed lead-containing water for a certain period of time, their blood-lead contents were subsequently measured, and the variations in the spermatogonia cell's SCE and chromosome aberration rates were determined.

Materials and method

I. Materials

Healthy and mature male mice with body weights of 20 to 25 g were used as the experimental results. 15 mice were randomly divided into 4 groups, with the control group consisting of

6 mice. Testing groups I, II, and III were given drinking water (deionized) containing 500, 1000, and 2000 ppm of lead acetate (corresponding to 275, 546, and 1092 ppm of lead) respectively, while the control group was only given plain deionized water. The mice were allowed to freely drink the water for a continuous period of 50 days. At the 48th day, all mice were given 0.6 mL of BrdU (Fluka) solution adsorbed onto activated carbon once through abdominal injection. The preparation of the carbon-adsorbed BrdU solution was carried out by Kanda's method [8] with a slight modification. Twenty g of activated carbon were first ground in an agate mortar into a fine powder, then suspended in 500 mL of distilled water. After testing for 5 min, the upper part of the suspension was transferred and it was centrifuged at 2000 rev/min for 8 min to separate out the fine activated carbon powder. This fine powder was then washed with 2.5% NaOH, distilled water, and 2.5% HCl in sequence for five times and finally washed with distilled water again to neutralize. The suspension was again centrifuged and the collected precipitate was dried and disinfected at 180°C for 30 min. In a separate operation, 10 mg/mL of BrdU aqueous solution were prepared, filtered, and disinfected. The BrdU aqueous solution was added with the disinfected activated-carbon powder at a concentration of 50 mg/mL. The solution was fully stirred at room temperature for 1 hour prior to use. Twenty-six hours after the injection of BrdU, 3 mice taken from the control group which was fed 0 ppm of lead were administered mitomycin C (0.4 μg/g body weight) once through abdominal injection and they were used as a positive reference. The remaining 3 mice in the control group were used as a negative reference. Fifty-four hours after the injection of BrdU, all of the mice in the test and control groups were given colchicine through abdominal injection (4 mg/kg body weight) and they were sacrificed 4 hours later.

II. Determination of blood-lead content

The blood samples were collected through the excision of the eyeballs while killing the mice. After the anticoagulant treatment with heparin and homogenization by shaking, the lead contents of the blood samples were determined with a Hitachi 180-80 atomic absorption spectrophotometer using a graphite furnace.

III. Preparation of chromosome specimen

The chromosome specimens were prepared by a modified Evan and Meredith method. After removing the testis, the white membrane was cut off and the convoluted tubules were hypoosmotically treated with 1% sodium citrate at room temperature for 30 min. A mixed solvent of acetic acid and methanol (1:3) was used to fix this sample and a 60% acetic acid solution was used for softening. The tubules were then broken by blowing to form a cell suspension. After centrifuging the suspension at 1000 rev/min, the specimen was prepared by the regular gas-dry method. A part of the chromosome specimens were used for the sister-chromatid difference (SCD) treatment by the UpG chromatic method.

IV. Chromosome observation and rate counting

The SCE frequency of the spermatogonia cell was counted by the regular method. For each mouse, 25 chromatically clear metakinesis phases were counted. The exchanges at the terminal of the chromosome and the centromere were counted once and the exchange at the middle of the chromosome was counted twice. When dealing with the chromosome aberration of the spermatogonia cell, 100 metaphases were counted for each mouse; the aberrations involve chromatid and chromosome breakage, space, depletion and fragmentation.

Results

The sister-chromatid difference is clearly seen in the meta chromosome picture of the mouse spermatogonia cell after the UpG treatment conducted 54 hours after the abdominal injection of BrdU adsorbed onto activated carbon (Figure 1). All chromosomes had a relatively light chromatid combining with BrdU. Figure 2 shows the phenomenon of chromosome aggregation between multiple cells. This phenomenon was seen in both the negative control group and test groups and therefore it may not necessarily reflect the change in chromosome number. In the literature, the phenomenon has been explained as a result of the mutual aggregation between the meta chromosomes of adjacent synchronous spermatogonia cells and it is considered to be a normal phenomenon associated with the periodic and synchronous splitting and differentiation process of the male genital cells [9]. For the above reason, the statistics of such chromosome aggregations have not been studied in our current experiment.

