Of Mice and Men follows the lives of George Milton and Lennie Small over three days. On the first day, the two men sit by the Salinas River in California, resting on their journey to a ranch where they’ve found work. Lennie is large and strong but has a mental disability and relies on George’s assistance to function well in society. At the riverside, George sees that Lennie has been keeping a dead mouse in his pocket. George throws the mouse away, but Lennie later tries to retrieve it because he loves stroking its soft fur. Lennie begins to cry over the mouse, and George tries to console him. In his frustration, George complains about having to care for Lennie. When Lennie offers to leave him, however, George refuses and tells Lennie that they have to stick together. George and Lennie discuss their dream of owning a piece of land. Before going to sleep, George tells Lennie to memorize the location of the riverbank. He tells Lennie to return to that spot if he runs into any trouble while working on the ranch.

When George and Lennie arrive at the ranch, they are taken to the ranch hand’s bunkhouse. They meet Candy, an aging, one-handed menial laborer—called an “old swamper”—who keeps the bunkhouse clean. The ranch’s boss enters and admonishes George and Lennie for being late. George does all the talking for Lennie, which makes the boss suspicious. Upon hearing Lennie speak, the boss sees that Lennie has a mental disability and assumes that George is taking advantage of Lennie. George lies to the boss, telling him that Lennie is his cousin and that he was kicked in the head by a horse as young boy. This story quells the boss’s suspicion, although George realizes that the boss will be watching them from now on.

Shortly afterwards, the boss’s son, Curley, comes into the bunkhouse. When he sees Lennie, Curley immediately tries to pick a fight with him. After Curley leaves, Candy explains to George and Lennie that Curley is a boxer and is intimidated by men larger than him. George warns Lennie against getting involved with Curley. They then meet Curley’s wife, who arrives while looking for Curley. George immediately dislikes her and sees her as troublesome, whereas Lennie finds her pretty. George warns Lennie to stay away from Curley’s wife. Slim, the wise and patriarchal ranch hand, comes in and speaks with George. He proves to be much kinder than the boss or Curley. They speak about the new puppies that have been born on the ranch, and George arranges for Lennie to get a puppy.

Later on, George talks to Slim about Lennie. George tells Slim that he and Lennie grew up in the same town together and that after Lennie’s aunt died, George took him in and cared for him. George admits he used to play tricks on Lennie but stopped after seeing that Lennie would do anything he asked. George claims Lennie is simple and doesn’t mean any harm. Lennie then comes into the bunkhouse where the men are talking. George sees that Lennie is holding one of the new puppies. He tells Lennie to put it back with its mother or it will die. Lennie complies, and Slim notes that Lennie is an essentially good but childlike person.

George and Lennie then meet Crooks, the African American stable hand. Crooks calls Slim away, leaving George and Lennie in the bunkhouse. Candy comes into the bunkhouse with his very old and smelly dog. One of the ranch hands, Carlson, complains about the dog and asks to shoot it to put it out of its misery. Candy doesn’t want to do it, but he allows Carlson to.

Curley then comes in, angrily looking for his wife. He thinks Slim has been flirting with his wife and wants to fight him. The other men follow Curley, leaving George, Lennie, and Candy in the bunkhouse. George and Lennie discuss their dream again. Candy overhears and offers to contribute all his savings to help purchase the land if he can live with them. George and Lennie agree, and the three men feel confident about achieving their dream. Slim returns, followed by Curley, who failed to convince Slim to fight. Curley then aggravates Lennie, who lets Curley hurt him until George tells Lennie to fight back. Lennie then accidentally crushes Curley’s hand. Lennie feels sad about hurting Curley, and says that he never wanted to hurt anyone.

George, Slim, and the other ranch hands travel to town to visit a brothel. Lennie, Crooks, Candy, and Curley’s wife are the only ones left on the ranch, being uninvited or unable to go. Lennie visits Crooks, who speaks to Lennie about his isolation as an African American man and his lifelong experiences of overt racism. Candy joins the two and tells Crooks about the dream to own a piece of land with Lennie and George. Crooks asks if he can join and help them work the land. Then, Curley’s wife comes in and provokes Candy and Crooks. When Crooks tries to tell Curley’s wife to leave his bunkhouse, Curley’s wife threatens Crooks. Curley’s wife leaves, and Crooks claims he was joking about joining Candy, George, and Lennie in their dream for a piece of land.

The next day, Lennie accidentally kills his puppy in the barn. Lennie hides it, unsure of what to do and afraid of getting in trouble. Curley’s wife comes in and sits next to Lennie. Lennie at first refuses to talk with her, but she reassures him. Curley’s wife tells Lennie about her disappointment with Curley, her isolation on the ranch, and her dream of becoming an actress. Lennie then shares his fears over having killed the puppy, his desire to own rabbits, and his penchant for petting soft things. Curley’s wife then offers to let Lennie pet her hair. When he pets her too hard, she panics, which makes Lennie latch onto her more firmly. When Curley’s wife tries to scream, Lennie shakes her and accidentally breaks her neck. Lennie flees to the riverbank where George told him to hide in the novella’s opening scene.

Candy finds Curley’s wife’s body and calls for George. When George sees her body, he realizes what happened. He and Candy both know that Curley and the other men will want to lynch Lennie for killing Curley’s wife. George knows where Lennie has gone and takes Carlson’s gun. He runs ahead of the other men to find Lennie first. George finds Lennie at the riverside. At first he tries to scold Lennie, because Lennie asks to be punished for accidentally killing Curley’s wife. When George hears the men approaching from behind him, he asks Lennie to look out across the river. George describes their dream of owning a piece of land and starting a farm. Lennie listens with joy. George then takes Carlson’s gun and aims it at the back of Lennie’s head. George shoots Lennie before the other men can arrive and hurt him. Slim consoles George, understanding what happened and why George killed Lennie. George lies to the other men, telling them that he had to take the gun from Lennie and shoot him out of self-defense. The novella ends as Slim reassures George that he did the right thing. The two men walk away together, leaving Lennie’s body with Curley and another ranch hand.