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The mummy of Cangrande della Scala Lord of Verona (1291-1329): A case of Medieval acute *Digitalis* intoxication

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On 18 July 1328 the entrance of Cangrande, Lord of Verona to the city of Treviso represented the crowning achievement of his long struggle to submit the entire region of Veneto (northern Italy).

However, his triumph was marred by the fact that he had become seriously ill as a result, according to contemporary accounts, of a fever with vomit and diarrhea, which he had contracted a few days before by drinking from a polluted spring.



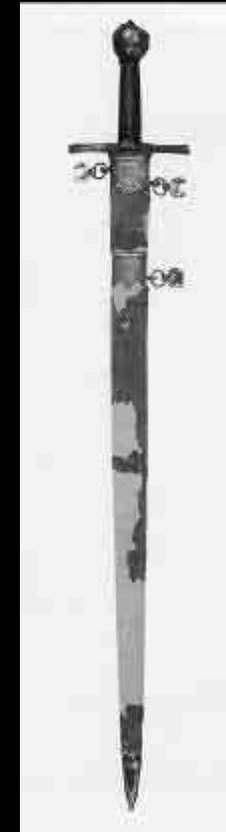
As soon as he arrived at his lodgings he took to his bed and in the morning of July 22 he died, after having first settled his affairs at his best. Rumors of poisoning immediately started to spread.



In the year 2004 Cangrande's tomb was opened to allow a paleopathological study. When the very heavy stone lid of the sarcophagus was raised, a well preserved body appeared.



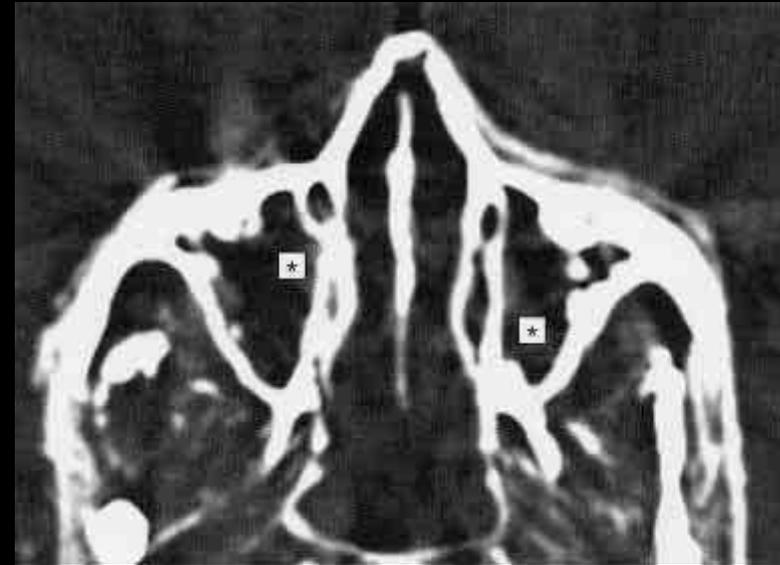
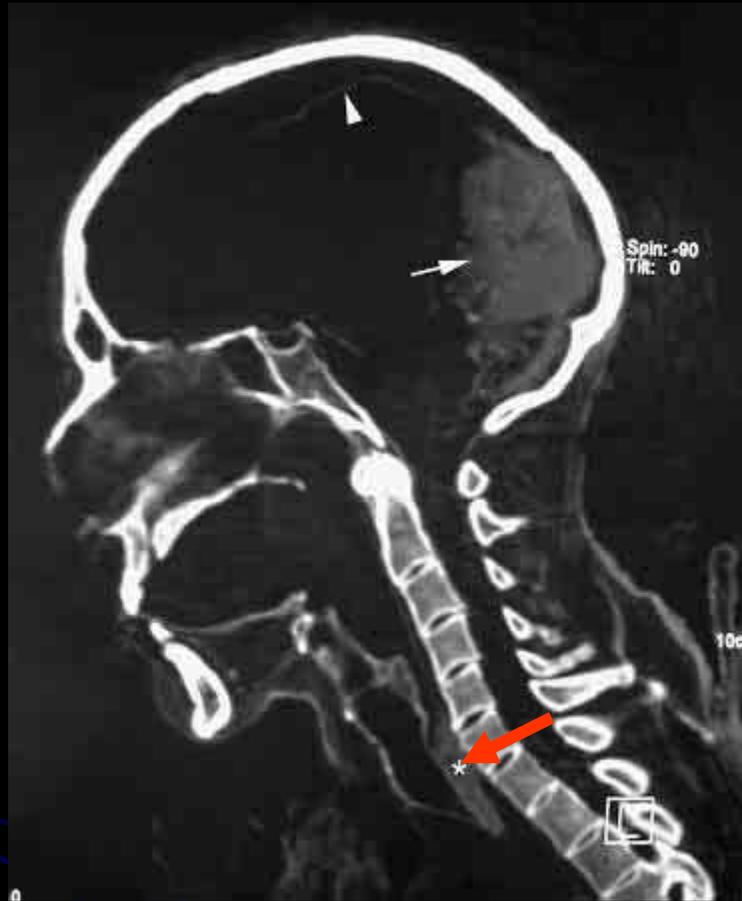
At the beginning of the autopsy, Cangrande's body appeared wrapped in precious silk textiles and was still wearing some clothes. He was lying on his back with his arms folded across the thorax and his lower limbs extended.



