7-1929

On the Nature and Cause of "The Walking Disease" of Northwestern Nebraska (Necrobiosis et cirrhosis hepatis enzootica)

L. Van Es
L. R. Cantwell
H. M. Martin
J. Kramer

Follow this and additional works at: http://digitalcommons.unl.edu/ardhistrb

Part of the Agriculture Commons, Large or Food Animal and Equine Medicine Commons, Other Animal Sciences Commons, and the Veterinary Pathology and Pathobiology Commons

Van Es, L.; Cantwell, L. R.; Martin, H. M.; and Kramer, J., "On the Nature and Cause of "The Walking Disease" of Northwestern Nebraska (Necrobiosis et cirrhosis hepatis enzootica)" (1929). Historical Research Bulletins of the Nebraska Agricultural Experiment Station (1913-1993). 244.
http://digitalcommons.unl.edu/ardhistrb/244

This Article is brought to you for free and open access by the Agricultural Research Division of IANR at DigitalCommons@University of Nebraska - Lincoln. It has been accepted for inclusion in Historical Research Bulletins of the Nebraska Agricultural Experiment Station (1913-1993) by an authorized administrator of DigitalCommons@University of Nebraska - Lincoln.
On the Nature and Cause of "The Walking Disease" of Northwestern Nebraska
(Necrobiosis et cirrhosis hepatis enzootica)

BY L. VAN ES, L. R. CANTWELL, H. M. MARTIN, AND J. KRAMER
Department of Animal Pathology and Hygiene

LINCOLN, NEBRASKA
JULY, 1929
On the Nature and Cause of "The Walking Disease" of Northwestern Nebraska
(Necrobiosis et cirrhosis hepatis enzootica)

BY L. VAN ES, L. R. CANTWELL, H. M. MARTIN, AND J. KRAMER
Department of Animal Pathology and Hygiene

LINCOLN, NEBRASKA
JULY, 1929
On the Nature and Cause of “The Walking Disease”
of Northwestern Nebraska
(Necrobiosis et cirrhosis hepatis enzootica)
BY L. VAN ES, L. R. CANTWELL, H. M. MARTIN, AND J. KRAMER

The investigation pertaining to “the walking disease of horses” prevalent in certain parts of northwestern Nebraska was undertaken at the request of the State Department of Agriculture and with its active co-operation.

In the course of the ten or twelve years which preceded the initial survey with which this investigation began (1925), farmers and ranchers of the affected region had frequently complained about a fatal disease which carried off their horses. When this disease was first observed has not been definitely ascertained. It is probable that it did not become economically important until after 1912, according to its story as told by the people who sustained the greater part of the losses. A few of the older settlers have reported observations of the disorder occurring sporadically since 1905 or even before, but it was not until a more recent period that the malady began to assume something like a formidable aspect.

The losses occasioned by the disease on certain farms or ranches were nothing short of ruinous. One owner who maintained 25 horses on the average lost 35 animals within ten years. Another one reported approximately 100 deaths within twelve years of which not less than 28 took place in 1924. A summary of the losses sustained by 20 ranchers shows that they have lost not less than 300 horses during the last few years. Another group of 33 owners lost 501 horses between 1917 and 1926 on account of the disease. Not many ranchers in the affected portion of Sioux County have entirely escaped horse losses during the years in which the disease became prevalent.

Losses among cattle were also reported altho there was no certainty that they had died from the same disorder until later in the course of the investigation the fact could be definitely established. The cattle losses are apparently not nearly so great as those in which horses are involved.

Altho some losses among mules were reported, there prevails a general opinion among the ranchers that these animals rarely, if ever, become affected with “the walking disease.”

“The walking disease” is regional in its distribution. In Nebraska the principal focus of the disorder is to be found

1 Representing the State Department of Agriculture.
in Sioux County with the exception of the northern one-fifth of its area. From there it extends for some distance into the counties of Dawes and Box Butte. The disease was also found to occur in more or less restricted areas in the counties of Scotts Bluff, Banner, Sheridan, and Hooker, while some evidence was revealed which tended to show that it may also have been recognized, as isolated outbreaks, in Cherry and McPherson counties. The disorder is known to occur also in parts of Wyoming and Colorado adjacent to Nebraska.

The area principally concerned with the disease occupies a more or less eroded table land with a topography varying from sharply rolling to gently undulating and characterized by soils of sandy loam texture with good drainage. The region has an elevation of from 4,000 to 5,000 feet. Its climate is characterized by relatively low rainfall (17 inches), wide temperature variations, and free wind movements. About half of the total rainfall takes place in May, June, and July. In the year of lowest precipitation (1897), 6.15 inches fell during the growing season, the total for the year being 10.40 inches. The wettest recorded year was 1892 with 32.34 inches of precipitation of which 24.70 inches fell during the growing season.

The district lies within the short grass country more or less extensively devoted to livestock grazing. Most of the ranches have an area of from 1,000 to 2,000 acres and
apparently all the livestock is being maintained in a good state of nutrition. Some of the pastures show evidence of being overgrazed, while others are manifestly understocked.

Among the plants growing in this region species of grasses and sedges predominate. These occupy the greater part of the surface, leaving the remainder to other species. The latter, with their succeeding waves of colorful bloom, lend a peculiar charm to this prairie country. Plants appear, bloom, mature, and disappear, to be replaced by successors, each species contributing its own tint and glow to the color scheme of the landscape.

Of the genera which include species known or suspected of being poisonous the area involved shows: Astragalus, Oxytropis, Cicuta, Lathyrus, Lupinus, Senecio, and Zygadenus.

Epizootologic inquiry revealed that the incidence of the disease is, to a most marked degree, subject to a seasonal influence. While cases occur throughout the year, most of the losses fall in June and July, with June at the peak of the curve.

Whether or not the factor of age plays a part in morbidity is difficult to say. For so far as the field survey disclosed

---

FIG. 2. The seasonal incidence of the disease
any evidence bearing on this point, it appears that nearly all the affected horses were mature and broken to work.

Reports from horse owners on the relation of rainfall to the incidence of the disease are quite contradictory. Some ranchers observed no difference between the incidence of the disease during dry years and during wet years while others report more losses during wet years and others again are of the opinion that drouth increases the morbidity rate.

If it could be proved that the disease under investigation is due to poisoning by plants it would be reasonable to suppose that an abundance of forage plants would have a dominant influence on the incidence of the disorder. To a marked degree the abundance of vegetation would be determined by the rainfall and the latter may thus become an influence affecting the morbidity rate. As there are no records of all losses during a series of years and as many factors, other than rainfall, may also exercise an influence, it was difficult to establish, with any degree of precision, a definite relation between morbidity and precipitation.

One observation having a possible bearing on this phase of the problem may have significance. During the seasons of 1926 and 1927 the field investigators were in part occupied with a clinical study of the field cases, with their gross pathology, and with the collection of materials for histologic examination. Cases were abundant in 1926 while during 1927 there was a marked reduction in the incidence of the disorder. These facts may acquire some significance when it is found that during the months of April, May, and June the rainfall recorded by the Weather Bureau stations of the region averaged 3.21 inches for 1926 and 7.96 inches for 1927. However, in the absence of a census of all cases of the disease during the years involved, such an observation may lose much of its validity.

It is probable that in most of the cases of "the walking disease" the pathologic damage peculiar to the disorder has already reached a more or less advanced phase before definite signs of illness commence to make their appearance.

A sick animal at pasture may attract attention by separating itself from its mates. It is found to be sluggish and drowsy and there is evidence of depression and impaired sensibility. Affected horses confined in corrals or stables often become conspicuous by stamping with their hind feet. This frequently is one of the earliest symptoms.

The body temperature as well as the respiratory frequency and the pulse rate are usually normal. The temperature rarely
exceeds 101° F. In only a few cases have higher temperatures been observed, but these cannot be regarded as typical of the disorder.

One of the earlier objective symptoms of the disease is frequent and persistent yawning and there is an inclination on the part of the affected animals to chew at mangers and fences. This habit and the manner in which the affected animals push themselves against all sorts of objects are probably accountable for the fact that so many cases show erosions of the lips. Even broken incisors which have been observed could be attributed to the same tendency.

Commonly the appetite is materially reduced even quite early in the course of the disease. In some cases it is perverted and the animals chew at earth, manure, and other substances. The ones that still have a desire to eat often prefer the dry, coarser kinds of forage. In one of the cases observed, an extraordinary desire for water was recorded.

The clinical picture may include slight abdominal pain, and a few of the affected animals show diarrhea. Ordinarily the
feces are normal in character aside from the few cases in which they are lighter in color and in which they may have become covered by inspissated mucus.

In the more advanced cases there is a marked general depression, sensibility is reduced, and evidence of cerebral disturbance is not lacking. The animals involved have a staggering or swaying gait, their fetlock joints knuckle over, and they may brace themselves with their legs apart in order to maintain a standing posture.

