Chronic Senecio Poisoning.

An attempted reproduction of cirrhosis of the liver by the continuous ingestion of Senecio.

In recent years there has been some discussion as to the toxic properties of the genus Senecio. Owing to the marked discrepancy in the views published concerning its action, as the causal factor in the production of that cirrhosis of the liver in cattle and horses known as Mollino, Winton, or Pietrow disease, it was felt that a further investigation upon the actions of this group of plants would be valuable.

Included in this genus are the ragwort (S. Jacobea) and the groundsel (S. Vulgaris).

Gilmour (1905) and Petticke (1902) described a disease in cattle and horses of which the chief pathological lesion is a cirrhosis of the liver. They showed, experimentally, that the disease might be due to ingestion of ragwort. Cushing (1909) adduced experimental evidence to show that Senecio is a virulent irritant poison, and the cause of Mollino, Winton, or Pietrow disease. Craig and Kehoe (1921) describe a similar cirrhosis of the liver occurring in horses. There was no evidence of ingestion of Senecio, but they make no new suggestion as to a causal factor. Adamis attributes the lesions described by Petticke to a secondary bacterial infection and not due to the plant.

Ragwort and groundsel with one or two closely
allied species of the same genus have been used as popular remedies since the time of Pliny.
Reference to De Plantis (1) and Dioscorides 'Materia Medica' shows that the early herbalists placed belief in Senecio or Erigeron, as it was then more commonly called, as a soothing application.

Lyle (3) in 1578 recommended the use of S. Vulgaris in the treatment of Queens Evil or Struma. A few years later, in the 1st edition of his book Gerrard employed S. Jacobea for the treatment of "the old ache in the hucklebones called sciatica," and in the 2nd edition of 1636 he first mentions its use as an Emmenagogue. Similar treatment was employed by other herbalists of the period. S. Vulgaris also seems to have been used as a vermifuge by English veterinary surgeons. The belief in the therapeutic value of Senecio by herbalists and others persisted well into the 19th Century. S. Aureus, the chosen species used by the eclectics under the name of "life root" or "female regulator" was extensively given as a tea in the treatment of menstrual disorders.

chemistry

The toxic principles of these plants are generally considered to be two alkaloids, Senecine and Senecionine. They were first isolated in 1894, from the whole plant by Groentvald and Lajoux, who found them to be present in amounts varying from 0.067 to 0.5 gms per Kg of the dried herb. The variability in amount of these substances was attributed to seasonal changes. Mayer's reagent among others was used to test for the presence of alkaloidal substances, and in addition specific tests for the alkaloids found in this genus are given. Lutz (12) confirmed these observations, but maintained that the alkaloids were entirely derived from the underground portions of the plant.
and were least abundant in the groundsel and ragwort.

Watt adapted the method usually employed for isolating alkaloids from plants, and obtained two alkaloids from S. Latifolius of South Africa, which he called respectively Senecefoline and Senecefolidine. His method was to exhaust the leaves with 95% alcohol, and then extract the residue with 2% hydrochloric acid. This solution was made alkaline with ammonia, and extracted with chloroform, which was later evaporated, leaving a brown varnish-like mass, which gave the usual alkaloidal reactions. This mass was redissolved in 2% hydrochloric acid, and purified until crystals of the nitrate salts of the alkaloids were obtained. He found that the amount of crude alkaloid varied from 1.72% in plants gathered before flowering, to only 0.72% in those gathered after flowering. Stockman, however, suggests that the flowering stage is a more poisonous.

Pharmacological Action

Murrell, who used this drug as an emmenagogue, experimenting upon himself, took up to two fluid ounces daily of a 1 in 1 tincture, for thirty days, but could detect no untoward action. The active principle is ecein, a dark brown resinous looking substance was also used in minimal doses of 0.39 gms daily. Dalché and Van administered pills of the resinous extract from Senecefoline in all 14.4 gms, to a small young bitch, and also gave large doses of the liquid extract to pregnant guinea pigs by intra muscular, and intra peritoneal injection, but obtained no indication of any specific pharmacological action. Toothergill, reviewing previous investigations confirms Murrell's results by his own experiments using similar preparations and doses. Welt, working with guinea pigs and frogs found that the Chlorhydrate of Senecefoline slows the heart's action, and when given...
in lethal doses stops the heart in Erythrina. He considers its action is somewhat similar to curare. Guillieret and Toussaint isolated a fatty acid from S. Canicida, which in doses of 200 mgms was fatal with strychnine-like effects to a small dog; age and sex not given. Later, Bunch found that intravenous injection of 0.2 gm of the drug into a dog weighing 6 kgs, induced a slight rise of blood pressure, and in larger doses, vasoconstriction dilatation of the small intestine with a subsequent fall of blood pressure.