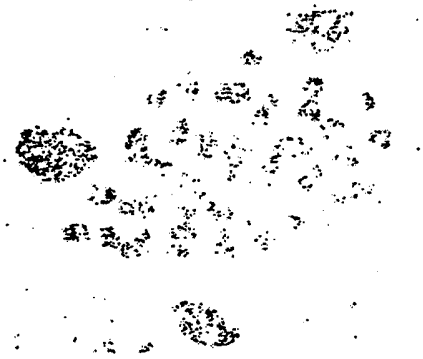

Figure 1.

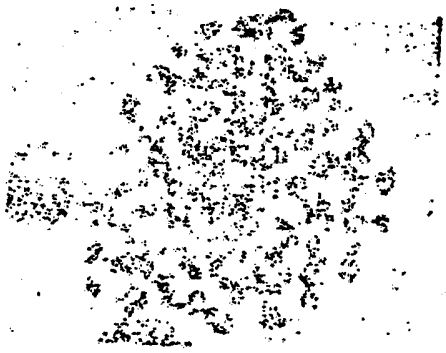

Figure 2.

The observation results for the SCE rates of the mouse spermatogonia cells are collected in Table I. The average SCE rate of each cell in the negative control group was 1.70 $\pm$ 0.13;

difference in the chromosome aberration rate was seen only in the 2000-ppm group and mitomycin C group ($p < 0.05$), but not in the other groups ($p > 0.05$).

Table II. Observation results for chromosomal aberrations of spermatogonia cells in mice after drinking lead-containing water (for 50 days).

Group	Dose of lead acetate (ppm)	Number of mice* (piece)	Average blood-lead content (μg/dL)	Number of cells observed	Chromated		Chromosome				Aberration rate (%)
					Breakage	Space	Breakage	Space	Depletion	Annulation	
Negative	0	4	12	400	—	2	—	—	—	—	0.5
I	500	4	42	400	1	3	—	—	—	—	1.0
II	1000	4	71	400	2	4	—	—	—	—	1.5
III	2000	4	87	400	1	6	—	1	1	—	2.3**
MMC	0	4		400	2	5	—	2	1	—	2.5**

* One mouse was added to each group and it was treated in the same manner as the previous mice.
** Statistical analysis exhibited a P value of less than 0.05.

Discussion

There have been some studies reported on the effect of lead on the chromosome aberration and SCE of some mammal cells (myelogram and hemolymph). Its effect on the chromosomes and SCE of genital cells, however, has not been well understood. The genital cell is the direct hereditary material and it is therefore an important research object in genetic toxicology. The success of the BrdU internal test method made the in vivo determination of SCE in mouse spermatogonia cells useful for an effective and sensitive detection of induced mutation by toxic substances. At the present time, SCE is considered to reflect the breakage and restoration processes of DNA chains. The SCE

those in the 500-ppm group and 1000-ppm group were 1.68 ± 0.18 and 2.11 ± 0.14, respectively. Compared to the negative control group, the 500-ppm and 1000-ppm groups did not exhibit significantly different results ($p > 0.05$). The average SCE rate of each cell in the 2000-ppm group was 2.84 ± 0.29; that in the mitomycin C group was 5.04 ± 0.69. Compared with the negative control group, these two groups had significantly different results ($p < 0.01$).

Table I. Comparison in SCE rates of spermatogonia cells in mice after drinking lead-containing water (for 50 days).

Group	Dose of lead acetate (ppm)	Number of mice (piece)	Average blood-lead content (μg/dL)	Number of cells observed	SCE frequency		t test
					Total	Average SCE/cell ($\bar{x} \pm S$)	
Negative	0	3	12	76	129	1.70±0.13	
I	500	3	42	75	126	1.68±0.18	>0.05
II	1000	3	71	75	148	1.99±0.24	>0.05
III	2000	3	87	76	216	2.84±0.29	<0.01
MMC	0	3		81	408	5.04±0.69	<0.01