Affected horses are inclined to push their heads against a wall or a fence, to walk either in a circle or in a straight line without any sense of direction or intent; hence the name "walking disease." Such animals often become mired in a bog or entangled in a barbed wire fence, or they kill themselves by falling over the rim of a canyon. Many cases become delirious before they die, walk thru several wire fences, and succumb in the manner indicated. Such horses are commonly emaciated and extremely weak. Their heads are often bruised and lacerated. Sweating may be marked, and in some of the cases observed in the field there was a marked jugular pulse. A slight icterus of the visible mucosae
is not a rare symptom and in a conspicuous number of cases laryngeal stenosis (roaring) was observed.

By far the greater number of the cases which showed evidence of the disease succumbed to it sooner or later. The periods elapsing between the appearance of the first symptoms and the moment of death vary greatly in length. They range between a few days and several months. In the majority of the cases the ascertainable course of the disorder does not exceed a period of four weeks in duration. There are exceptions to such a course. Some cases may even recover and others may linger for a year or more. Cases of this type are relatively rare while rapidly developing ones are far more frequent.

There was less opportunity to observe the disease in cattle, and all accounts of the disorder in this type of livestock could not be adequately checked up. So far as this was possible it appears that nervous excitement and even frenzy were the most conspicuous signs of the disturbance until the terminal debility and emaciation ushered in a period of quiet. During the course of the malady muscular tremors and spastic contractions of the legs were observed. The duration of the disease is apparently somewhat shorter than in the case of horses similarly afflicted.
Most of the 35 autopsies performed in the field pertained to cases that were killed while in the more advanced stages of the disease. The larger number of the animals concerned were in poor, if not emaciated, condition, and many showed the eroded lips and lacerations and bruises about the head which have already been described.

A yellow color of the visible mucous membranes and of the subcutaneous connective tissues and fasciae, either very slight or quite pronounced, was seen in many of the cases but by no means in all of them. The abdominal fat was also noted to have a yellow color in a number of the animals examined. It was also seen in the peritoneum and the omentum. In a few cases the abdominal fluid was increased and this also showed a tint from yellow to orange. Marked ascites was, however, not a common feature in the field cases examined after death. In two cases the perirenal tissues were infiltrated with fluid of a deep yellow or orange color.

A striking phenomenon in many cases is the greatly dilated stomach. One is tempted to believe that in a considerable number of cases there comes about a paresis of the gastric

**FIG. 6. Stomach of Horse No. 8994. Killed July 13, 1926**
musculature long before there is a complete cessation of the food intake. The constant forcing into the stomach of food which can not be evacuated into the duodenum causes the organ to become distended or even ruptured. Rupture of the stomach was encountered in a number of cases, while the intramural hemorrhages may be an indication of vascular injury as a sequel to the stretching of the parts.

Only in a very small number of the cases did the stomach show lesions of a histologic nature. These consisted of glandular atrophy, hyperemia, and in one instance the secreting parenchyma was involved in necrobiotic changes.

Very marked changes in the intestines were not often seen. The mucosa of duodenum and jejunum may have been hyperemic or even edematous in some cases, but these changes were often so slight that one hesitates to regard them as distinctly pathological. In a few of the animals examined, there were subserous petechiae of the intestinal wall and in at least one case, hemorrhagic areas close to or involving the patches of Peyer were encountered. Small hemorrhages were also seen in the mucosa of the colon, but such phenomena were quite uncommon in the material studied.

The mesenteric lymphnodes were occasionally found to be edematous and in one instance the portal lymphnodes were hemorrhagic. It does not appear that the disease leaves any pathognomonic impress on the lymphatic system.

The spleen does not seem to be specifically involved. In some cases this organ was firmer than normally, in others the color was conspicuously dark, and once or twice the spleen was found to be enlarged.

Microscopically examined, the spleens showed nothing of a pathologic nature that could in any way be connected with the disease under consideration. Some spleens were somewhat hyperemic. In others there was only a minimum degree of pigmentation and spleens were seen in which a maximum could be recorded. These conditions varied in a degree observable in a similar number of spleens of apparently normal horses.

In all of the cases examined the liver was found to be the organ most constantly and severely involved and in a large majority of animals examined it was the only organ which showed manifest pathologic changes.

The gross morphologic aspects of the organ were not markedly changed. In most instances the weight of the livers varied but little from what could be regarded as the normal average and in a small number of animals there was a slight reduction in size. The liver edges were not rounded and in the larger number of the cases the surfaces had retained their
Fig. 7. Liver of field case of "walking disease" in the horse
FIG. 8. Liver of horse affected with "walking disease"
normal, smooth aspect. In a small number only were the sur-
faces of the liver changed by the retraction of its connective
tissue elements, but in no case was anything like the “hob-
nailed” cirrhosis of the human liver encountered. In one
case only was there a slight approach to this condition and in
this the liver surface was but coarsely nodular.

The color of the affected livers is but rarely normal. Their
tints range between a pale brownish cast and a grayish brown
or a bluish gray. In most of the livers seen there was an ele-
ment of blue present and in some cases this helped to give
the organ a greenish tint. Nearly always is the liver colora-
tion a mottled one, dark and light areas irregularly alternating
so as to bring about a “nutmeg” effect.

The liver of many but not of all the affected horses is
firmer than normally. Upon being sectioned, such organs re-
sist the knife, and the cut surface also presents a mottled
appearance. Small hemorrhages scattered throughout the organs
are a common phenomenon, and but few of the affected livers
are free from them. Subserous petechiae are also seen.

The histologic appearance of the liver, much more than its
gross aspect, shows how deeply this organ is involved in dam-
age and even destruction. There are, however, marked varia-
tions in the degree and intensity to which this organ may
have been assaulted by the etiologic factor.

In most of the cases the chief lesions are parenchymatous,
but in others, few in number, the parenchyma is relatively
intact, while the connective tissue elements of the organ are
actively proliferating, frequently with a certain degree of
cirrhosis as their termination. Between these two extremes
one may find any imaginable combinations of necrobiotic dam-
age and reparative tissue response. For so far as can be
determined from the material collected in the affected areas,
the damage done to the parenchyma is initial and dominates
the further progress of the pathologic process. The degree
of the intensity of action by the causative factor, per se, is a
determining factor in lesion production, while the elements
of time, season, and environment may also constitute con-
tributing influences.

In many of the “walking disease” cases the assault on the
parenchyma must have been sudden and overwhelming. The
sections show that the intralobular arrangement of the liver
cells may have become entirely upset and all orderly place-
ments of liver cells have made way for a haphazard cell
grouping, in which compressed, deformed, damaged, and
dying cells lie side by side with the enormously enlarged ones
which appear to indicate an effort of compensatory hyper-
trophy.
All stages of necrobiosis are seen in the sections. Pycnosis, karyorrhexis, and karyolysis are apparent with varying degrees of frequency and intensity in all the sections. Yet cases were met in which the changes were more necrotic than necrobiotic. These changes impress the observer as being incidental to a sudden cell death. The nuclei of such cells are still intact, but are only faintly stained, and the cell protoplasm is finely granular and commonly there are bile deposits.

The damaged parenchyma often reacts with reparative attempts, and gigantic hypertrophic cells are encountered in the sections. In many of such enlarged cells the nuclei are perfectly intact and their granular substances stain rather deeply. These cells, however, are by no means exempt from injury and they also may show evidence of necrobiosis and ultimate deterioration. The enlarged cells commonly occur in groups and are conspicuous by their large nuclei and a rather hyaline or finely granular protoplasm.

Occasionally, groups of smaller, deeply stained cells are seen and they also may represent a compensatory reaction. They constitute a numerical hypertrophy, but this is not nearly so frequently observed as the enlarged cells already mentioned. The latter tend to emphasize, furthermore, the marked differences in cell sizes which are such a characteristic feature in liver materials derived from "walking disease" cases.

The aspect of the more gravely affected liver suggests a sudden whirlwind attack upon the cell community, leaving havoc in its trail, but followed by a prompt, altho usually ineffective, attempt on the part of the surviving cells to preserve the continuation of the hepatic functions. It is probable that the cellular hypertrophy is the first reaction after the damage has been inflicted.

There is an abundance of evidence that connective tissue proliferation begins early in the morbid process and that it continues with more or less intensity thruout the entire duration of the disease. In the majority of the cases it takes the form of a diffused intralobular fibrosis. The periportal connective tissue likewise is apt to proliferate, but in the material examined the increase of the delicate reticular tissue within the lobules is one of the more characteristic pathologic conditions.

The dominant characteristics of the morbid process are the necrobiosis of the parenchyma and the proliferation of the connective tissue elements. These determine the appearance of the affected livers. One or the other may predominate, but our own observations tend to indicate that they develop
simultaneously with parenchymatous intoxication as the initial factor. In the cases which occur later in the season or which have survived for several months, the interstitial lesions are the more prominent.

In many of the sections one frequently observes areas of disintegrated liver cells surrounded by young fibrillar connective tissue, or small islands of rather intact hepatic cells are found in the midst of wide patches of a denser, older, connective tissue. Leucocyte infiltration is not infrequently seen, but only very rarely is it a prominent feature. In some of the cases the proliferation of bile duct epithelium was quite marked, but in the majority of the specimens examined this phenomenon was not encountered.