In 1910 Cushing studied the possibility of this plant being the causative factor of the disease of cattle and horses known as Mollino, Winton, or Paclow disease. Throughout his experiments he used the alkaloids prepared for him by Watt (q.v.) He tested the substance upon frogs, white rats, rabbits, and cats. The results which he obtained in all animals were similar. In frogs for the first few days no specific symptoms were noted; these appeared gradually after varying intervals of from 5 to 15 days. In some cases the first effects were hemoptysis and collapse; in others, strychnine-like spasms developed, but some of his animals appeared persistently normal. Two series of symptoms were shown by the cat, small doses produced salivation and diarrhoea, with vomiting if the dose was larger (0.2 gm per Kg). These preliminary symptoms passed off in 24 to 48 hours, and the animal appeared normal. In from 3 to 7 days there appeared diarrhoea, anorexia, and a marked loss in weight which was soon followed by coma and respiratory failure. The average lethal dose for cats was 0.05 gm per Kg. In rabbits and rats there were no early symptoms, secondary symptoms resembled those in cats.

Upon post mortem examination he found evidence.
of haemorrhage in the intestines and lungs, and a well established necrosis throughout the liver substance. In every case he appears to have focussed the main action of the alkaloid upon the liver. Save in one instance, he does not appear to have found a definite cirrhosis - only signs of necrosis, and an abundant round-celled infiltration.

The effects of chronic poisoning by Senecio were shown in experiments upon one young cat and one rat. It should be noted that no symptoms were induced until more concentrated lethal doses were given to the cat, and that the longest experimental period that any of the animals survived was 41 days.

From the foregoing conflicting evidence, it is obvious that there is no general agreement as to the pathological action of this group of plants. In the investigation here described, I have endeavoured to determine the rôle, if any, played by Senecio in the production of hepatic cirrhosis.

By following the lines indicated by Professor Beshy's experiments, it was thought that there might be a possibility of explaining human cirrhosis of the 'hot-nail' type, commonly reputed to be due to alcohol, on the grounds of an insidious ingestion of the alkaloids of groundsel and ragwort. Two lines of inquiry were thus suggested. Firstly, to determine the rôle, if any, played by Senecio (as noted above), and secondly to search in the literature dealing with brewing and the culinary art for evidence of the use of Senecio as a herb.

The Source of the Material

All specimens of the Groundsel and Ragwort used in the experiments were identified at the Botanical School, Cambridge.
The alkaloids were prepared by me in accordance with the procedure described by Watt (q.v.) not only from the whole plant, but also from selected separate portions. In addition, the plant itself was administered in the form of a powder enclosed in gelatine capsules, in the moist form and as tinctures supplied by two leading manufacturing chemists. The administrations of the crude preparations was effected by the mouth, whilst purified alkaloids were also given to rabbits by intravenous injection. In the case of the more concentrated extracts, the intravenous method could not be adopted, owing to the presence of particulate matter in such extracts even after neutralising and filtering. These were therefore given by the mouth.

The animals used.

The animals used for this investigation were white mice, guinea pigs, and rabbits. The livers removed from each experimental animal were compared with those of normal animals from stock. Each animal was weighed at a fixed hour, as their weights were found to fluctuate considerably according to the time of day. The duration of the experiments varied from 34 to 170 days. Upon death, whether induced or spontaneous, the bodies were subjected to careful post-mortem examination, and the tissues prepared for histological examination.

Histological technique.

The tissues were cut in small pieces, 1 mm. x 2 mm., and fixed in the picric formal mixture of Bouin, dehydrated in alcohol, and rapidly embedded in paraffin.
Report of Experiments.

The following are typical protocols of my experiments.

Experiment I. Four guinea pigs (Cavia Porcellus) were fed on S. Vulgaris, collected in February. The dried powder, 1:75 of the moist plant, was administered in gelatine capsules. Of this group, one died.