The observation results for the chromosome aberrations of the mouse spermatogonia cells are collected in Table II. In the negative control group, only 2 cells with a chromatid space were counted, with the aberration rate being 0.5%. In the 500, 1000, 2000 ppm and mitomycin C groups, the observed aberration rates were 1.0%, 1.5%, 2.3%, and 2.5%, respectively. The chromosome aberrations counted involved spacing, breakage, and depletion, with the space type of aberrations as the most frequently encountered. The result of the statistical analysis indicated that in comparison with the negative control group, a significant

determination of mammal cells often serves as an effective way of detecting mutagens and carcinogens [10]. In our present experiment, the BrdU internal test was carried out by Kanda's adsorption method, using a reduced amount of activated carbon (from 100 mg/mL to 50 mg/mL). The obtained results were satisfactory. The SCE rate for the mice in the negative control group was found to be 1.70/cell, close to the spontaneous SCE rate of mouse spermatogonia cells (1.3-2.18/cell) reported abroad [8]. The cell's SCE rate, however, was found to be significantly increased for mice in the positive control group to which mitomycin C was injected. Since the concentration of BrdU used in our experiment was very low (6 mg/mouse) and moreover its release from the activated carbon surfaces was quite slow, the direct effect of BrdU itself on SCE can be essentially neglected. Our experimental results have proven that the conditions selected here cannot only save BrdU, but also make the method simpler and more reliable.

As indicated by our experimental results, when a mouse was fed water containing lead acetate for a long period of time, its blood-lead content increased with the amount of lead introduced. For the mice that drank water containing either 500 ppm or 1000 ppm of lead acetate for 50 days, the chromosome aberration and SCE rates of their spermatogonia cells were not found to be significantly increased. A significant increase in the chromosome aberration and SCE rates was found for the mice that drank water containing 2000 ppm of lead acetate. The observed aberration was, however, the chromosome space type in most cases, indicating minor DNA damage. Although the increase in the SCE rate of the mouse spermatogonia cells induced by a high content of lead was quite significant ($p < 0.01$), the SCE number counted for each cell did not reach twice the SCE number in a spermatogonia cell

found for the negative-control group mice. According to the criterion proposed by Taft et al., those agents which induce SCE at less than twice the SCE number originally found for a control cell should be considered to be weak SCE inducing agents [10]. Our experimental results therefore suggest that the long-term exposure of a male mouse to lead acetate at a relatively high dose could cause damage to its genital cell chromosomes, and the induced mutation of mouse spermatogonia cells by lead appeared to be a relatively weak one. To answer the question as to whether the observed mutation is related to sperm irregularity, teratism, and stillbirths caused by lead over-exposure and lead poisoning, further investigations are needed.

So far, the mechanism by which lead induces mutation is still unclear. Some researchers think that because lead is a heavy metal element, it can undergo combination reactions with some biological materials present in the body. Nucleic acids, for example, contain purine bases and phosphoric acid which possess high reactivities with metals. Among purine bases, guanine and adenine have N, OH, or NH_2 functional groups which can readily react with many metals. Once a metal element enters a biological entity, it combines with the basic groups of the nucleic acid. Consequently, a change in the stereoscopic structure of the nucleic acid and a mismatching of the bases could be induced. These alternations of the nucleic acid may influence the genetic property of the cell and cause aberrations and cancer in the biological entity.

At the present time, a tendency to replace old morphological viewpoints with modern molecular biological viewpoints has been formed in evaluating the toxicities of industrial and environmental pollutants. The evaluation of toxicity has been carried out based on genetic considerations. The results of our present

experiment provide useful reference data for the evaluation of the genetic toxicity of lead.

