Liver histology of Wistar rats (Rattus norvegicus) following oral administration of 50% ethanol

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ABSTRACT

Ethanol, also known as ethyl alcohol, pure alcohol, and alcohol, is a toxic, volatile, flammable, and colorless liquid. Alcohol is the most commonly consumed alcoholic beverage in everyday life. EtOH is a common abbreviation for ethanol, where "Et" stands for the ethyl group (C2H5). Sugar fermentation to ethanol is one of the earliest organic reactions ever performed by humans; ethanol consumption has also been known for a very long time. This study aims to determine the histology of the liver in Wistar rats (Rattus norvegicus) by orally administering ethanol at a concentration of 50 percent. The method used in this study was an experimental study by looking at the histology of rat liver. Rats were divided into two groups, with seven rats each. Group 1 was given 50% ethanol orally for seven days, and group 2, as a control, was only given orally with distilled water. After seven days, the rats were slaughtered, and their livers were extracted for further histological preparations. In the histology results of group 1, the histological images of the livers of the rats P1, P2, P3, P4, P5, P6, and P7 were abnormal or damaged. In the presence of necrotic cells, oral administration of 50 percent alcohol causes damage to hepatocyte cells, as determined by the study's findings. However, in general, hepatocyte cell damage in the liver produces a score of 1.7, which indicates a change leading to cell damage.

KEYWORDS
Histology of liver, ethanol, Wistar rats, Rattus norvegicus

INTRODUCTION

Ethanol, also known as ethyl alcohol, pure alcohol, and alcohol, is a toxic, volatile, flammable, and colorless liquid. Alcohol is the most commonly consumed alcoholic beverage in everyday life. Ethanol is an isomer of dimethyl ether and a single-chain alcohol with the chemical formula C2H5OH and the empirical formula C2H6O. EtOH is a common abbreviation for ethanol, where "Et" stands for the ethyl group (C2H5) (You & Arteel, 2019).
Alcohols such as beer, wine, and whiskey contain ethanol, which has been used for centuries. Ethanol is a neurotoxic substance that inhibits central nervous system (CNS) activity. In some countries, ethanol abuse is prevalent. 75% of the population in the United States consumes ethanol-containing beverages, and 10% of them cannot be restricted. Approximately 1.5 percent of the population in Indonesia consumes ethanol, with the most recent estimate reaching five million people. Abuse of ethanol increased by an average of 28.9 percent per year in Indonesia. Chronic alcohol consumption can result in morphological, neurophysiological, and biochemical changes to the central nervous system (Basuki & Anggraini, 2016).

Typically, ethanol poisoning is the result of an intentional or accidental overdose, resulting in metabolic acidosis. The majority of ethanol metabolism occurs in the liver. Using ethanol in large quantities or for an extended period of time can cause liver damage. Ethanol-induced liver damage is caused by free radicals, acetaldehyde, and the NAD:NADH ratio. After acidosis develops, the symptoms of acute ethanol toxicity begin with depression of the central nervous system, followed by nausea, vomiting, and headache. If excessive exposure to ethanol can result in coma and death (Suhendra et al., 2019).

The majority of ethanol metabolism occurs in the liver. Due to free radicals, acetaldehyde, and the NAD:NADH ratio, excessive or prolonged consumption of ethanol can result in liver damage. ADH is a systolic enzyme that catalyzes the conversion of alcohol to acetaldehyde, a highly reactive and toxic substance that can cause tissue damage (Ramadhani et al., 2017).

Wistar rats or white rats have several advantageous characteristics as research test animals, including rapid reproduction, a larger size than mice, and ease of large-scale maintenance. Wistar rats or white rats also have morphological characteristics such as albino, small head and longer tail than body, rapid growth, good temperament, high lactation ability, and resistance to thyroxine arsenic (Durachim & Mahmud, 2017).

The largest organ and gland in the human body is the liver. It weighs approximately 1.6 kilograms per adult. A reddish-brown, dense, wedge-shaped connective tissue covers the liver like a sponge. Hepatocyte cells, endothelial cells, macrophage cells or so-called Kupffer cells, and into cells play a role in liver metabolism (fat hoarding cells) (Merdana et al., 2019).