Protocol 1. Number of animal 2.

<table>
<thead>
<tr>
<th>Day of Experiment</th>
<th>Weight</th>
<th>Dose</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>660 gms</td>
<td>2 gms</td>
<td>No salivation. No early symptoms</td>
</tr>
<tr>
<td>8th</td>
<td>700</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>16th 17th 23rd 26th</td>
<td>740</td>
<td>1 each day</td>
<td></td>
</tr>
<tr>
<td>36th</td>
<td>740</td>
<td></td>
<td>(No further administration of drug.)</td>
</tr>
<tr>
<td>68th</td>
<td>740</td>
<td></td>
<td></td>
</tr>
<tr>
<td>82nd</td>
<td>740</td>
<td>165</td>
<td>Found dead, no cause ascertainable</td>
</tr>
</tbody>
</table>

Total dose equals 7 gms of the dried powder, = 0.1 gm per Kg.

Post-mortal examination showed the guinea pig to be in an advanced state of pregnancy. The thymus gland was much enlarged, equal in size to the heart, which with the lungs were normal. The liver showed typical nutmeg congestion with greyish areas, its weight being 25 gms. The gall bladder was thick walled, and contained a watery brownish liquid. The kidneys were pale and weighed 36 gms each. The suprarenals, weighing 15 gms each, were much enlarged and congested. (The normal weight being 0.6 gms.) The mucous membrane of the stomach was normal. The uterus, containing two foeti showed inflammation of the peritoneum.

Microscopically, the liver showed slight congestion. gelatine frozen sections showed no increase of fat. The cells and nuclei stained well. There was a slight even infiltration of round cells over the whole...
whole organ, little clusters of two or three being found at the portal spaces. There was no further evidence of new connective tissue formation.

The fetal liver, unfortunately was not fixed until the next day. Microscopic examination showed poorly stained cells and nuclei, the whole substance was invaded by an evenly distributed round cell infiltration. No comparison with the normal was available during the time of the experiment.

Protocol 2. Number of the animal - 1.

Day of experiment. Weight. Dose. Results.
8th 580 " 2 9m. "
26th 590 " 3 " No more drug given.

The weight on the 69th day was 620 gms, on the 84th, 680 gms; on the 100th, 660 gms; the 118th 660 gms, the 128th 650 gms and on the 161st 610 gms. It was killed on the 170th day, its weight then being 575 gms. The weights of most of the experimental animals fell during the drought this summer, and after such a period of time elapsing from the last dose as to eliminate the drug as the causal factor.

All the organs appeared normal on post-mortem examination; the liver weighed 199 gms and each Kidney 2.2 gms.

Microscopic changes.- The cells and nuclei of the liver stained well. No evidence of a round cell infiltration was seen nor any abnormality in the bile ducts large or small. Animals 3 and 4 showed similar post-mortem and microscopic appearances.

Experiment II. Three guinea pigs (numbers 5, 6, 7) of an approximate weight of 350 gms were fed on 50 gms of fresh Senecio vulgaris, mixed with oats and water, from the 14th to the 18th March inclusive. The dose corresponds to 5 gms of the powder daily, allowing for wastage.
Protocol 3  Number of Animal 5.

In all 25 gms (approximate) of the dried powder were given by the mouth. Its weight at death (spontaneous) was 350 gms showing a loss of 20 gms during the 34 days of the experiment. Post-mortem examination showed a single large abscess of the liver, otherwise the organs were of normal appearance.

Microscopic examination of a section of the liver through the abscess cavity showed a typical appearance. The cavity was filled with the debris of liver cells, of blood corpuscles, and polymorphonuclear leukocytes, and was surrounded by four or five layers of connective tissue. Other sections showed the liver cells and their nuclei staining well. There was no congestion and no abnormal increase in the number of round cells, one or two of which were seen in each field near the central vein, in addition to the elongated nuclei of the cells lining the sinusoids. The epithelium of the bile ducts appeared normal.

On the 44th day of the experiment, the weight of No. 6 was 350 gms, and of No. 7, was 320 gms. No. 6 was kept as a control, and No. 7 continued its daily feed from the 85th day to the 140th day. Both were killed on the 144th day of the experiment.