In one case the liver showed what appeared as an arrested cirrhosis. The animal had apparently recovered from a previous attack of the disease and a conspicuous cirrhosis was all that remained of the initial disturbance.

In a large number of the affected livers if not in nearly all, there were conspicuous hemorrhages within the lobules or rather in what there was left of the latter.

The protoplasm of the hepatic cells is commonly granular, and pigment deposits (bile) within the cell substance is a frequent phenomenon in many of the specimens examined. Fat droplets are occasionally encountered in the broken-down cells.

The kidneys more rarely present a damaged appearance and even in these it is not always apparent that the lesions found can be identified with the disorder under consideration. In a preponderating number of the cases the urinary apparatus showed no pathologic changes. In a few cases the kidneys were congested and in one the organ had a parboiled appearance and was later found to be involved in a more or less marked parenchymatous degeneration. The microscopic examination of the kidneys revealed a minimum degree of damage, or none at all, in most of the specimens examined. Only in a few kidneys were degenerative changes of the parenchyma observed. These may include the glomeruli as well as the secreting tubules. Occasionally a periglomerular leucocyte accumulation may also be seen in other parts of the cortex. In the kidneys of a small number of the “walking disease” cases these organs were hyperemic, and even capillary hemorrhages may be observed in these.

The respiratory organs were nearly always normal. In a number of the cases the pulmonary surfaces showed small hemorrhagic areas, but the organs were always functionally intact.
The heart also showed but few changes and these consisted of subendocardial and subepicardial small hemorrhages, and on one occasion the pericardial sac was found to contain a markedly abnormal amount of deep yellow fluid. Only in one case was a slightly hypertrophic heart encountered. The hearts of a number of affected horses were examined histologically. Only in a small number could changes of a pathologic nature be discovered. In these the muscle fibers of certain areas or bundles were quite granular in appearance and their nuclei had failed to become stained. In others the disintegration had advanced to a more pronounced degree, but in all instances these changes pertained to certain bundles of fibers only and did not affect the entire myocardium.

In only a small number of the cases were the central nervous organs examined, and so far as their gross appearance may indicate they were normal throughout.

The examination of the bone marrow of a number of affected horses revealed nothing which could be interpreted as damage or as change associated with the disease.

Only two bovine animals affected with the disease could be examined by autopsy. In these also the livers appeared to have borne the brunt of the assault. In both, the organ was harder and denser than it is normally. In one the color was rather pale and in the other it was a light, reddish brown. The abdominal viscera showed more or less extensive hemorrhages and many petechiae. The kidneys and spleens were normal. The histologic character of the livers of the bovine cases was quite similar to that observed in those of the horses affected with the "walking disease."

Liver diseases involving the parenchyma in necrobiotic changes and the connective tissue elements in proliferation are by no means uncommon among the domestic animals. Apparently they are associated with intoxications of an infinite variety and with damage due to purulent infections or to gross parasites which either find in the liver their natural abode or appear there while in transit in the course of their normal migrations.

Among the intoxicants capable of injuring the liver cells and of setting into motion certain reparative processes, spoiled or fermenting foods, toxic substances arising during various infections, poisonous plants, phosphorus, arsenic, and others may be mentioned. Most of the liver disorders of a toxic origin among farm animals are sporadic in their occurrence, but in several instances their enzootic character early attracted attention and has been quite definitely established.
The epizootological, clinical, and patho-anatomical evidence presented by the disease under investigation indicates that in a marked degree it resembles the enzootic liver diseases of other parts of the world. It is of some historic interest to note that a disease called "bottom disease" was once prevalent in certain parts of the Missouri valley, and that in this disorder the liver also was particularly involved. The disease was described by Schroeder (69) and Smith (70) in 1893 and 1897 and was again mentioned in a public document (77) in 1908.

More recently Kalkus, Trippeer, and Fuller (39) gave an account of a disease occurring in a number of districts of the Pacific Northwest. This is also designated as "the walking disease" and in all particulars closely resembles the disorder concerned in this discussion.

It is not possible to say when liver diseases of enzootic character commenced to attract attention. It is not improbable that a disease mentioned by White (81, 82, 83) during the early part of the nineteenth century under the name of "stomach staggers" may have been one belonging to this group. At least there is a striking similarity between the symptoms described by this author and those observed in the more modern cases. The stomach impactions mentioned by him are not lacking in significance when their frequent occurrence in the cases of today are taken into consideration. However, in as much as White failed to examine or describe the condition of the liver it would perhaps be quite futile to draw conclusions.

The earliest accurate descriptions of an enzootic liver disease of the horse pertain to one occurring in certain parts of Germany where it is known as the "Schweinsberger disease." The accounts by Roloff (63), Friedberger (20), Dieckerhoff (16), Kunke (43), Eberbach (19), Mugler (52), Fröhner and Zwick (22), Stroh and Ziegler (73), Dobberstein (18), and Bernhardt (2, 3), scarcely leave any doubt that in its clinical and pathologic anatomic aspect the German disease is identical with the enzootically occurring liver maladies of other parts of the world.

Park (58), Gilruth (23, 24, 25, 26, 27, 28, 29, 30, 31), and others described an enzootic liver disorder of horses and cattle in New Zealand, known there as the "Winton disease." In all its aspects the New Zealand disease shows a close resemblance to similar diseases occurring elsewhere. New Zealand workers (26, 28) were the first to establish the etiology of the local disease upon a sound foundation and they succeeded to a degree in showing the character of the cause.
An enzootic liver disorder, the Pictou disease of cattle, which has occurred for many years in a section of Nova Scotia, has been adequately described in the Canadian public reports (7), and by such observers and investigators as Osler (55), McEachran (47), Johnston (38), Adami (1), Rutherford (64, 65), and Pethick (60). The Canadian workers also distinguished themselves by establishing the toxic cause of the disease and their results served as a valuable guide for similar attempts in other countries where enzootic liver disease is a problem.

The Molteno cattle disease and the dunziekte of horses in South Africa are also liver diseases of an apparent enzootic character. These diseases are described by Chase (9), Robertson (62), Dixon (17), Chambers (8), Verney (78), and Theiler (74, 75), who account for a pathologic condition very similar to the one encountered in Nebraska and contribute to the knowledge of its character and etiology.

Norwegian official reports (53, 54) and one published by Holmboe (33), throw light on an enzootic liver disease locally known as “sirasyke” which is prevalent among the cattle of the islands of Utsire, Falö, Rovaer, and Karmö. More recently Jalving (36) published the results of an investigation of an enzootic liver cirrhosis among cattle in certain parts of the Netherlands.

The descriptions of enzootic liver disease occurring in widely separated regions of the world are in close agreement with one another and there can scarcely be any doubt that the pathologic processes described were identical although not necessarily inaugurated by the same etiologic factors.

Thru the kind co-operation of fellow workers in other countries the writers were enabled to examine liver material from many affected animals. They were impressed not only with the identical characters of the fundamental lesions, but also by the fact that nothing was seen that could not be duplicated with sections of livers originating in the affected areas of Nebraska.

Before the knowledge of enzootic liver disorders in other parts of the world could be fully utilized in the planning of an inquiry into the cause of the disease affecting Nebraska livestock, it seemed appropriate to take into account the opinions of local ranchers, farmers, and veterinarians. In this connection the writers gave consideration to three hypotheses commonly advanced by local observers in regard to the causes of the disturbance. In one it was held that the problem is associated with a specific infection; in another, gross parasites were considered to be responsible; and in the
third the disease was attributed to intoxication by plants and more particularly so by the species of lupines belonging to the regions involved.

The possibility of gross parasites could readily be disposed of without special experimental efforts and the fact that cattle were also found to be suffering from the same liver lesions as the horses strengthened the conclusion that intestinal helminths had no connection in an etiologic sense.

There were no special indications that a transmissible virus played a part in the causation of "the walking disease." However, in order to set aside all doubts, a few inoculation experiments were made. The results may be ascertained from the following account.

Blood, spleen, and liver obtained from autopsies held on cases of "walking disease" in Sioux county during the late summer of 1925 were used in an effort to determine, if possible, the transmissible nature of the disease. Rabbits and cavias were included in this experiment. They received inoculations with a mixture of the blood and spleens taken from each of three cases of the disease.

One of the two rabbits inoculated with the material from one of the horses died ten days after the injection. This subject had a large intrathoracic abscess which apparently antedated the inoculation. A specific cause of death could not be shown by culture tests or by inoculation of two other rabbits with the blood taken from the heart and spleen of the one that died. The other rabbit and the two cavias belonging to this group were still in good health when they were discharged six weeks after the inoculation.

One of the rabbits injected with material taken from the second horse sickened ten days after the inoculation and died four days later. All attempts to associate a micro-organism with this animal's death resulted negatively. The other rabbit and the two cavias of this series were discharged in a good state of health six weeks after they were inoculated.

All animals inoculated with material removed from the third horse remained well and were discharged at the same period as the ones reported above.