This is the reconstruction of the magnificent mantle of Cangrande and of his sword, found in 1921, during a past recognition.



At first, the mummy of Cangrande was studied by digital radiography and by volumetric CT.

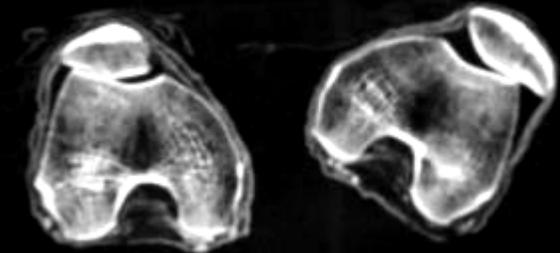


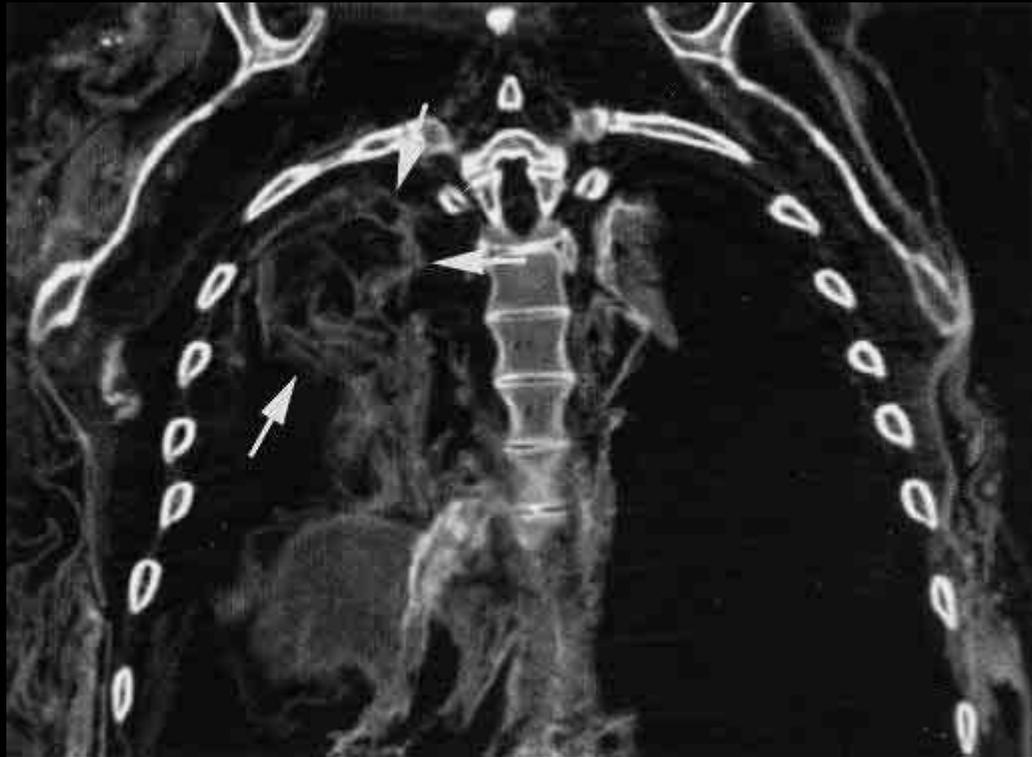
Some dense material appears in the esophagus lumen (red arrow), consisting in alimentary material, regurgitated immediately before death. Maxillary sinuses are partially occupied by dense, inhomogeneous material (black stars), as a possible result of chronic sinusitis.