Liver damage due to chemical compounds is characterised by biochemical lesions that provide a series of changes in function and structure. Some changes in the form of the liver are due to chemical compounds that can be seen in microscopic observations, such as inflammation, fibrosis, degeneration, and necrosis. Necrosis is the death of cells or tissues in living organisms. The dead cell nucleus looks smaller, and the chromatin and reticular fibres become more folded. The heart becomes denser, and the cell becomes eosinophilic (karyolysis) (Haines, 2001).

Regarding studies of the effects of ethanol on the livers of Wistar rats (Rattus norvegicus), including research conducted by Nabila & Santoso (2012), The research revealed that methanol and 50% ethanol had a similar, but insignificant effect on liver cells. However, when administered together, methanol and ethanol had a synergistic effect, increasing liver cell damage significantly in comparison to other treatment groups. In addition, a study revealed that the level of liver cell damage in Wistar rats increased with increasing doses of methanol or 50 percent ethanol. When administered at or above 4 mL/kg BW, there was a significant difference in the control group (Desprinita, 2010).
This research was conducted on experimental animals, specifically Wistar rats (Rattus norvegicus), whose internal vital organs are similar to those of humans; ethical considerations were also a factor in conducting this research on Wistar rats (Rattus norvegicus). Given this context, scientists are interested in studying the liver histology of Wistar rats (Rattus norvegicus).

LITERATURE REVIEW

Ethanol

Ethanol, also known as ethyl alcohol, pure alcohol, and alcohol, is a toxic, volatile, flammable, and colorless liquid. Alcohol is the most commonly consumed alcoholic beverage in everyday life. Ethanol is an isomer of dimethyl ether and a single-chain alcohol with the chemical formula C2H5OH and the empirical formula C2H6O. EtOH is a common abbreviation for ethanol, where "Et" stands for the ethyl group (C2H5). Sugar fermentation into ethanol is one of the earliest organic reactions carried out by humans; the consumption of intoxicating ethanol has been known for a very long time (Nabila & Santoso, 2012).

Ethanol poisoning is typically caused by an intentional or unintentional overdose that results in metabolic acidosis; in the liver, ethanol is converted to formaldehyde by the alcohol dehydrogenase enzyme, which then undergoes oxidation catalyzed by the enzyme formaldehyde dehydrogenase to produce formic acid. The formic acid will then be oxidized to carbon dioxide; since this process is slow, formic acid will accumulate in the body and cause metabolic acidosis. Symptoms of acute methanol toxicity include depression of the central nervous system following the development of acidosis, followed by nausea, vomiting, and headaches. Excessive methanol exposure can result in coma and death (Desprinita, 2010).

Ethanol metabolism occurs primarily in the liver; excessive or prolonged consumption of ethanol can cause liver damage. Alcohol-induced liver damage is caused by free radicals, acetaldehyde, or the NAD:NADH ratio. ADH is a systolic enzyme that catalyzes the conversion of alcohol to acetaldehyde, which is a highly reactive and toxic substance that can cause tissue damage. In the liver, the acetaldehyde is oxidized in a reaction catalyzed by NAD-dependent aldehyde dehydrogenase (ALDH) in the mitochondria. This reaction produces acetate, which is then metabolized into carbon dioxide and water. When ethanol is converted to acetaldehyde, hydrogen ions from the alcohol are transferred to the Nicotinamide Adenine Dinucleotide (NAD) factor to form NADH. In the end, alcohol oxidation reduces the amount of substances in the liver, particularly NADH (Ramadhani et al., 2017). The following describes how ethanol enters the body:

a. Absorption

Ethanol can be absorbed into the body via the gastrointestinal tract, skin, and respiratory tract, specifically the lungs, and distributed throughout the body's fluids. The absorption rate of ethanol depends on a number of factors, with the concentration of ethanol and the presence or absence of food in the digestive tract being the most significant. A solution of ethanol is absorbed more slowly than pure ethanol, and the presence of food in the digestive tract, particularly fat and protein, will slow the absorption of methanol. Ethanol is distributed to all tissues and body fluids after absorption, with the exception of adipose tissue and bone.
b. Distribution
   After absorption, ethanol is distributed to all body tissues and fluids with the exception of fat and bone. With a distribution volume of 0.6L/kg, ethanol is widely distributed in body fluids. After exposure, peak blood levels can be reached within 30 to 90 minutes.