Two horses, in good health, were given intravenous injections of 10 c.c. of a mixture of the blood and spleen pulp of all three of the field cases mentioned above. One of the horses showed a febrile reaction some ten days after the inoculation, but no other disturbance could be observed. As this animal was still in good health more than ten weeks after the inoculation and as the other horse failed to show any reaction whatever, the conclusion seems to be warranted that these inoculations yielded negative results.
In the course of 1926 three horses were inoculated with a suspension of the spleen and blood of a field case, but nothing indicating a positive inoculation result developed.

While many of the ranchers of the affected regions had more or less firm convictions in regard to the transmissible or contagious nature of the malady here considered, others leaned to the opinion that poisoning by native plants might be a deciding factor. This opinion was shared by at least one veterinarian stationed in this region. His wide experience and intimate acquaintance with range problems were full warrant for considering his ideas on the subject.

It was known that species of lupines were reputed to be poisonous and that in the lupinosis described by German authors (21, 22, 37, 41), disease of the liver is a conspicuous phenomenon.

In the region in which "the walking disease" is a problem there are three species of lupines more or less universally distributed, namely: (1) *Lupinus pusillus*, a small annual plant, not particularly abundant; (2) *Lupinus argenteus*, and (3) *Lupinus platensis*. The latter two species are perennials and their area of distribution coincides with that where the horse disease is common. There seemed to be some warrant thus to challenge the toxicity of at least the common perennial lupines as one of the details of the investigation, even if field observations yielded no very positive indications that would tend to implicate these plants. The following feeding experiments were undertaken with this object in view:

No. 9305. A mare nine years old, weighing about 1,000 pounds, consumed between July 16 and September 9, 1926, 207 pounds of the green and dried plants of *Lupinus platensis*, or approximately the equivalent of 380 pounds of the fresh plants. The daily quantities consumed ranged between 1½ and 4½ pounds. The subject was killed on September 18, 1926, while in good health and in a fair state of nutrition. The autopsy revealed nothing of an abnormal nature and the histologic examination of liver, kidneys, and other organs was negative in its results, so far as pathologic changes were concerned.

No. 9306. A ten-year-old mare weighing approximately 1,000 pounds was caused to consume between July 4 and September 7, 1926, 249 pounds of the green and dried plants of *Lupinus platensis*, a quantity approximately equivalent to 450 pounds of fresh material. At the end of the feeding period the animal's health and state of nutrition were good. The subject was killed on September 18, 1926. The autopsy and the histologic examination of the various organs failed to reveal any pathologic changes.
No. 8927. A one-year-old mare colt weighing about 600 pounds received between June 1 and 15, 1926, 20 pounds of *Lupinus argenteus*, but did not consume all of it. This animal died before a sufficient amount of the plants could be ingested. The histologic examination of its liver and kidneys showed these organs to be entirely normal.

No. 9294. A four-year-old gelding, weighing 1,200 pounds, consumed, between June 1 and September 4, 1926, 352 pounds of green and dried plants of *Lupinus argenteus*, representing approximately 640 pounds of the fresh plants. The daily quantity eaten ranged between 1 and 8 pounds. About August 15, 1926, the subject showed a tendency to gnaw at feed boxes, mangers, etc. The animal was killed September 17, 1926. At that time it showed a few erosions on the external surfaces of the lips, but otherwise its health and state of nutrition were good. The autopsy revealed nothing of an abnormal nature and the histologic examination of the liver, kidneys, and other viscera showed these organs to be intact and unimpaired.

No. 9295. A yearling colt weighing about 500 pounds received 214 pounds of green and dried plants of *Lupinus argenteus* between June 12 and September 4, 1926. This amount was the equivalent of approximately 390 pounds of the fresh plants. The subject was killed September 17, 1926, and was at that time in a fair state of health and nutrition. It showed some abrasions about the right labial commissure and numerous erosions on the tip of the tongue. The autopsy did not reveal any gross pathologic changes and the histologic examination of the various organs revealed nothing of a morbid character.

No. 16534. A mare seven years old and weighing about 1,400 pounds, consumed 259 pounds of dried plants of *Lupinus argenteus* between June 24 and September 4, 1926. This was not followed by any manifestation of disturbed well-being and on September 16, 1926, this animal was turned out to pasture to be destined for a continuation of the lupine feeding during the following season. In accordance with this plan the feeding with *Lupinus argenteus* was resumed on June 14, 1927, and continued until September 4, 1927, when 275 pounds of the plants had been consumed. The subject, in a good state of health, was killed on September 18, 1927. At that time its general condition was good. The only gross lesions revealed by autopsy were a few parasitic nodules in the liver and some surface adhesions pertaining to the same organ.

Histologically there were found some small hemorrhages between the glands of the stomach, while in the latter the nuclear stain had not taken well. The fibers of the myocard-
ium were granular, perhaps even fatty, in some areas. In a few sections the nuclei of the myocardium were poorly stained, while in others they reacted normally. In the liver sections the central vein had a dilated appearance, but otherwise this organ was quite intact. The organ showed nothing comparable with the lesions found in the field cases of "the walking disease."

No. 16535. A nine-year-old mare weighing approximately 1,000 pounds was fed with 195 pounds of dried plants of *Lupinus argenteus* between July 16 and September 4, 1926. On September 16, 1926, this subject, then in good health and condition, was turned out to pasture and reserved for the continuation of the feeding experiment during the following year. Pursuant to this plan the subject consumed 275 pounds of *Lupinus argenteus* between June 14 and September 4, 1927. This second feeding was not followed by any disturbance of the animal's health. The subject was killed on September 18, 1927, and the autopsy and subsequent histologic examination did not reveal anything of a pathologic nature.

The results of these feeding experiments seem sufficient to exculpate the eating of lupines as a factor in the cause of the disorder under investigation. The experimental animals consumed relatively large quantities of these plants and if poisonous there should have been observed at least something approaching the lesions in the liver which in the spontaneous disease are striking and profound.

A few feeding experiments were made with materials which had attention attracted to them in an incidental manner or were deemed worthy of consideration as a matter of investigational technique or for orienting purposes. The results of these experiments were negative as the following account will show.

No. 9304. A mare ten years old and weighing about 1,000 pounds received, between July 9 and August 31, 1926, 112 pounds of green and dried plants of *Oxytropis lamberti*, the approximate equivalent of 185 pounds of fresh plants. The amounts consumed daily ranged between 2 and 3 pounds. The animal suffered no deterioration of health and condition during the period of observation, which was terminated on September 18, 1926. The subject was killed on that date. The autopsy and the histologic examination disclosed no gross and no microscopic lesions.

No. 16605. Three rabbits received between July 21 and August 29, 1927, 31 pounds of fresh plants of *Lathyrus ornatus incanus*. These animals were in good health on Octo-
ber 7, 1927. The autopsies revealed nothing of an abnormal nature. Only the livers were subjected to a histologic examination. The latter did not disclose any changes of a pathologic character.

No. 16607. Three rabbits received between August 20 and September 21, 1927, not less than 29 pounds of the fresh plants of *Orophaca sericea*. These animals were in good health and condition when they were killed on October 7, 1927. The autopsies showed nothing of an abnormal nature and the histologic examination of the livers revealed these organs to be entirely intact.

No. 16540. A six-year-old gelding weighing about 1,100 pounds, consumed between July 18 and August 28, 1927, not less than 117 pounds of the green and dried plants of *Orophaca sericea*. The subject presented no evidence of disturbed health during the period of observation, which came to a close on September 19, 1927, when the subject was killed. Autopsy findings were negative. The histologic examination of the liver revealed an intact parenchyma, but the interlobular connective tissue appeared to be more prominent than in the majority of normal horses. The change, however, could not be classified as pathological. The other viscera examined microscopically were found to be normal.

No. 16541. A gelding six years old and weighing approximately 1,200 pounds was drenched with 1 1/2 quarts of the intestinal contents of a typical field case of the so-called "walking disease" on August 1, 1927. This animal, in a good state of health, was killed on September 19, 1927. The autopsy and the histologic examination of several organs disclosed no changes of a pathological nature.

With the exception of the Schweinsberger disease of Germany and of the "walking disease" of the Pacific Northwest, no enzootic form of liver disease thus far described has occurred without its etiologic relation with *Senecio* poisoning either having been definitely proved or seriously suspected.

How it came about that plants of the genus *Senecio* became suspected of causing liver or other disturbances in livestock could not be ascertained. It is quite certain, however, that the notion is not of very recent origin, because White (81, 82, 83), already quoted in connection with "stomach staggers," writes that a Mr. Poole, "an intelligent farrier," attributes a disease, which White called "lethargy," to the eating of ragwort, staggerwort, or St. James' wort (*Senecio Jacobaea*). From the editions of White's book open to the inspection of the writers, it is not possible to determine when Mr. Poole, quoted by White, made this statement, but it must have been
during the first quarter of the last century, if not before, thus not less than 100 years ago.

Gilruth (26, 28) of New Zealand proved the toxicity of Senecio Jacobaea in 1906, and Pethick (60) in 1906 convicted the same plant of being the cause of the Pictou disease of Canada, as far as this is possible to do by experimental feeding.