Mild arthritis of the column, elbows and hips, and also meniscus calcification of the knees, can be related to the strong physical activity of the Prince, as knight and soldier.

The *rotulae* appear laterally dislocated owing to a typical taphonomic process of initial decomposition in an empty space.

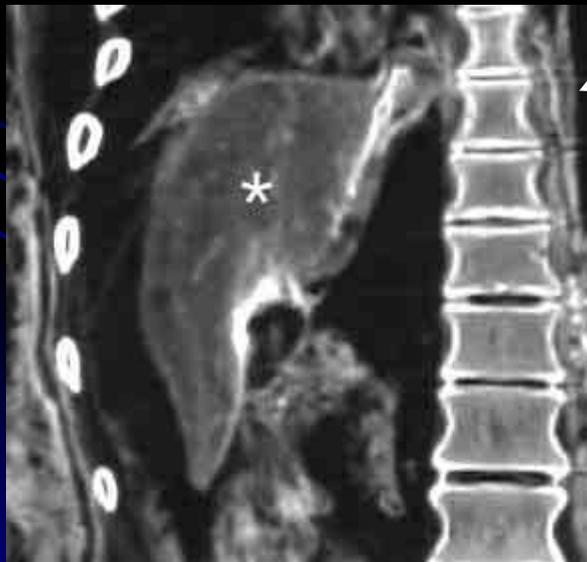




The right thoracic cavity shows some residuals of the lung (arrows), formed by some irregular cavities surrounded by dense fibrous tissue. These cavities can be interpreted as emphysematous *bullae*, delimited by fibrous septa.

Abdominal CT shows:

- good preservation of the liver, positioned in the right thoracic cavity, with its typical anatomic shape;
- presence of feces in rectal *ampulla*.





At the moment of autopsy the abdomen appeared very expanded, probably due to putrified changes. The skin showed a dark brown color at the head and legs, light brown under the clothes. The soft tissues of the face appeared preserved, with retracted lips revealing the upper anterior incisors and a flattened nose. The incisors showed some enamel hypoplasia lines. The hair was curly and brown. The stature was 1.73 m.