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铅对小鼠生殖细胞染色体的影响

黄旭培　许娟华　王小萍*
卫生系劳动卫生学教研室
冯致英**　翟为雷**

内容提要　4组雄性小鼠自由饮用含醋酸铅0、500、1000、2000ppm的水连续50天后，测得其平均血铅值分别为12、42、71和87μg/dL。用BrdU体内实验方法作精原细胞染色体制片观察染色体畸变率和姊妹染色单体互换率。结果提示：雄性小鼠长时间接触高剂量的醋酸铅可能导致对生殖细胞遗传物质某些损伤效应。

关键词　醋酸铅；小鼠，精原细胞；5-溴脱氧尿嘧啶核苷，染色体畸变，姊妹染色单体交换

铅是一种普遍性的环境污染物质和工业毒物。近年来，国内外学者对其遗传学效应进行了许多研究。动物实验证实铅可引起小鼠、大鼠和地鼠胚胎死亡和/或畸形[1,2]。进食含醋酸铅1%的饲料8周的小鼠异常精细胞数显著高于对照组[3]。Browder等通过流行病学调查报道，夫妻任何一方从事铅作业，均可使早产，流产增加；双亲中任何一方铅中毒，会导致死产的增加[4]。尽管对于过量铅接触和铅中毒可致离体或活体人外周血淋巴细胞微核率、染色体畸变率和姊妹染色单体交换（SCE）率增高已有许多报道[5,6]，动物实验也表明过量铅接触可使小鼠、大鼠、山羊、猴的骨髓染色体畸变率增高[7]，但铅对生殖细胞染色体影响的研究报道甚少。生殖细胞的遗传物质如发生变异和损伤，将会给后代带来直接影响，检查铅对生殖细胞染色体的影响是研究铅的遗传毒理必不可少的一环。为此，我们给小鼠饮用一段时间的含醋酸铅水后，测定其血铅值，进行了活体精原细胞SCE率和染色体畸变率的观察。

材料和方法

一、实验材料和药物处理

实验动物为健康的成熟雄性小鼠，体重20—25 g。将15只小鼠随机分成4组，对照组为6只，Ⅰ、Ⅱ、Ⅲ实验组分别给予含醋酸铅500、1000、2000ppm（实际含铅275、546、1092ppm）的饮用水（用去离子水配制）；对照组给予去离子水。自由饮水，连续50天。上述动物均于48天分别一次腹腔注射用活性炭吸附的BrdU（Fluka牌）溶液0.6ml。BrdU吸附在活性炭上的制备是根据Kanda的方法稍加修改而进行的[8]。取20g活性炭，在玛瑙钵中研成细粉末，然后将其悬浮在500ml蒸馏水中，静置5分钟后，吸取上半部悬液，以2000转/分离心8分钟，以获得较细的活性炭粉末；再将此粉末用2.5% NaoH、蒸馏水和2.5%HCl顺序洗5次，然后用蒸馏水洗涤至中性，最后将其离心，离心沉淀物在180℃干燥灭菌30分钟。另外配成10mg/ml BrdU水溶液，过滤除菌，再将灭菌的活性炭以50mg/ml的浓度加入到BrdU水溶液中，使用前在室温下充分搅拌1小时。BrdU注射后26小时，从0 ppm对照组中取出3只小鼠分别进行一次腹腔注射丝裂霉素C（0.4μg/g体重）作为阳性对照，剩余3只为阴性对照。BrdU注射后54小时，所有实验组和对照组动物分别腹腔注射秋水

*卫生系进修生　**指导老师

仙素（4mg/kg体重），4小时后处死动物。

二、血铅测定

处死动物时摘眼球收集血，肝素抗凝，摇匀，用日立牌180—80型原子吸收分光光度计石墨炉法测定血铅。

三、染色体标本制备

按稍加修改的 Evan 氏和 Meredith 氏法制备标本。取出睾丸，剪去白膜，将曲精小管以1%枸橼酸钠溶液于室温下低渗30分钟左右，以1：3冰乙酸-甲醇混合液固定，60%冰乙酸软化，吸管吹打成细胞悬液，1000转/分转速离心，常规气干法制片。部分染色体标本按贺氏UpG染色法进行姊妹染色单体差别染色（SCD）处理。

四、观察计数

按常规计数精原细胞SCE频率，每一动物计数25个分色明显的中期分裂相。染色体端部及着丝点处交换计数一次，染色体中部交换计数两次。计数精原细胞染色体畸变时，每只小鼠数100个中期相，畸变包括：染色单体和染色体断裂、间隙、缺失和断片等。