Chase (9), Robertson (62), Dixon (17), and Theiler (74, 75) succeeded, between 1904 and 1920, in implicating Senecio latifolius and Senecio burchelli as the etiologic factors of the South African "dunziekte" of horses and of the Molteno cattle disease. Verney (78) found that feeding Senecio latifolius to guinea pigs brought about fatal results, one of the animals dying within sixteen hours after eating a good supply.

Willmot and Robertson (85) describe a number of cases of hepatic cirrhosis in man which they could attribute to the presence of the seeds and other parts of Senecio burchelli and Senecio ilicifolium in the wheat used for bread making. Guinea pigs and white rats fed with the suspected flour sickened in the course of time and in one of the cavias lesions similar to those found in affected human beings could be demonstrated. In three of the rats similar lesions had developed.

Stockman (72), Thompson (76), Craig and Kehoe (12), Standley (71), Knowles (42), Leyshon (44), Reeks (61), and Rutter (66) report cases of poisoning by Senecio Jacobaea among the livestock of the British Isles. Definite feeding experiments were not reported, but the circumstantial evidence so strongly implicates this plant that there can scarcely be any doubt with regard to its etiologic connection. The danger associated with the plant has received official recognition (5, 35), and plans for the eradication of ragwort were proposed by M'Govern (48).

The connection of ragwort with the "sirasyke" of the cattle of certain insular localities of Norway was not proved by experiment, but according to Holmboe (33) the etiologic relation of the plant is so obvious that there can scarcely be doubt that the "sirasyke" of Norway and the Senecio disease of England are identical.

Jalving (36) made some feeding experiments with Senecio aquaticus and Senecio Jacobaea and while his results were not very striking there were indications that a degree of liver damage may have been actually inflicted in the animals used in the experiment.

After the elimination of specific infection and intoxication by the lupines as possible factors in the causation of the "walking disease," the data furnished by foreign workers and
observers were warrant that at least the most prevalent local Senecio species should be challenged with regard to their toxicity. Two species, Senecio integerrimus and Senecio Riddellii, are commonly found in the area involved. The genus Senecio is one of the largest known plant genera, having a wide distribution. It is represented by about 1,200 species of which not less than one hundred are known to occur on the North American continent. Plants belonging to this genus are commonly designated as ragwort, groundsel, or squaw weed.

Senecio integerrimus Nutt is a perennial herbaceous plant composed of a single unbranched, sparingly leafy stem arising from a basal rosette of leaves and terminating in a corymb of from 8 to 20 large yellow heads. The plant is more or less woolly when young, becoming glabrous when old. Its roots are short and semi-fleshy. The basal, lower leaves are entire, rather fleshy, oval or oblong, obtuse, and from 3 to 6 inches long and 1 to 1½ inches wide. The upper leaves are lanceolate and rather small.

This species is one of the earliest to appear with the beginning of the growing season in the territory involved (May). At first it appears in a dandelion-like form with a low rosette of from 4 to 6 or more leaves. The plant soon sends up a single, unbranched stem, commonly 12 to 18 inches in height, which early in June carries several yellow composite flowerheads.

The roots of this species being quite shallow probably accounts for an early cessation of growth and disappearance. The growing season of this species lasts only from four to six weeks. The ripened fruits or achenes are very conspicuous, each being surmounted by a crown of numerous, slender, white bristles (pappus). They persist for some time, imparting to the plant a characteristic fuzzy appearance.

The plants are apt to be found in patches or colonies, disappearing rather rapidly between June 20 and July 10. The habitat of Senecio integerrimus in the region where the plant was studied is in general restricted to areas having a favorable moisture condition, such as slight depressions, swales, old sand grass patches, and similar places. During more recent years the plant is apt to be found around old straw stacks because of an optimum moisture condition prevailing in such locations. Owing to the variations in moisture content of the soil, the distribution of Senecio integerrimus is a restricted one and the plant is not universally found in the area concerned in the horse-disease investigation.

Senecio Riddellii differs markedly from the preceding one. Its mode of growth is of another type and the plant is more
branched and leafy. It has a longer growing period and, being adapted to wider variations in climatic conditions, the plant grows in abundance on the prairies of the range.

*Senecio Riddellii* is a perennial plant with a long tap root from the crown of which arises a branched, very leafy stem from 12 to 24 inches in height. The leaves are from 1 to 3 inches in length, pinnately parted into from 3 to 9 narrow linear or filiform segments. Each branch ends in a corymb of from 8 to 20 flower-heads.

Altho some specimens of this plant may be found during June, most of them appear during July and reach their maximum development in August. At first the plants grow up from their woody perennial base as one or two slender, upright stems with several delicate feather-like leaves. They form a scattered growth amongst the prairie vegetation and are, hence, not very conspicuous to a casual observer.

As the season advances the plants branch and leaf out more profusely and become taller and wider to attain their maximum development. The flowering season extends thru July and August and the plants become prominent on the prairie with their numerous yellow heads. After the flowering season, the ripened achenes, with their numerous, slender, white bristles, persist for a long time to impart to the plant tops a characteristic cottony appearance.

In overgrazed areas and in other disturbed places in the prairie where there is but little competition, the plants become very large and bushy and then a single plant may measure more than two feet across. Wherever *Senecio Riddellii* must take its place among other plant species it grows smaller and never attains such a luxurious growth. The species is well adapted to its environment and constitutes a component part of the prairie vegetation.

The feeding experiments made with the two *Senecio* species predominating in the horse disease territory may be divided into three groups: (1) consecutive feeding with *Senecio integerrimus* and *Senecio Riddellii*, (2) feeding with *Senecio integerrimus* only, and (3) feeding with *Senecio Riddellii*.

*No. 16536.* An aged mare consumed 151 pounds of plants of *Senecio integerrimus* between May 21 and July 12, 1927. Between August 9 and September 17, 1927, the same animal received 150 pounds of *Senecio Riddellii*. The subject was killed September 17, 1927, while in good condition. The autopsy showed nothing abnormal with the exception of a few necrotic nodules of the liver and this organ also showed a few hemorrhagic areas on its surface.
The histologic examination showed the stomach, the heart, the spleen, and the kidneys to be normal. In the liver some derangement of the lobular structure was observed in the area immediately surrounding the central vein. There were pigment deposits here as well as in some of the interstitial structures. The liver cells, on the whole, were fairly intact and did not warrant the opinion that the organ was functionally impaired. There was an increase in the connective tissue elements of the interstitium. The organ was certainly damaged, but only in a slight degree.

No. 16538. A nine-year-old gelding consumed between May 24 and July 9, 1927, 115 pounds of the plants of Senecio integerrimus and between August 23 and September 17, 1927, 48 pounds of plants of Senecio Riddellii. The animal was in good condition when killed on September 18, 1927. The autopsy revealed nothing of an abnormal nature altho the color of the liver was of a rather unusual grayish brown cast. The histologic examination of the stomach, spleen, and kidneys showed these organs to be quite intact. Most of the sections of the heart revealed a normal tissue, but in some others the fibers were granular, showed some evidence of edema, and took the stain in an imperfect manner.

The liver was slightly pathologic. Near the center of certain lobules a few cells appeared to be slightly damaged and showed some pigment granules in their protoplasm. The intralobular structure was well preserved altho there was an increase in the endothelial elements. A few liver cells were certainly necrobiotic. In some lobules there was a leucocyte infiltration near the periphery and young connected tissue elements were encountered in the interstitium. Bile stasis was more or less general.

No. 16537. A two-year-old colt, gelding, was fed 151 pounds of the plants of Senecio integerrimus between May 21 and July 12, and 150 pounds of the plants of Senecio Riddellii between August 9 and September 17, 1927. On the latter date the colt was killed while in good condition. The autopsy showed all organs to be normal with the exception of the liver, which presented a marked fibrosis with numerous reddish brown areas thruout its substance. Microscopically examined, the stomach, heart, spleen, and kidneys were found to be normal. The liver showed a marked connective tissue thickening of the interstitium with proliferation of the bile duct epithelium. There were necrobiotic changes in the liver cells, especially in the ones around the central vein. Hemorrhages were observed, but they were not very common. In some lobules the cell cords were deranged. Pigmentation and bile stasis were quite pronounced. The organ was markedly pathologic.
While the autopsies of these three horses revealed a degree of liver damage in all, it is quite apparent that nothing was produced comparable with the profound changes characteristic of the field cases.

Only in one animal (No. 16537) was a conspicuous result obtained in the form of a marked interstitial thickening and this type of lesion is comparatively rare in the cases arising spontaneously in the field in which this type of damage may be an indication of a sublethal intoxication.

No. 16161. Four rabbits consumed between May 20 and July 13, 1927, mature plants of *Senecio integerrimus*. The plants were 107 in number and were quite large. The rabbits were killed on August 8, 1927. The autopsy revealed no conspicuously abnormal appearance of the organs of any of these rabbits. Microscopically examined, three of the four livers showed slight evidence of interstitial irritation altho the parenchyma was entirely intact. In the fourth liver there were no changes in the interstitium. The parenchyma cells, with perfectly intact nuclei, showed a peculiarly coarse granulation. This was interpreted as evidence of a digestive phase rather than of a pathologic character.