Protocol 4  No. of Animal 7

Before post-mortem examination the animal appeared in good condition and weighed 680 gms. The heart, lungs, and liver, appeared normal. The liver weighed 19 gms, was of firm consistency, and easily cut; a small area was adherent to the right kidney. The kidneys were pale, weighing together 4.6 gms. The mucosa of the stomach and intestines showed no submucous haemorrhages. The spleen was granular in appearance, showing grey areas on section.
The testes were embedded in layers of fat. Microscopic examination showed that the cells and nuclei of the liver stained clearly. There was no increase of lymphocytes, nor of connective tissue, and no abnormally was noticed in the bile ducts. The spleen showed an apparent increase of muscular tissue round the Malphigian corpuscles. The cells of the kidney stained poorly, and no other change could be detected.

The control animal (No. 6) showed similar appearances.

Experiment No. III. Five young mice, (Nos 8, 9, 10, 11 and 12), were injected subcutaneously with an extract (No. 11) of S. vulgaris, prepared as follows: 10 gms of S. vulgaris, collected in February, was dried in the open, powdered, and extracted in a Soxhlet apparatus with absolute alcohol for six or seven hours. Walt's method was followed until the 2nd extraction with 2% hydrochloric acid. The solution was then neutralised, and made up to 100 cc of 0.8% saline solution, 1 cc - 0.001 gm of alkaloid approximately; if 1% alkaloid be present. (vide Ashby.) On testing the solution with Meyer's reagent, a faint opalescence was obtained; and with ferric chloride and ferric cyanide, a faint prussian blue colour was obtained.

Protocol V. No. of the animal 10.

The initial weight of the animal was 22 gms. A single dose of 0.001 gm, corresponding to 0.2 gms per kg, was given subcutaneously. No symptoms were at any time induced, and the mouse was killed on the 4th day.

Postmortem examination showed all organs normal. Microscopic examination of sections of the liver, kidney, and spleen showed no observable pathological changes.
The cells and nuclei of these organs stained well. There was no congestion, or round celled infiltration present, nor any other evidence of new connective tissue formation.

The urine of this group of animals was tested for albumen. Esbach's albuminometer and reagent was used. Albumen was present up to 16 gms per litre. As a control, 10 normal mice were put in a urine cage, draining into a filter packed with glass wool. The urine tested in the same way gave 3.75 gms per litre.

Experiment IV. Three mice (numbers 13, 14 & 15) were given subcutaneous injections of 1/2 cc of Allen & Hanburys extract of S. Vulgaris. This amount was equivalent to 12 gms of the dried powder, and would correspond to a dose of 0.25 gms per Kg.


The initial weight was 18 gms. The total dose amounted to 1/2 cc given in 8 days. The mouse was killed on the 30 1/2 day; prior to that, it was in good condition and weighed 19 gms.

Postmortem examination showed the spleen to be enlarged and congested; it weighed 4.2 gms. The liver was normal in appearance as were the other organs.

Microscopic examination; the cells and nuclei of the liver substance stained well. No congestion, no infiltration of round cells, and no evidence of increase of connective tissue was present.

Experiment V. One rabbit (No 16) was used in this experiment.

Protocol 7. No. of the animal 16.

The initial weight of the rabbit was 400 gms. Intravenous injections of 5 mgs were given on the 1st, 4th, 6th, and 13th day. The weight now recorded was
800 gms. A further 30 mgms was given on the 16th day; 10 mgms on the 24th; and 15 mgms on the 36th day. The weight was now 900 gms. No symptoms of any kind were noted, but the rabbit turned very ill-tempered. From the 36th to the 51st day, the animal was given as much fresh groundsel as it could eat (about 1 lb per day allowing for wastage), besides a small amount of oats. The weight had increased to 1420 gms by the 91st day. On the 96th day, an extract prepared as before, (q.v.), from 200 gms of the dried and powdered leaves of S. Vulgaris was given by the mouth at short intervals. No symptoms were observed to follow the administration of the above extract, and up to the 110th day the animal appeared normal and had not lost weight.

Experiment VI One rabbit (No 17) was used for this experiment.

Protocol 8 No. of the animal 17.