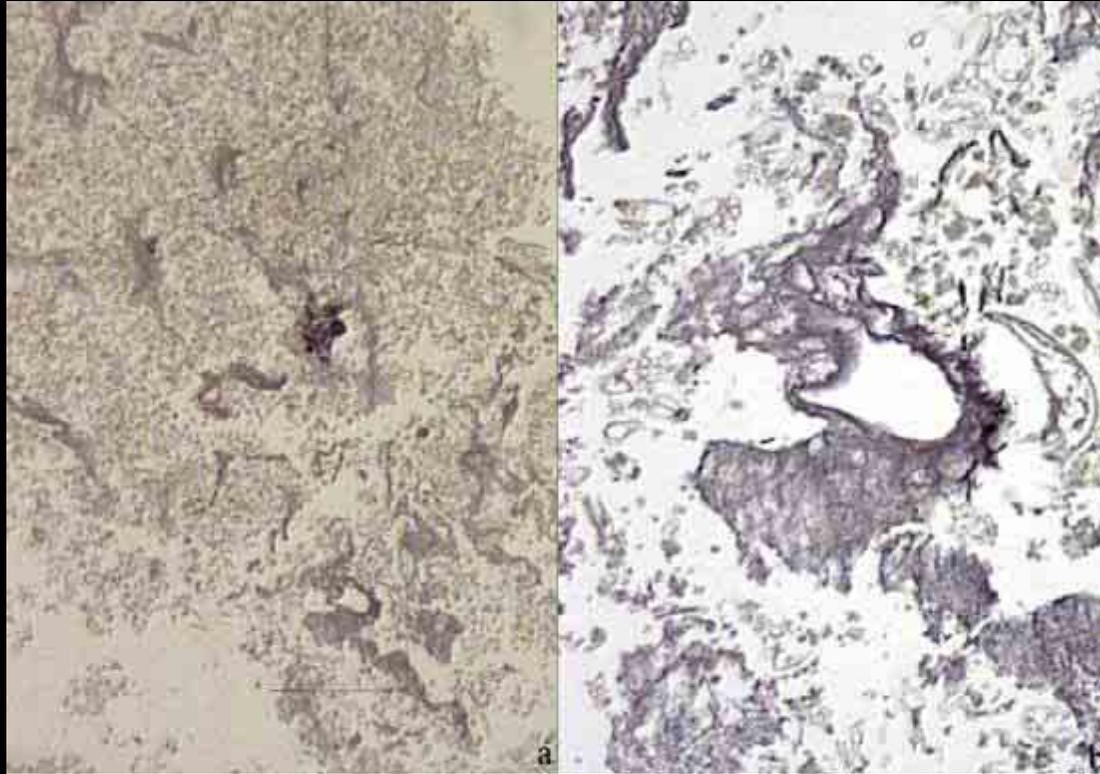


To avoid damage to the mummy, autopsy was performed by a circular opening of the abdomen, from the sternum to the pubis, which allowed us to reach the abdominal and thoracic cavities.

The viscera appeared totally collapsed on the posterior wall, forming an omogeneous layer of about 5 cm. Samples for histology were collected according to the topography of the organs.



The liver was highly positioned in the right thoracic cavity under the hemidiaphragm, and showed a typical anatomic shape, with a transversal diameter of 30 cm, antero-posterior diameter of 15 cm, and a weight of 220 g.