No. 16539. An aged gelding received between May 24 and July 9, 1927, not less than 115 pounds of plants of *Senecio integerrimus*. The animal was killed September 17, 1927, and the autopsy showed no gross pathologic changes. The microscopic examination showed a few leucocyte conglomerations in the interstitial spaces. Otherwise nothing was encountered indicating a pathologic condition.

No. 23126. A seven-year-old gelding of 1,100 pounds weight consumed 288 pounds of fresh plants of *Senecio integerrimus* between May 23 and June 26, 1928. The animal was killed on August 31, 1928. The subject at that time was in a fair condition, but had been observed to be rather sluggish in its movements for about two weeks. The autopsy showed all organs to be normal in appearance, except the texture of the liver, which appeared to be somewhat firmer than usually encountered, altho color and general appearance were normal.

The liver weighed 14½ pounds, the spleen 2 pounds, and the stomach and contents 16 pounds. The histologic examination of spleen and kidney showed these organs to be normal. The liver showed evidence of impairment consisting of necrobiotic changes in the cells. However, the lobular structure was preserved and no tendency to fibrosis, regeneration, or hyperplasia was observed. There was a slight bile stasis and occasionally a central vein showed signs of hyalin degeneration.
No. 23127. A mare ten years old weighing 1,300 pounds ate 40 pounds of fresh Senecio integerrimus between May 23 and June 26, 1928. This animal was of a wild and unmanageable disposition and a poor subject for experimental purposes. It was killed on August 31, 1928, and at that time the animal was in a fair state of nutrition. The autopsy showed all organs and tissues to be of normal appearance. The spleen weighed 2½ pounds, stomach and contents 32 pounds, and the liver 15 pounds. The histologic examination showed the parenchyma of the liver to be intact altho areas were seen in which the nuclei showed a reduced affinity for the dye. There was a marked bile stasis and the intralobular capillaries were somewhat distended. Spleen and kidneys were found to be intact.

No. 23249. An aged gelding weighing 1,375 pounds consumed, between May 10 and June 28, 1928, not less than 157 pounds of plants of Senecio integerrimus. The animal was killed in a good state of health and nutrition on September 21, 1928. The autopsy showed no gross pathologic condition. The liver weighed 19 pounds, the spleen 4 pounds, and the stomach and contents 11 pounds. The histologic examination of liver, spleen, and kidneys revealed nothing of a pathologic nature.

No. 23720. A mare weighing approximately 1,100 pounds consumed, between May 17 and June 28, 1928, 158 pounds of plants of Senecio integerrimus. The animal, while in a good state of health, was killed October 17, 1928. The autopsy disclosed no gross pathologic conditions. The spleen weighed 3½ pounds and the liver 13½ pounds, and the microscopic examination of the liver, spleen, and kidneys showed these organs to be normal.

No. 23783. A mare weighing approximately 1,000 pounds consumed 157 pounds of plants of Senecio integerrimus between May 21 and June 28, 1928. The animal was killed on October 31, 1928, while in a good state of health and nutrition. The autopsy showed no gross lesions (spleen 2 pounds, liver 12 pounds). The microscopic examination showed the parenchyma of the liver to be normal, but the interstitium showed some evidence of cell proliferation. The spleen was normal and the kidneys intact.

No. 24037. An aged gelding weighing about 900 pounds consumed 4,750 grams of the dried fruit tops of Senecio integerrimus between October 1 and November 1, 1928. The subject was killed while in good condition on December 26, 1928. The autopsy showed no gross pathologic changes. The spleen weighed 4½ pounds, the liver 11. The histologic examination showed the spleen and kidneys to be normal. The
In some places the triangles of Glisson were more conspicuous than is usually the case in the average normal horse liver. If these slight changes are pathologic at all, doubt still remains with regard to their origin in as much as they are common enough in the liver of apparently normal animals.

No. 24075. A mare weighing about 900 pounds received May 8 and June 28, 1928, about 170 pounds of fresh plants of Senecio integerrimus. The subject was killed on November 14, 1928. The autopsy showed the carcass to be in excellent condition with an abundance of adipose. The organs were found to be normal. The spleen weighed 1¼ pounds and the liver 11, and the histologic examination of spleen, liver, and kidneys disclosed no pathologic changes.

No. 24076. A pony weighing approximately 700 pounds consumed about 158 pounds of fresh plants of Senecio integerrimus between May 21 and June 28, 1928. The subject was killed November 14, 1928, while in a good state of health and nutrition. The autopsy disclosed no pathologic changes. The spleen weighed 1¾ pounds, the liver 9 pounds. The histologic examination of spleen and kidneys showed these organs to be normal. The liver showed some evidence of irritation expressed by a slight increase in the areas of Glisson's triangles and by some connective tissue proliferation in the interstitium. The parenchyma could be regarded as intact altho a few cells showed degeneration changes. There was a rather marked divergence in the size of the liver cells. On the whole the organ could be regarded as unimpaired and fundamentally normal.

In this series of experiments no lesions were produced which could be regarded as the base for liver impairment and nothing was observed which clinically or patho-anatomically resembled the field cases.

No. 16606. Four rabbits received 40 pounds of fresh plants of Senecio Riddelli between July 16 and August 26, 1927. They were killed October 7 without having shown illness and their organs had a normal gross appearance. Only the livers were subjected to a histologic examination. Two of them showed a development of interstitial lesions well under way. There was also some increase in the intralobular reticular tissue. In both these organs the parenchyma was quite intact. In a third, liver changes were observed, but somewhat less pronounced. In the remaining liver, interstitial irritation was manifest and there were slight degenerative changes in
EXPLANATION OF PLATES

PLATE I

Fig. 1. Necrobiosis and intralobular fibrosis of liver of a horse affected with "walking disease."

Fig. 2. Liver lesions in a horse fed with 188 pounds of Senecio Riddellii between June 20 and September 1, 1928.

PLATE II

Fig. 1. Liver from a field case of "walking disease" in a horse, showing parenchymatous deterioration and intralobular hemorrhages.

Fig. 2. Liver of a horse fed with 172 pounds of Senecio Riddellii between June 29 and September 1, 1928.

PLATE III

Fig. 1. Interstitial liver lesions in a field case of "walking disease."

Fig. 2. Interstitial liver lesions in a horse fed with 151 pounds of Senecio integerrimus between May 21 and July 12, 1927, and with 150 pounds of Senecio Riddellii between August 9 and September 17, 1927.

PLATE IV

Senecio Riddellii

PLATE V

Senecio integerrimus
the liver cells. None of these changes was at all pronounced.

No. 23466. One of four rabbits which together consumed 155 pounds of fresh plants of *Senecio Riddellii* between June 18 and August 29, 1928, was killed on September 30, 1928, while in a good state of health. The autopsy revealed no gross pathologic changes and the histologic examination of the liver did not disclose any lesions.

No. 24039. One of four rabbits which together consumed 155 pounds of fresh plants of *Senecio Riddellii*, between June 18 and August 29, 1928, was killed while in a good state of health November 8, 1928. Its organs were found to have a normal, gross aspect. The microscopic examination of its liver revealed an intact parenchyma and a slight, but apparently active interstitial proliferation.

No. 24040. One of four rabbits which together consumed 155 pounds of fresh plants of *Senecio Riddellii* between June 18 and August 29, 1928, was killed on November 8, 1928, while in a good state of health and nutrition. The autopsy did not reveal gross pathologic changes. Only the liver was examined histologically. The parenchyma of this organ showed some impairment. A slight increase of the connective tissue elements could be observed. In some places there was an intralobular round cell infiltration and in a number of the lobules the normal arrangement of the liver cells had been disturbed. The parenchyma was partially made up of large (hypertrophic?) deeply stained cells, and here and there groups of cells were seen which were manifestly atrophic. The latter had a more coarsely granular protoplasm than the large cells of which the protoplasm was finely granular and diffusely stained. The nuclei of the liver cells were still intact. Fatty cells were only occasionally seen.

No. 24041. One of four rabbits which together consumed 155 pounds of fresh plants of *Senecio Riddellii* between June 18 and August 29, 1928, was killed on November 8, 1928, while in good health and in a good state of nutrition. The autopsy revealed no gross lesions. The liver was the only organ subjected to a microscopic examination. The sections showed the capillaries to be distended with blood. Some degenerative changes in the parenchyma were observed. The nuclei of the liver cells stained but faintly altho in general they were morphologically intact. There was a slight proliferation of the interlobular connective tissue. The organ was slightly impaired.

No. 23210. A nine-year-old gelding, weighing 850 pounds, consumed 188 pounds of plants of *Senecio Riddellii* between June 20 and September 1, 1928. The subject was killed September 13, 1928. At that time the animal was dull and emaciated. Its gait was dragging and its appetite poor. The
autopsy revealed a liver very firm in texture with a greenish cast on the cut surface. The organ weighed 9½ pounds. The stomach was impacted with food and with its contents weighed 29 pounds. The other organs had a normal appearance. The spleen weighed 2 pounds. The histologic examination showed the latter organ to be normal. The kidney sections revealed areas of parenchymatous disintegration. In these the epithelium was swollen, granular, and the nuclei had often entirely disappeared. Here and there peritubular edema was in evidence and shrunken glomeruli were observed.