The initial weight was 1140 gms. The rabbit was fed on approximately two pounds (2 lb), allowing for wastage of S. Jacobea daily; besides this an allowance of oats was frequently given. The whole plant was used, and in all stages of growth, from young seedlings to flowering and seeding plants. Feeding was continued until the 48th day of the experiment, oats and grass being given after this date. Between the 8th and the 22nd day, an extract from 100 gms of the dried and powdered leaves of S. Jacobea was injected intravenously. The weight recorded on the 22nd day was 1250 gms. On the 66th day the extract from 260 gms of the dried and powdered aerial portions of S. Jacobea was administered. Only 3 cc was given intravenously, as the solution was thick, and contained precipitated matter in spite of filtering. The remainder was given by the mouth. No symptoms were observed to follow this administration. The rabbit...
rabbit was apparently normal when killed on the 78th day; the weight being 1280 gms. A total dose of over 360 gms of *Succisa* had been administered and no unusual symptoms noted. During this period the weight had increased by 15% per cent.

Postmortem examination showed a normal appearance of all the organs, the liver was of a dark red color, smooth, and on section, cut with a sensation of toughness, and weighed 36 gms. The kidneys were very pale, and weighed 3.6 gms each.

Microscopic examination showed no trace of a round-celled infiltration, nor of an increase in connective tissue formation. The cells and nuclei of the liver substance stood well, and the portal spaces appeared normal in structure.

**Experiment VII.** One rabbit No. 18 was used for this experiment.


The initial weight was 7100 gms. This rabbit was kept with the preceding one and similarly fed, and on the 32nd day weighed 1180 gms. On the 60th day an extract from 25 gms of the powdered roots of *S. Vulgaris* extracted as above (q.v.) was administered, 10 cc being given intravenously and 10 cc by the mouth. Tested with Meyer's reagent, an alkaloidal reaction was strongly positive and when titrated against 1% morphine solution the percentage of the alkaloid present corresponded to about 0.1% to 0.2%. The weight remained stationary, about 1200 gms. No symptoms were observed. It is noteworthy that none of the rabbits or guinea pigs feeding on fresh *Succisa* died during the drought this summer, although over 50% of the stock or other experimental rabbits succumbed.

The rabbit was killed on the 78th day apparently normal, after a total dose of over 50 lbs of fresh plant
and 2.7 gms of the dried powder. The weight at death was 1200 gms, again of 10% during the period of the experiment. All organs appeared normal on post-mortem examination. The results of both this and the microscopic examination were very similar to those of No. 17 just described.

Resume of Experiments.

Out of a total of 15 animals, 16 appeared normal in every respect; of the remaining 2, the only suggestion of a cirrhotic lesion consisted of a slight round-celled infiltration in the portal fissures and spaces in the liver of one pregnant guinea pig. Here however, the liver cells were normal and the vascular and biliary capillaries showed no pathological change.

Discussion

The conclusions drawn by the previous investigators mentioned, viz. that Senecio poisoning is a direct cause of cirrhosis of the liver, appear to lack support justifying them in their entirety. The causal factor and its effect do not seem to be sufficiently correlated, and too much reliance is placed on circumstantial evidence.

A government commission in 1882 failed to connect the cirrhosis with the ingestion of the Senecio plant, and the disease was thought to be infective in nature. Gilmour, working in New Zealand, observed that cattle affected by cirrhosis of the liver had been eating ragwort. A steer, a cow, and a horse which had been pastured upon land badly affected by ragwort dying in 3, 4, and 4.4 months respectively. He based his views on experiments upon two calves which died soon after partaking of 108 lbs. each of ragwort cut and dried when in flower, during a period of 18 days, and upon one horse which died after being fed for 85 days
upon 93 lbs. of dried ragwort. No mention is made of control animals having been used, nor of what other food the experimental animals had during the period of his investigation. At the same time, two sheep fed with upon half a pound of ragwort for six months, showed no lesion of the liver upon microscopic examination. His conclusion as regards sheep was that ragwort was usually non-poisonous. He also drew attention to the fact that horses naturally avoid the weed. Pethick, working in Canada, based his views upon observations upon a herd of 32 cattle. Sixteen of these served as control animals, and were housed as in a byre previously occupied by diseased cattle, and were fed upon hay from Quebec. The remaining sixteen which served as the experimental subjects were fed with hay from Brome which contained amongst other things a certain amount of ragwort. These sixteen died within twelve months. Another fed on Quebec hay mixed with ragwort, died in twelve months with acute cirrhosis, while a control, fed on Quebec hay alone, remained healthy. Bhase found only four ounces of 3 Burchell's given on 4 successive days to an ox caused death on the fifth day, -- a very different sequence to that shown by Gilruth and Pethick. The diagnosis of cirrhosis of the liver was based upon microscopic appearance only. Of the animals described by Cushing, only two appear to have survived over a month, one of these being a cat, and the other a rat. The longest period of the experiment was only 41 days, a very short period in which to develop cirrhosis of the liver.