c. Metabolism
   When alcohol is consumed in small amounts, alcohol dehydrogenase breaks it down into acetaldehyde in the liver. Nearly 95% of the ethanol in the body is oxidized to acetaldehyde and acetate, while the remaining 5% is excreted through the urine.

d. Excretion
   Ethanol can be eliminated through vomiting and in minute quantities through the breath, sweat, and urine. Slowly, ethanol is eliminated from the body. After excretion, ethanol remains in the body for four days after a single dose. When blood ethanol levels are low, the half-life is between two and three hours. The half-life in mild intoxication is 14 to 20 hours. Nonetheless, if the blood level exceeds 300 mg/dL (severe intoxication), the half-life increases to 27 hours (Wahyu, 2017).

Wistar rat (Rattus norvegicus)

   Wistar rats (Rattus norvegicus) are destructive rodents and agricultural pests. In addition to being a nuisance, these animals pose a threat to human life. As dangerous disease carriers, these animals are capable of transmitting diseases like bubonic plague and leptospirosis. These animals inhabit a burrow in groups. One group can accumulate 200 tails. These rats inhabit coconut plantations, ditches, and meadows in the wild. These rats possess an acute sense of smell (Durachim & Mahmud, 2017). As research test animals, Wistar rats or white rats have several advantageous characteristics, including rapid reproduction, a larger size than mice, and the ability to be maintained in large numbers. Wistar rats or white rats also have albino, small head, and longer tail than body, rapid growth, good temperament, high lactation ability, and resistance to thyroxide arsenic morphological characteristics (Durachim & Mahmud, 2017).

Liver

   The largest organ and gland in the human body is the liver. It weighs approximately 1.6 kilograms per adult. A reddish-brown, dense, wedge-shaped connective tissue covers the liver like a sponge. The Glisson capsule is the layer of connective tissue that covers the liver. The liver resides in the abdominal cavity, which is the region between the chest and pelvis. This organ has three surfaces, the superior, inferior, and posterior surfaces (Kholodenko et al., 2019; Nava et al., 2008; Xu et al., 2020).

   The liver is soft, flexible, and located just below the diaphragm in the upper portion of the abdominal cavity. The majority of the liver resides deep in the right costal arch, and the right hemidiaphragm separates it from the pleura, Pulmo, pericardium, and spleen (Kholodenko et al., 2019). The liver extends to the left until it reaches the left hemidiaphragm and is composed of hepatic lobules. The central vein in each lobule drains into the hepatic vein, and between the lobules is the hepatic canal, which contains branches of the hepatic artery, hepatic portal vein, and a branch of the ductus choledochus (hepatic triad). Arterial and venous blood
flow through sinusoids and into the central vein between liver cells (Susantiningsih et al., 2018). The celiac plexus is composed of sympathetic and parasympathetic nerves that innervate the liver. In addition, an anterior vagal trunk with numerous branches, the hepatic rami, runs directly to the liver (Susantiningsih et al., 2018).

**Histology of the wistar rat liver**

Stroma. At the hilum, where the veins enter, the liver is covered by a thin loop of thickened connective tissue. ports and arteries. The exit of the hepatic ductus dextra et sinistra and lymph vessels from the liver. Along their journey to the portal gaps between the liver lobules, these vessels and ducts are surrounded by connective tissue (Miyai et al., 2019).

Liver lobules. Hepatocytes are composed of interconnected plates of epithelial cells. Hepatocytes, which are functional and structural units of the liver, are composed of thousands of small polyhedral liver lobules (-0.7 x 2 mm) and are composed of hepatocytes. In the center of each lobule is a venue surrounded by 3-6 portal areas. Connective tissue, a venule, an arteriole (a branch of the hepatic artery), and cuboidal epithelial ducts make up the portal zone at the corner of the lobule (Ben-Moshe & Itzkovitz, 2019).

Hepatocytes. Approximately fifty percent of hepatocytes have a large spherical nucleus with two or more nucleoli and are polyploid. The polyploid nucleus is disproportionately large given its polyploid nature. Through the gap of Disse, the surface of each hepatocyte is in contact with the sinusoidal walls and with the surfaces of other hepatocytes. At the site of contact between two hepatocytes, a tubular cleft, the biliary canaliculus, is formed (Ben-Moshe & Itzkovitz, 2019; Lee et al., 2019).