结　果

小鼠精原细胞在腹腔注射一次活性炭吸附的BrdU54小时后所展示的中期染色体图象经UpG处理后可见姊妹染色单体差别染色清晰，所有染色体均有一个并合BrdU染色较浅的染色单体（图1）。图2示多细胞染色体聚合现象，此现象在阴性对照组和各剂量组均多见，所以很难说是染色体数目的改变。有文献报道认为这是邻近同步精原细胞中期染色体互相聚合的结果，是雄性生殖细胞的周期性、同步分裂和分化过程的一种正常现象[9]。所以本实验对此未作统计。

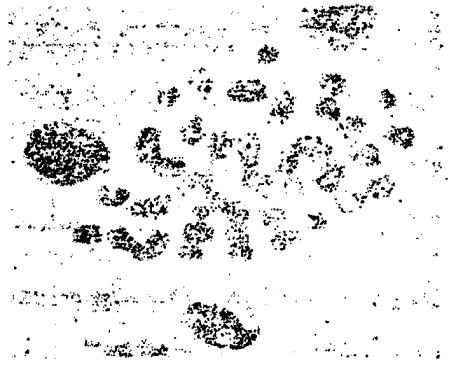

图　一

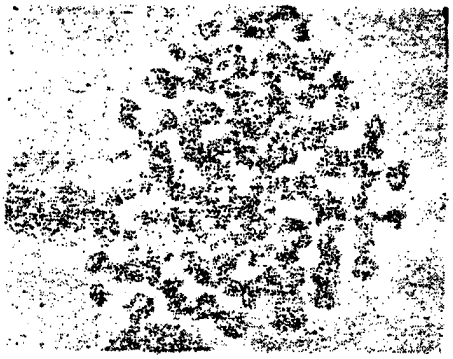

图　二

表 1　　饮用含铅水(50天)后小鼠精原细胞SCE计数比较

组　号	剂　量 含醋酸铅 (ppm)	供试动物数 (只)	平均血铅值 (μg/dL)	观察细胞数	SCE 频 率 总数	SCE 频 率 平均SCE/细胞 ($\bar{x}\pm S$)	t 检 验
阴性	0	3	12	76	129	1.70±0.13	
Ⅰ	500	3	42	75	126	1.68±0.18	>0.05
Ⅱ	1000	3	71	75	148	1.99±0.24	>0.05
Ⅲ	2000	3	97	76	216	2.84±0.29	<0.01
MMC	0	3		81	408	5.04±0.69	<0.01

小鼠精原细胞SCE的观察结果列于表1。阴性对照组每个细胞SCE平均为1.70±0.13；500ppm组每个细胞平均SCE率为1.68±0.18；1000ppm组每个细胞平均SCE率为2.11±0.14。500ppm和1000ppm组与阴性对照组比较均无显著性差异($p>0.05$)。2000ppm组每个细胞SCE平均出现率为2.84±0.29；丝裂霉素组每个细胞平均SCE率为5.04±0.69，这两个组与阴性对照组相比均有非常显著性差异($p<0.01$)。

表2　饮用含铅水(50天)后小鼠精原细胞染色体畸变观察

组号	剂量 含醋酸铅 (ppm)	供试动物数* (只)	平均血铅值 (ug/bL)	观察 细胞数	染色单体 断裂	染色单体 裂隙	染色体 断裂	染色体 裂隙	缺失	环状	畸变率 (%)
阴性	0	4	12	400	—	2	—	—	—	—	0.5
Ⅰ	500	4	42	400	1	3	—	—	—	—	1.0
Ⅱ	1000	4	71	400	2	4	—	—	—	—	1.5
Ⅲ	2000	4	87	400	1	6	—	1	1	—	2.3**
MMC	0	4		400	2	5	—	2	1	—	2.5**

*每组增补一只小鼠，处理同前。　**经统计学分析$P<0.05$。

小鼠精原细胞染色体畸变的观察结果列于表2。阴性对照组仅见具染色单体裂隙的细胞2只，畸变率为0.5%；而500、1000、2000ppm组以及丝裂霉素C组染色体畸变率分别为1.0%、1.5%、2.3%和2.5%。畸变包括裂隙、断裂、缺失，而以裂隙多见。经统计学分析表明2000ppm组和丝裂霉素C组与阴性对照组相比其染色体畸变率有显著性差异($p<0.05$)；其余各组与阴性对照组相比无显著性差异($p>0.05$)。