The liver was badly damaged. All semblance of the normal intralobular arrangement was lost and the cords were no longer to be recognized. Small hemorrhages were encountered and there was a conspicuous connective tissue proliferation, interlobular as well as intralobular. Bile stasis was apparent and there were biliary deposits amongst the cellular elements. The parenchyma cells were involved in an active necrobiosis. Masses of leucocytes were seen in some areas. There were signs of regeneration, and hypertrophic cells were seen, but the compensatory effort was not so marked as in some of the field cases examined. In a few sections areas approaching the normal were observed and there the interstitial thickening was not marked.

No. 23248. A gelding, nine years old and weighing 900 pounds, consumed 117 pounds of the plants of Senecio Riddelli between July 20 and September 1, 1928. The animal was killed on September 21, 1928. At that time its state of nutrition was poor, its gait dragging, and its appetite lacking. The autopsy revealed the various organs to have a normal aspect with the exception of the liver (12 pounds) which had a distinctly firm consistency and a greenish color. The abdominal adipose had a dirty, yellow color. Microscopically examined, the spleen showed marked pigmentation, but was otherwise normal. The kidney parenchyma was generally damaged, but this damage showed considerable variation in intensity, according to location. In some areas there were many nearly intact tubules and in others the renal epithelium had entirely disappeared. Between these extremes all stages could be seen. Many of the glomeruli were damaged.

The parenchyma of the liver was badly damaged and interstitial connective tissue proliferation was conspicuous. Owing to the latter the lobular boundaries could be readily recognized. In many of these the normal arrangement of the cells had been lost, while in a few a semblance of cord formation had been preserved. The liver cells showed all phases of necrobiosis. Round cell infiltration into the interstitium was quite common. There were biliary deposits throughout the organ, but hemorrhages were not observed.
No. 23721. A mare, weighing approximately 800 pounds, consumed 172 pounds of plants of *Senecio Riddellii* between June 29 and September 1, 1928. For some time prior to the final disposal of the subject the latter had shown manifest illness. The mare had sustained a substantial loss of weight, had become dull, and her rather wild and combative character had given way to a passive indifference as to what happened in the environment. For several days her appetite had completely failed and approaching death made the killing of the animal advisable in order to secure the organs in as fresh a condition as possible. This was done on October 17, 1928. The autopsy showed the subcutis and conjunctival mucosa to have acquired a dirty, yellow color. The ascites was marked and the abdominal fluid had an orange-yellow color. The omentum and the mesenteries were very edematous. The spleen (2½ pounds) was normal in appearance. The kidneys showed evidence of advanced degeneration. The liver (8 pounds) had a mottled appearance and a bluish cast of color. It showed resistance to the knife and was a perfect replica of the livers of horses which, on the range, had succumbed to "the walking disease." All of the mucosae showed jaundice. The heart showed sub-endocardial ecchymoses. The histologic examination was confined to the spleen, kidneys, and the liver. The former presented nothing of a morbid character.

On the other hand the kidneys were badly impaired. In many areas the parenchyma was completely destroyed and fatty degeneration was a marked feature. Fairly intact tubules were encountered, but on close examination, no parenchymatous cell could be found which was not involved in necrobiotic damage. All functional parts, including the glomeruli, were damaged and differed only in degree of destruction.

The liver also was pathologic throughout. Parenchymatous destruction was almost complete. Focal hemorrhages were abundant and dominated the histologic picture. All phases of necrobiosis were observed. Of lobular demarcation and architecture, not even a vestige was left. Large hypertrophic cells were seen and they also showed degenerative changes. The connective tissue element of the interstitium showed evidence of proliferation. The intralobular reticulated tissue was increased in volume.

No. 23784. A gelding weighing about 1,000 pounds consumed 116 pounds of *Senecio Riddellii* between July 13 and September 1, 1928. After the latter date the animal lost some weight, appeared a bit dull, but beyond this did not present any symptoms of organic disease. The subject was killed October 31, 1928. The autopsy did not reveal gross pathologic
Fig. 9. Liver lesions resulting from the feeding of plants of Senecio Riddellii to a horse.
Fig. 10. Liver lesions resulting from the feeding of plants of Senecio Riddellii to a horse.
changes in any of the organs with the exception of the liver (10 pounds) which had a mottled, grayish brown color and was firmer in texture than livers of normal animals usually are. The histologic examination of the spleen showed this organ to be normal. The kidneys were found to be intact with the exception of some swelling of the epithelium and a few areas in which degenerative changes were apparent. The liver was found to be damaged. The intralobular arrangement was badly upset. The liver cells, often very large, were found, to a noticeable degree, necrobiotic. The interlobular connective tissue was conspicuously increased and active proliferation seemed to be still in progress. Round cell infiltration in the interstitium was frequently observed. There was bile stasis, mostly seen near the center of the lobules. In many of the latter the radiating cords of cells could still be traced, but in a considerable number they had been lost. While the destruction of the parenchyma had not been as ruthless and complete as in some of the field cases of "the walking disease," the organ showed many features common in the latter. The organ was badly impaired.

In the rabbits fed with Senecio Riddellii but a small amount of liver damage was produced, but in the horses fed with this plant the liver lesions were conspicuous and intense in character. They simulate in all respects the lesions encountered in the field cases, and the animals, at the time they were killed, presented clinical features seen in the spontaneous "walking disease" cases. The experimental horses, being stabled, could not show the wandering disposition so often encountered in the field cases. However, even without this phenomenon they revealed all the evidence of grave illness presented by the field cases. In some of the cases remarkably severe kidney lesions were produced. It seems probable that the prolonged feeding in the experiment may have been responsible for the kidney damage. After the liver parenchyma had been so damaged, perhaps saturated with the toxic principle of the plant, the excess of the latter overflowed into the general circulation and inflicted injury on the next vulnerable parenchyma, that of the kidney. The disparity between the experimental kidney lesions and those shown by the field cases may not be without significance with regard to the nature of the intoxication under field conditions.

The results obtained in attempts to transmit the disorder under investigation by means of inoculation appear to be decisive. They merely confirm prior conclusions based on epizootologic and pathologic evidence. In this the sharp in-
cidence curve of the disease was very suggestive of the remoteness of the possibility of transmissible factors playing an etiologic part.

The inoculation experiments were warranted because of a considerable volume of local opinion that the disease may be associated with, or identical to, equine infectious anemia. At the time bovine cases of "the walking disease" had not come to light to refute this theory.

The negative results of the inoculation experiments set aside all doubt on this point, yet it may be of interest to show that the belief in the connection of an enzootic liver disorder and equine infectious anemia is not exclusively an attribute of the lay mind. Oppermann and Ziegler (56) regard the Schweinsberger disease of Germany as a chronic form of infectious anemia. Were this true the fact should help to prove that the equine infectious anemia (swamp fever) of North America and the infectious anemia of the horse in Germany are not identical. At the same time it should also show that the "walking disease" of our country has no etiologic relation with the Schweinsberger disease. The bibliographic references available to the writers do not show to what extent the etiology of the latter disease has been investigated or to what extent the occurrence and distribution of Senecio species as revealed by Karsten (40) was given consideration.

The feeding experiments with the local lupines showed that these plants have no etiologic relation to the disease under investigation. The use of considerable amounts of these plants and the feeding of two horses during two consecutive seasons showed that the two species concerned are quite harmless to equines, whatever they may be to other forms of farm livestock.

The experimental feeding with miscellaneous plants and intestinal contents was undertaken only when local circumstances seemed to warrant a trial. These experiments also gave negative results.

The results obtained by feeding to rabbits any one of the two Senecio species used in this experiment were not sufficiently marked to permit them to be accepted as evidence bearing on the problem in hand. Some slight liver damage could be shown, but nothing which, in the least, resembled the marked changes which are so constantly observed in the liver of horses affected with "the walking disease."
On the other hand the horses in the experiment appeared to be quite vulnerable to a toxic agent present in one of the plants and probably, to a less extent, also in the other.

Altogether, sixteen horses were used in the feeding experiments and while this number may be relatively small, there can be no doubt that grave liver lesions developed in the animals fed exclusively with plants of *Senecio Riddellii* and that very slight changes were observed in the livers of the subjects which ingested comparable amounts of the plants of *Senecio integerrimus*.

The liver lesions as well as the clinical manifestations of the subjects which became sick after being fed with plants of *Senecio Riddellii* are so markedly identical to those encountered in the field as to warrant the conviction of this species as the causative factor.

In an investigation concerned with a problem such as the one related in this report, an absolute conviction would be impossible without a test of most of the plant species of the range. The character of the lesions, furthermore, could not be regarded as bearing the impress of an exclusively *Senecio* intoxication. While in certain intoxicaions the resulting lesions may be somewhat pathognomic, there is no reason to believe that a tissue reaction would be so characteristic as to warrant it to be associated with a definite intoxicant. While the validity of this reasoning cannot well be questioned, the fidelity with which the liver lesions of "the walking disease" were reproduced by the feeding with plants of *Senecio Riddellii* is warrant for regarding this plant as the determining etiologic factor of the malady under consideration.