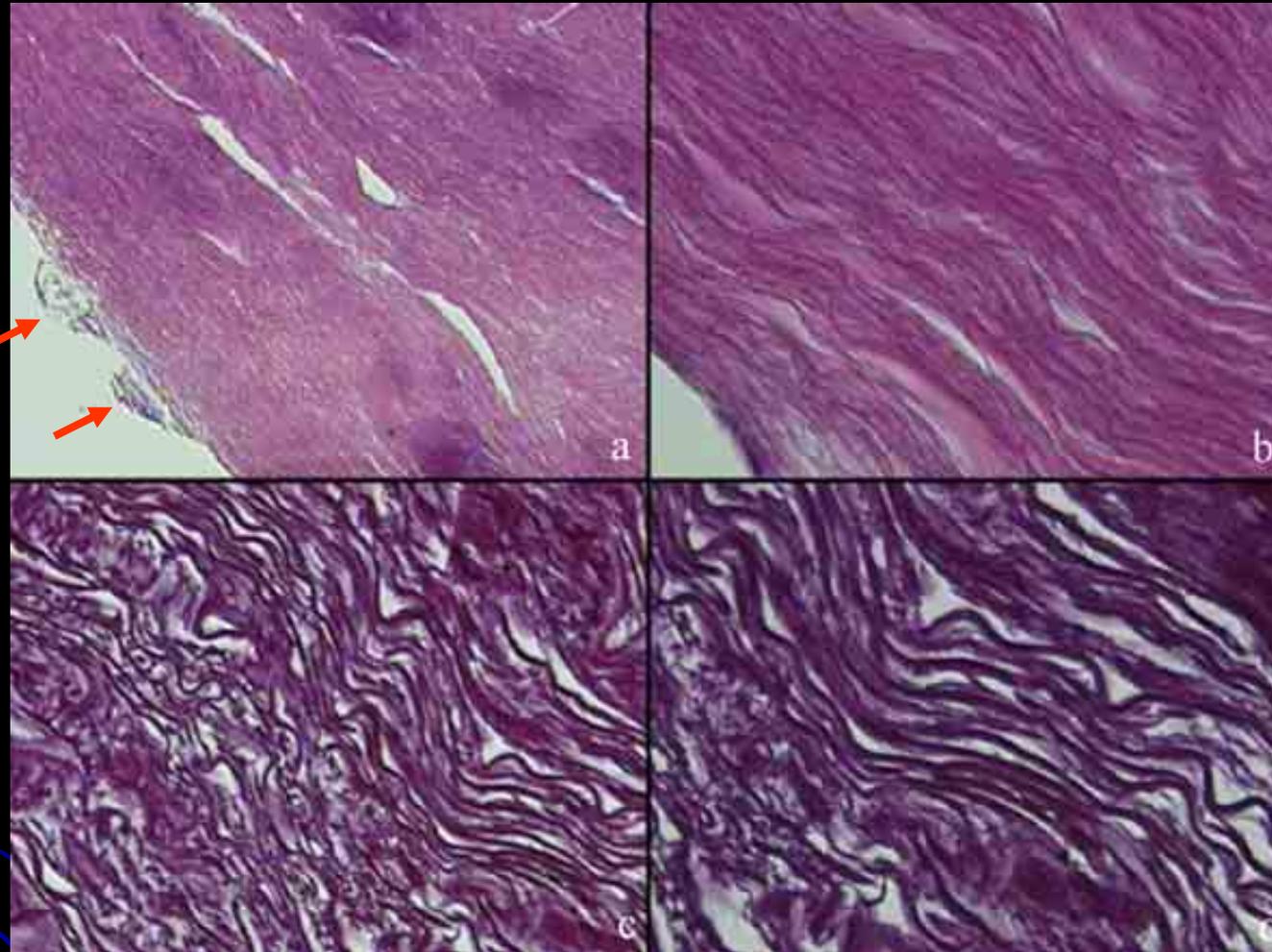


Hematoxilina eosin 10X, 50X

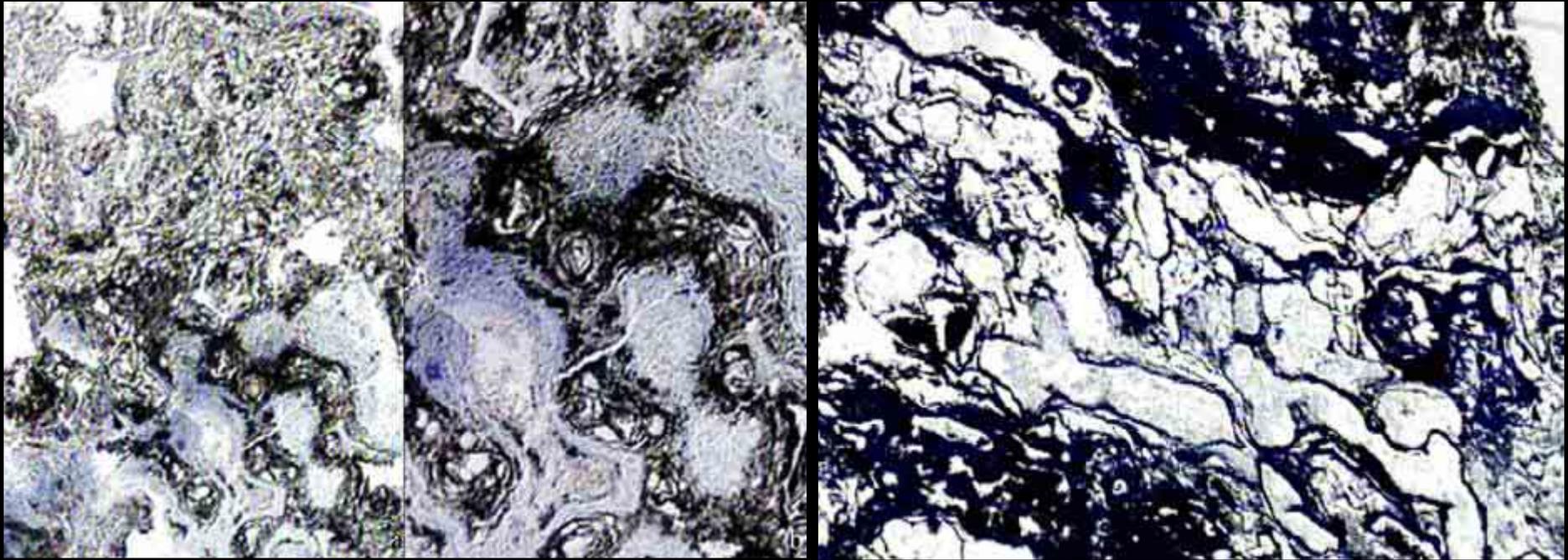
Histology of the liver shows a hepatic tissue with many collapsed fibrous portal zones close, but not confluent to each other, by liquefaction of the hepatic cells (a).