As is now recognised, livers of cats are peculiarly variable as regards the amount of fibrous tissue developed in their substance under normal conditions. The liver from many apparently normal cats displaying at least microscopically, a markedly cirrhotic condition, and suggesting upon cutting an appreciable toughness of structure. Stirling and Conclusions appear to have been founded on observations upon
upon an outbreak of disease affecting a herd of cattle in which 50% died after they had fed for 33 days upon hay containing S. Jacobea. Pathomtor examination of one of the cows revealed a fine cirrhosis of the liver. His observations were not supported by experimental inquiries, and there was no direct proof that the outbreak was due to Senecio poisoning. Robertson and Heilmot describe a disease apparently due to Senecio poisoning, endemic and epidemic in certain parts of S Africa. The disease occurs in the homes of the poorer white population, and is ascribed to the adulteration of wheat flour with S. heliosorus. Experimentally, of twelve guinea pigs fed with the weed for 10 weeks, one died, a not unreasonable normal death rate. Senecio is not commonly found growing with cereals in this country, and the two species examined by me did not produce the acute typhoid-like symptoms noted by the above two workers.

The most recent published investigation is that of Craig and Kehoe who found symptoms corresponding to Winton disease, and at post-mortem a typical cirrhosis of the liver in three horses. These had been at pasture in fields definitely known to be no more infested with ragwort than other parts of the district and there was no evidence that the animals partook of the plant in question, nor did they avoid it naturally. Craig and Kehoe could not differentiate the conditions they found from those occurring in Moltino disease.

In many parts of this country ragwort is given to rabbits as an aphrodisiac in accordance with old established beliefs in its virtue and without any known ill-effects accruing. In New Zealand and elsewhere, it is a practice of stockkeepers to clear their land of Senecio by grazing sheep, and these show no ill-effects, unless the animals are fed almost exclusively on ragwort for very long periods, when the flesh occasionally becomes yellow.
We set out to determine whether cirrhosis was produced or not, as by direct stimulation of the round cells by the alkaloid, or by the products of disintegration of the liver cells, which have been described by Lushy. By setting up changes in the stomach and intestinal canal, similar to those ascribed to alcohol and other irritants which cause chronic gastritis and enteritis. Changes which open the portal of entry for bacteria, or conduc to the accumulation of toxins which may be absorbed from the alimentary canal. In all our experiments the evidence was entirely negative. We found no acute or chronic inflammation of the mucus membranes, no necrosis of the liver cells, no increased activity of the round cells or of the cells of Glisson's capsule, or indeed any of the changes usually associated with anoxia. The kidneys likewise showed no change.

From this investigation I have come to the following conclusions. S. Jacobaea or S. vulgaris gathered in this country does not induce cirrhosis of the liver in mice injected subcutaneously, guinea pigs fed by the mouth, or rabbits either fed by the mouth or injected subcutaneously or intravenously, even after an experimental period of 140 days. No animal died as the result of the exhibition of the drug with the one possible exception of a pregnant guinea pig. With this one exception all the animals used appeared to have thrived rather than to have lost weight. Sermici as given as above does not appear to exert any recognisable toxic action, not to produce any pathological lesions in the above animals. In a more recent observation Lushy states that it is extremely unlikely human beings are ever endangered by the possible ingestion of Sermici and this is certainly borne out by the above research.

I am very grateful to Professor Sir German Sims Woodhead.
for his unfailing help and criticism throughout the research, and to Dr. Henwood Harvey for invaluable advice.

The expenses of this research were partly defrayed by the John Lucas Walker Trust.

Bibliography

5. Hills Herbal. 1756.
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Numerous ancient and modern works dealing with cooking, brewing, and the cultivation of fungi were consulted, but no reference to bunio was found.