Liver sinusoids. The hepatic sinusoids are dilated and tortuous blood vessels lined by a porous and incomplete basal lamina and an incomplete layer of fenestrated endothelial cells (Endotheliocytus fenestrated). The subendothelial perisinusoidal (Disse) space separates the hepatic sinusoids and hepatocytes, which are located beneath them. This allows nutrients flowing through the sinusoids direct access through the endothelial wall, which is devoid of hepatocytes. On the luminal side of the endothelial cells, the sinusoids also contain macrophages known as Kupffer cells (Macrophagytus stellatus) (Matsumoto et al., 2018).

**METHODS**

The purpose of this experimental study was to determine the liver histology of normal Wistar rats administered 50 percent ethanol at a dose of 2 mL/0.2 kg BW. An experimental method is a study in which experimental activities are conducted to determine the symptoms or side effects of particular treatments.

**Sample preparation**

This study utilized male Wistar rats aged 8-12 weeks and weighing 0.2 kg as its sample population. The research sample consisted of 14 male Wistar rats divided into two groups with different treatments, each containing seven male Wistar rats.

In this study, the liver of Wistar rats (Rattus norvegicus) was used as a sample to determine the liver histology of Wistar rats (Rattus norvegicus) given 50% ethanol at a dose of 2 mL/0.2 kg body weight of rats for seven days. To make histological preparations, the rat liver was harvested surgically and placed in a container...
containing a 10 percent formalin solution that had been labeled according to the group of rats. Additionally, the tissue was cut with a sharp knife to a size of 1.5 cm x 1 cm x 0.5 cm, inserted into a cassette with the aid of tweezers, labeled according to the group, and then resealed. The cassette was then placed in 10 percent formalin for fixation.

Organs that have been stabilized are then subjected to tissue processing. The cassette containing tissue is placed in a formalin buffer containing 10 percent formalin; at this stage, there are two phases: I 10 percent formalin buffer for 30 minutes and II 10 percent formalin buffer for 60 minutes. Then, add alcohol ranging from 70% to 100%, 70% alcohol for 30 minutes, 80% alcohol for 60 minutes, 90% alcohol for 60 minutes, and 100% alcohol for 60 minutes. This is referred to as Dehydration. After dehydration, the cassette was placed in a xylol solution, Xylol I for 30 minutes, Xylol II for 60 minutes, and Xylol III for 60 minutes; this is known as Clearing. While waiting for the clearing process, heat the paraffin to 56°C to 60°C, and then pour it into Paraffin I for 60 minutes and Paraffin II for 12 hours. In this procedure, the cassette is placed in an oven to maintain the paraffin liquid at a temperature between 56 and 60 degrees Celsius (impregnation). Then, pour a small amount of liquid paraffin into the block tool, place the histology in the center, and add paraffin until the tool is full and refrigerated so that the paraffin block becomes solid (Harjana, 2011).

**Histology block cutting**

Place the tissue-containing cold paraffin block on the microtome's paraffin seat. Specify the desired cut thickness, which is typically between 4 and 10 μ. Place the paraffin block against the knife and cut the block consistently and rhythmically until the tissue becomes visible. This is referred to as trimming. After that, continue cutting the blocks consistently and rhythmically to form tissue bands. With the aid of tweezers, carefully remove the tissue-containing bands. The cut results are placed in cold water to facilitate tissue separation. After that, mounting, paraffin tape attachment, and hematoxylin-eosin staining procedures are performed (Harjana, 2011).

**RESULTS**

In August, 14 male Wistar rats were divided into two groups, each containing seven male Wistar rats, for the purpose of collecting research data. On the 8th day, ethanol was administered to groups P1, P2, P3, P4, P5, P6, and P7 and equates were administered to groups K1, K2, K3, K4, K5, P6, and K7 for 1 week. On the 16th day, surgery was performed to remove liver tissue, which was then processed into tissue preparations. The image that follows is a histological representation of the liver of Wistar rats.