Portal area with fibrosis surrounding a dilated vessel (b).

These findings can “create the illusion of a pattern of interconnected, proliferative portal areas suggestive of cirrhosis” (Aufderheide).



Histology of the aorta reveals a small atheromatous plaque on the luminal surface. The aortic media is well preserved, with regular layered patterns of elastic tissue and lamellae, stained by Weigert's method.

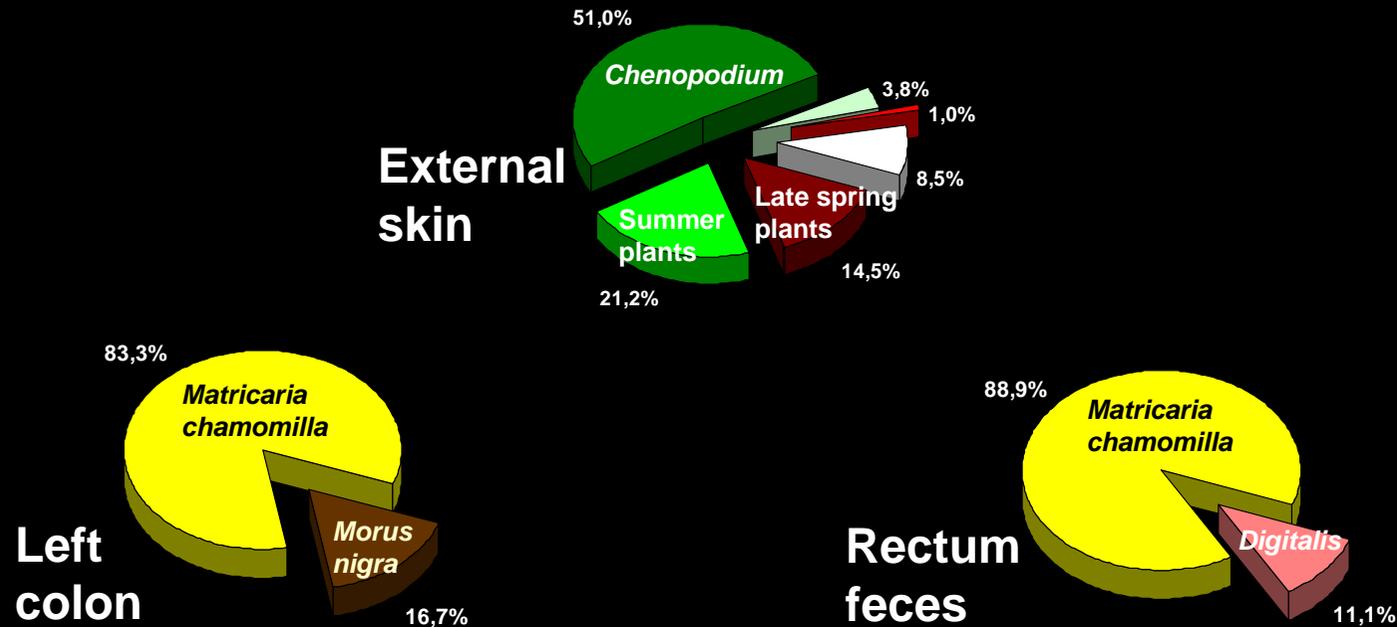


Histology of the right lung shows areas of collapsed alveoli with fibrosis and fibro-hyaline nodular formations, surrounded by massive anthracosis (left). The pulmonary tissue surrounding two fibrous and anthracotic areas appears to be still expanded, with dilated and confluent alveoli, destruction of the septal walls and presence of cell-rich exudate in the lumen (right). This is a classical picture of irregular emphysema.

The severe anthracosis, very similar to a “coal workers’ pneumoconiosis”, is easy to explain because the palaces of the late Middle Ages were heated with large braziers, resulting in very smoky environments.

The nodular fibrosis of the lungs could attest the results of lung tuberculosis, a very common disease in the crowded and unhealthy Medieval towns of those times.

Pollen analysis



The pollens on the external skin derive by external application of chenopodium - probably in the form of an ointment - and by pollinic rain at the moment of the prince's death (late spring and summer plants). Internally there is a large quantity of pollens of chamomile, black mulberry and, totally unexpected, of foxglove (*Digitalis sp.* perhaps *purpurea*) in the feces.

In the Middle Ages chamomile was largely used *by os* as sedative and antispasmodic, and black mulberry as astringent; on the contrary foxglove was considered only a poisonous plant.

	Method	Sensibility ng/ml	Precision C.V.%
DIGOXIN	Digoxin IMMULITE® (immuno-competition)	0.1	3.5-5.7
	Digoxin Tina-quant® (immuno-competition)	0.15	2.7-4.5
	Digoxin Assay Emit®2000 (immuno-enzymatic)	0.2	2.0-4.4
DIGITOXIN	Digitoxin IMMULITE/IMMULITE®1000 (immuno-competition)	0.65	3.9-4.6

In order to establish the presence of digoxine and digitoxine in samples of liver and feces, immunochemical methods with different antiserums were used, to minimize the risk of errors caused by cross-reactions.

	<i>Digoxin-DPC</i>	<i>Digoxin Roche</i>	<i>Digoxin Syva</i>	<i>Digitoxin-DPC</i>
<i>LIVER (ng/g)</i>	14.0	5.6	16.8	62.4
<i>FECES (ng/g)</i>	15.6	7.2	11.2	41.6
<i>Toxicity (ng/ml)</i>	2.1-8.7	>2.0	>2.0	>45

After rehydration of the samples, the tests made it possible to identify compounds immunoreactively similar to two glycosides of *digitalis* in toxic concentrations, of the order of tens of ng/g in the two samples.



Digitalis purpurea

Conclusions

1. the concentrations of digoxine and digitoxine in the liver and in the feces of Cangrande are toxic;
2. digoxine and digitoxine are the active principles of *Digitalis* (*Digitalis purpurea* and *Digitalis lanata*);
3. the origins of intoxication are to be searched in the oral administration of an infusion or decoction of *Digitalis* (leaves and flowers);
4. the gastrointestinal symptoms manifested by Cangrande, characterized by vomiting and gastroenteric irritation with diarrhea, as reported by the sources with great clinical details – *corporei fluxus stomachique doloris acuti, fluxu obiit, fluxu ventris et febre ob laborem exercitus* – are compatible with the early phase of *Digitalis* intoxication;
5. deliberate poisoning under the guise of medical treatment is probable;
6. one of Cangrande's physicians was hung by his successor Mastino II, emphasizing on this possibility.