The types of lesions are most likely determined by quantitative rather than by qualitative factors. The variations found in the lesions shown by the field cases must be regarded as evidence, not of quality differences of intoxicants, but of being due to variations in the degree of intoxication.

The epizootological as well as the pathological evidence presented by the spontaneous cases of "the walking disease" tends to show that the severest damage is inflicted during the earlier periods of the season and it is by no means improbable that the very young plants are especially involved in the intoxication. There is some foundation for the belief that in the majority of the cases a few pounds of the young leaves of the more toxic one of the two *Senecio* species may be sufficient to produce a fatal liver necrobiosis.

While the number of the experimental cases is far too small to justify dogmatic conclusions on this point, the experimental data, nevertheless, tend to confirm the correctness of the field observations. It will be noted that in Table 1 the comparable
### TABLE 1.—Summary of results in horses fed with Senecio

<table>
<thead>
<tr>
<th>Exp. Horse No.</th>
<th>S. integrerimus</th>
<th>S. Riddelli</th>
<th>Lesions</th>
<th>Parenchyma</th>
<th>Interstitium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lbs. from</td>
<td>to</td>
<td>Lbs. from</td>
<td>to</td>
<td></td>
</tr>
<tr>
<td>16539</td>
<td>115 5-24‘27</td>
<td>7-9‘27</td>
<td></td>
<td></td>
<td>O</td>
</tr>
<tr>
<td>23126</td>
<td>288 5-23‘28</td>
<td>6-26‘28</td>
<td></td>
<td></td>
<td>O</td>
</tr>
<tr>
<td>23127</td>
<td>40 5-23‘28</td>
<td>6-26‘28</td>
<td></td>
<td></td>
<td>O</td>
</tr>
<tr>
<td>23249</td>
<td>157 5-10‘28</td>
<td>6-28‘28</td>
<td></td>
<td></td>
<td>O</td>
</tr>
<tr>
<td>23720</td>
<td>158 5-17‘28</td>
<td>6-28‘28</td>
<td></td>
<td></td>
<td>O</td>
</tr>
<tr>
<td>23783</td>
<td>157 5-21‘28</td>
<td>6-28‘28</td>
<td></td>
<td></td>
<td>O</td>
</tr>
<tr>
<td>24037</td>
<td>* 10-1’28</td>
<td>11-1'28</td>
<td></td>
<td></td>
<td>O</td>
</tr>
<tr>
<td>24075</td>
<td>170 5-8‘28</td>
<td>6-28‘28</td>
<td></td>
<td></td>
<td>O</td>
</tr>
<tr>
<td>24076</td>
<td>158 5-21‘28</td>
<td>6-28‘28</td>
<td></td>
<td></td>
<td>O</td>
</tr>
<tr>
<td>16536</td>
<td>151 5-21‘27</td>
<td>7-12‘27</td>
<td>150 8-9’27</td>
<td>9-17‘27</td>
<td>+</td>
</tr>
<tr>
<td>16538</td>
<td>115 5-24‘27</td>
<td>7-9‘27</td>
<td>48 8-23‘27</td>
<td>9-17‘27</td>
<td>+</td>
</tr>
<tr>
<td>16537</td>
<td>151 5-21‘27</td>
<td>7-12‘27</td>
<td>150 8-9’27</td>
<td>9-17‘27</td>
<td>+</td>
</tr>
<tr>
<td>23210</td>
<td></td>
<td></td>
<td>188 6-20‘28</td>
<td>9-1‘28</td>
<td>+</td>
</tr>
<tr>
<td>23248</td>
<td></td>
<td></td>
<td>117 6-20‘28</td>
<td>9-1‘28</td>
<td>+</td>
</tr>
<tr>
<td>23721</td>
<td></td>
<td></td>
<td>172 6-29‘28</td>
<td>9-1‘28</td>
<td>+</td>
</tr>
<tr>
<td>23784</td>
<td></td>
<td></td>
<td>116 7-13‘28</td>
<td>9-1‘28</td>
<td>+</td>
</tr>
</tbody>
</table>

* 4,750 grams of seeds.
results with Senecio Riddellii fed in the years 1927 and 1928 showed conspicuous differences. The results obtained in 1927 were relatively benign and the damage which resulted from the 1928 feeding was particularly severe and destructive. This phenomenon acquires significance after a comparison of the feeding dates. In the 1927 experiments only mature plants were used, while for the 1928 feedings the plants were collected as soon as they made their appearance and could be recognized.

It seems reasonable to believe that once the poisonous Senecio Riddellii plants attain a size large enough to set them apart from the surrounding vegetation, they are no longer eaten by livestock. As small, fine leaves amidst the grass they can scarcely be avoided by a grazing animal, but when the plants grow out above the ground, and possibly acquire a stronger taste in addition, they are rejected.

Another observation made during this inquiry may have a bearing on the phenomenon referred to above. In the feeding experiments, the animals were forced to consume the plants long after their stage of growth might have made them attractive to grazing livestock on the range.

At least two of the four animals fed with plants of Senecio Riddellii developed kidney lesions of a severity never encountered in the field cases. It is quite probable, thus, that the relative mildness or complete absence of kidney lesions in the spontaneous cases is an indication that the plant is only taken in during a rather brief period. It would seem that after the liver has become impaired in the experimental horses and the feeding continued, the hepatic parenchyma could retain no more of the toxic agent. The latter then passes on to the general circulation, by means of which it reaches the renal parenchyma, next in vulnerability to the hepatic one.

The account of the feeding experiments with Senecio integerrimus reveals only a minimum of toxic effect in the quantities consumed. It is possible that the results would have been different if much larger amounts had been fed. Whether or not more than was fed in the experiments would be eaten by animals on the range cannot be readily determined, but it appears to be rather doubtful. It should, however, be remembered that this species is early, quite luscious, and more or less attractive to livestock. It tends to grow in patches where grazing animals could ingest a considerable quantity of the forage in a minimum of time.
CONCLUSIONS

1. The "walking disease" of Northwestern Nebraska is essentially an enzootic necrobiosis and cirrhosis of the liver due to a toxic agent and does not materially differ from similar disorders occurring in other regions or countries.

2. The disease affects horses and cattle but it is most commonly encountered in the former.

3. The disease in all its clinical and pathological manifestations may be reproduced with the utmost fidelity by the feeding with plants of Senecio Riddellii.

4. It was not possible to exculpate entirely the Senecio integerrimus, altho no experimental evidence was obtained which would indicate that this plant is a factor in the causation of "the walking disease."

5. Feeding experiments showed that Lupinus argenteus and Lupinus platenis are harmless to horses.

6. There is evidence, epizootologic as well as pathologic, which tends to show that the poisoning by Senecio Riddellii is limited to a relatively short period.

7. Preventive measures may be based upon these observations. In these measures the use of sanctuary pastures during the critical season may have a definite place.
BIBLIOGRAPHY


34. Imperial Institute. The causation of Molteno, Pictou or Winton disease. Bul. 9, p. 346, 1911.
54. Norge. Veterinaervaesenet (1906), S. 34, 1908.
68. Rydberg. Flora of the Rocky Mountains, etc. 2nd Ed., N. Y., 1922.
77. United States. Dept. of Ag. 23rd Rept. B. A. I., 1908.
ACKNOWLEDGMENTS

The writers gratefully acknowledge the loyal support and efficient help received in the pursuit of this inquiry from the Hon. H. J. McLaughlin, State Secretary of Agriculture, and from Dr. C. H. Hays, Chief, State Bureau of Animal Industry. Thanks are due to Mr. N. F. Petersen of the Department of Experimental Agronomy, University of Nebraska, for initial survey work and for valuable counsel, to Mr. W. P. Snyder, Superintendent of the North Platte Experimental Station, and to Mr. O. J. Grace, of the same station, for many courtesies in addition to the actual feeding and observation of the experimental horses.

The opportunity to examine liver sections of cases of enzootic hepatic disease in other areas and countries was of material aid in this investigation and the writers hereby express their gratitude and deep obligations to those who so generously supplied them with material. They are Dr. O. Bederke, Berlin, Germany; Dr. P. J. du Toit, Director Veterinary Services, Pretoria, South Africa; Mr. C. S. M. Hopkirk, Officer in Charge, Veterinary Laboratory, Wallaceville, New Zealand; Dr. J. W. Kalkus, Superintendent, Western Washington Experiment Station, Puyallup, Washington; Mr. W. J. Leyshon, Institute of Animal Pathology, University of Cambridge, England; Dr. C. D. Marsh, B. A. L., U. S. Dept. of Agriculture, Washington, D. C.; Mr. H. Caulton Reeks, Spalding, England; and Dr. E. A. Watson, Chief Pathologist, Dept. of Agriculture, Ottawa, Canada.

Last but not least do the investigators acknowledge their great obligations to the ranchers and farmers of the areas where the field work was done. Their courtesy, hospitality, and helpfulness immeasurably facilitated the work and contributed to the successful conclusion.