| Group | Image | Description |
|-------|-------|-------------|
| Control 1 | In the image, the cells are generally healthy, with chromatin granules and pink cytoplasm visible in the nucleus (black arrow). Nevertheless, a few cells undergo karyolysis, a form of cell death in which the cell loses its nucleus (red arrow). |
| Control 2 | In the image, the cells are generally healthy, with chromatin granules and pink cytoplasm visible in the nucleus (black arrow). However, a few cells undergo parenchymal degeneration (green arrows) and karyolysis, a form of cell death in which the cells lose their nucleus (red arrow). |
| Control 3 | There are normal cells (blue arrow) in the adjacent image, but many cells have hydrophilic degeneration (blue arrow) and few cells are necrotic (black arrow). |
| Control 4 | In the image, the cells are generally healthy, with chromatin granules and pink cytoplasm visible in the nucleus (black arrow). A few cells, however, undergo adaptation in the form of hydrophilic degeneration (blue arrows) and death in the form of karyolysis, in which the cells lose their nucleus (red arrow). |
| Control 5 | There are normal cells (black arrow) in the image, but there are also cells experiencing parenchymal degeneration (green arrow) and necrotic cells (red arrow). |
| Control 6 | In the image, the cells are generally healthy, with chromatin granules and pink cytoplasm visible in the nucleus (black arrow). Nevertheless, a few cells undergo karyolysis, a form of cell death in which the cell loses its nucleus (red arrow). |
Control 7

Cells undergoing necrosis (red arrows) and some cells undergoing hydropic degeneration (blue arrows) indicate severely damaged cells in the image (blue arrow). Nonetheless, there are some healthy cells (black arrow).

Treatment 1

In the image, the cells are generally healthy, with chromatin granules and pink cytoplasm visible in the nucleus (black arrow). Nevertheless, a few cells undergo karyolysis, a form of cell death in which the cell loses its nucleus (red arrow).

Treatment 2

There are normal cells (blue arrow) in the image, but many cells have hydrophilic degeneration and some cells are necrotic (black arrow).

Treatment 3

There are normal cells (blue arrow) in the image, as well as cells undergoing hydrophilic degeneration (blue arrow) and necrotic cells (black arrow).

Treatment 4

In the image, the cells are generally healthy, with chromatin granules and pink cytoplasm visible in the nucleus (black arrow). Nevertheless, a few cells undergo karyolysis, a form of cell death in which the cell loses its nucleus (red arrow).

Treatment 5

In the image, the cells are generally healthy, with chromatin granules and pink cytoplasm visible in the nucleus (black arrow). Nevertheless, a few cells undergo karyolysis, a form of cell death in which the cell loses its nucleus (red arrow).
Treatment 6

Normal-appearing cells (black arrow) are depicted in the image, but many cells are dying or necrotizing (red arrows).

Treatment 7

There are normal cells (black arrows) in the image, as well as cells undergoing hydrophilic degeneration (blue arrow) and death/necrosis (red arrow).

In each field of view, twenty normal cells, parenchymal degeneration, hydrophilic degeneration, and necrosis were isolated and counted.

| Group | Mean | Score |
|-------|------|-------|
| K1    | 1.09 | 1     |
| K2    | 1.07 | 1     |
| K3    | 1.18 | 1     |
| K4    | 1.11 | 1     |
| K5    | 1.09 | 1     |
| K6    | 1.09 | 1     |
| K7    | 1.16 | 1     |
| P1    | 1.74 | 2     |
| P2    | 2.24 | 2     |
| P3    | 1.18 | 2     |
| P4    | 1.65 | 2     |
| P5    | 2.52 | 2     |
| P6    | 1.21 | 2     |
| P7    | 1.64 | 2     |

DISCUSSION

The subjects of this study were Wistar rats. The rats used were male Wistar rats aged 8 to 12 weeks and weighing 0.2 to 2.5 kg BW. White Wistar rats are commonly used in toxicology studies, fat metabolism, drug testing, and the study of infectious disease mechanisms. White Wistar rats are suitable for use in research because they are simple to maintain and breed, allowing researchers to quickly obtain uniform experimental animals and because they are straightforward to manage in the laboratory. In addition, Wistar rats are typically
calm, easy to handle, not photophobic, and unaffected by human presence. Prior to being used in research, rats were acclimatized for one week to allow them to adapt to their environment.