讨　论

铅对哺乳动物体细胞（骨髓细胞、淋巴细胞）染色体畸变及SCE的分析已有报道，而对生殖细胞染色体及SCE的影响尚有待研究。生殖细胞是遗传的直接传递者，以生殖细胞为材料进行研究，是遗传毒理学面临的研究课题。BrdU体内试验方法的成功，使小鼠活体精原细胞SCE检测方法成为检测有害物质诱变效应的一个相当灵敏而又有效的指标。目前认为SCE反映了包括DNA链的断裂和修复过程，哺乳类细胞SCE试验是检测致突变剂和致癌剂的有效手段[10]。本实验采用了Kanda氏的活性炭吸附BrdU体内实验法，但减少了活性炭用量（100mg减至50mg/ml），得到了满意的结果。本实验中，阴性对照组小鼠的SCE出现率是1.70/细胞，与国外报道的小鼠精原细胞SCE自发率(1.3—2.18/细胞）接近[8]，而用丝裂霉素C处理动物作阳性对照时，细胞SCE发生率则明显提高。我们使用的BrdU浓度很低(6mg/1只小鼠），而且吸附在活性炭上缓慢释放，基本上能排除BrdU本身对SCE的直接影响。实验结果表明此法既节省BrdU又简便可靠，是一种值得推荐的方法。

本实验结果表示，给小鼠长期饮用含醋酸铅的水，小鼠体内血铅值随着给铅量的增高而明显升高，在给予500和1000ppm醋酸铅饮水50天后并未发现明显的精原细胞染色体畸变和SCE频率的增加；在2000ppm组发现小鼠精原细胞染色体畸变率和SCE率均显著性增高，但畸变是以裂隙多见，属于轻微的DNA损伤。高浓度铅诱发精原细胞SCE的增加虽有非常显著性差异($p<0.01$)，但每个细胞的SCE数未能达到为对照组精原细胞SCE数的两倍，按Tatt等提出的标准，处理组诱导细胞SCE发生数未能达空白对照组细胞SCE数两倍者为诱导SCE弱阳性剂[10]。

因此，本结果提示，雄性小鼠长期接触较高剂量的醋酸铅可能导致对生殖细胞染色体的损伤，铅对于小鼠精原细胞具有较弱的诱变作用。过量铅接触和铅中毒所致精子异常、畸胎和死胎增加是否与此有关，尚须作进一步的探讨。

关于铅的致突机制目前尚不很清楚。有人认为铅是重金属，进入体内能与体内生物成分结合起反应。核酸中有与金属反应性较强的嘌呤碱基与磷酸，嘌呤碱其中的鸟嘌呤与腺嘌呤含有极易与金属反应的N、OH或NH_2基团，因此，金属一旦侵入生物体，与核酸碱基结合会引起核酸立体结构的改变和碱基的错误配对，这种核酸的参与就会影响细胞的遗传，有可能使生物体畸变或致癌。

目前，在评价工业毒物与环境污染物时，逐步以分子生物学的观点代替过去以形态为主的观点，并进一步提出从遗传学角度评价这些有害物质。本实验结果为评价铅的遗传危害提供了参考数据。

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摘　译

毛细胞性白血病伴发局灶性血管损害

M Klima等报告了一例毛细胞性白血病，患者男性，63岁，经外周血液和骨髓的血液学检查发现细胞呈典型的毛细胞形态而确诊。尸体解剖发现所有器官都有白血病细胞浸润，在肺、肾脏最明显；另外许多中等或较大的内脏动脉发生节段性血管损害。以前有人报告这种伴发的灶性血管损害病例常类似结节性多动脉炎的改变，然而本文报告的病例，血管并没发现典型的坏死、多形核白细胞浸润以及动脉瘤样改变，而是由水肿、内膜广泛性纤维性增生和肿瘤细胞浸润组成的血管病变。作者认为其病理机制可能是肿瘤细胞和血管壁成分或血管内沉积物局部免疫相互作用所致，提示毛细胞性白血病和血管损害之间有直接联系。

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李淑兰摘　王三锡校）