In this study, fourteen Wistar rats were divided into two groups, each containing seven rats. The control group received only aquadest, while the treatment group received 2 mL/kg BW/day of 50 percent ethanol. During the test, the control group was treated to determine the liver histology of normal rats, while the treatment group was required to demonstrate the differences between normal and abnormal rats. On the eighth day, ethanol was administered to groups P1, P2, P3, P4, P5, P6, and P7, while distilled water was administered to groups K1, K2, K3, K4, K5, P6, and K7 for one week. On the sixteenth day, liver tissue was removed from Wistar rats and processed into tissue preparations. In accordance with the outcomes of histological examinations, the ethanol-induced deterioration of the liver tissue of rats varies. Because ethanol is volatile, flammable, colorless, and toxic, administering it continuously to rats every day will result in ethanol-induced liver damage. Because the liver is neutralizing toxins in the blood, a histological examination of the Wistar rats’ liver revealed that the Wistar rats’ livers were damaged.

In the K1 group’s results, generally normal cells with visible chromatin granules and pink cytoplasm were observed (normal cells). Nevertheless, a few cells undergo karyolysis, a form of cell death in which the cells lack a nucleus (there is damage to body tissues). In the K2 group, normal cells with visible chromatin granules and pink cytoplasm were generally observed (normal cells). However, a few cells undergo parenchymal degeneration (abnormal cells) and karyolysis, a form of cell death in which the cells lack a nucleus (there is damage to body tissues). There were normal cells in the K3 group, but many cells exhibited hydropic degeneration (level of damage) and a few cells were necrotic (death). In the K4 group, normal cells with visible chromatin granules and pink cytoplasm were typically observed (normal cells). A few cells, however, undergo adaptation in the form of hydropic degeneration (level of damage) and death in the form of karyolysis, in which the cell loses its nucleus (damage to body tissues).

In the K5 group, there were cells that tended to be normal (normal cells), but also cells with parenchymal degeneration and necrotic cells (death). In the K6 group, normal-appearing cells with visible chromatin granules and pink cytoplasm were observed (normal cells). Nevertheless, a few cells undergo karyolysis, a form of cell death in which the cells lack a nucleus (there is damage to body tissues). In the K7 group, cells tended to be severely damaged, as indicated by necrosis (cell death) and hydropic degeneration in certain cells (level of damage). There are however some normal cells.

In contrast, the P1 group contained predominantly normal cells with visible chromatin granules in the nucleus and pink cytoplasm (normal cells). A few cells, however, undergo karyolysis, a form of cell death in which the cells lack a nucleus (there is damage to body tissues). There were normal cells in the P2 group, but many cells had hydrophilic degeneration (level of damage) and some cells were necrotic (death). In the P3 group, there were normal cells as well as cells with hydropic degeneration (a measure of damage) and necrotic cells (death). In the P4 group, the majority of the cells exhibited normal characteristics, including chromatin granules and pink cytoplasm.

In the P5 group, the cells were generally normal, with chromatin granules and pink cytoplasm visible in the nucleus. Nevertheless, a few cells undergo karyolysis, a form of cell death in which the cells lack a
nucleus (there is damage to body tissues). In the P6 group, there were cells that tended to be normal, but a significant number of cells underwent necrosis/death (death). In the P7 group, there were generally normal cells, but there were also cells with hydrophilic degeneration (level of damage) and death/necrosis. In the presence of necrotic cells, it can be concluded that oral administration of 50 percent alcohol damages hepatocyte cells.

In each field of view, 20 cells were extracted, after which the number of normal cells, the number of parenchymal degeneration, the number of hydrophilic degeneration, and the number of necrotic cells were calculated and divided by 20 to yield a score (the value of the degree of damage). A normal score of 1 is followed by scores of 2 for parenchymal degeneration, 3 for hydrophilic degeneration, and 4 for necrosis. The control group received a score of 1, indicating normal cell structure, whereas the treatment group received a score of 2, indicating the loss of normal cell structure.

In the descriptive table, the control group’s score is 1.11 with a standard deviation of 0.04, whereas the treatment group’s score is 1.74 with a standard deviation of 0.49. Then, the normality test for the control and treatment groups revealed a value greater than 0.05, indicating that the group data is homogeneous (there is a change), allowing the T-test to be conducted.

CONCLUSION

In the presence of necrotic cells, oral administration of 50 percent alcohol can cause damage to hepatocyte cells, according to the findings of the study. However, the average score for hepatocyte cell damage in the liver is 1.7, indicating that there is a change leading to cell damage.

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