



dialysers would have to be discontinued for the same period. These measures would severely disrupt the delivery of dialysis support to patients and would also lead to greatly increased costs (R200 000 - R300 000) due to the suspension of re-use. Therefore it would be important to consider any measure that could further reduce the risk of infection. The fact that hepatitis B vaccination has minimal adverse effects and results in cost saving means that it can be recommended even though the response rate is lower than in healthy subjects and additional benefit is difficult to prove in our setting.

We conclude that all patients should be screened for hepatitis B antibodies and vaccinated as required on or before commencement of haemodialysis.

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## TUMOURS AND CANCERS IN GRAECO-ROMAN TIMES

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In Graeco-Roman times all tumours (Greek: *onkoi*, abnormal swellings) were considered to be of inflammatory origin, the result of unfavourable humoral fluxes, and caused by an extravascular outpouring of fluid into tissue spaces. The neoplastic nature of tumours is a more recent concept, barely two centuries old. In Hippocratic literature tumours were mainly classified as *karkinomata*, *phumata*, and *oidemata*. *Phumata* included a large variety of tumours, inflammatory and neoplastic in origin, and mostly benign (in modern terms), while *oidemata* were soft, painless tumours and even included generalised oedema (dropsy). Although all categories possibly included occasional cancers, the vast majority of what appears to have been malignant tumours were called *karkinoi karkinomata* (Latin: *cancrum/carcinoma*). There was, however, no recognition of benign and malignant, primary and secondary tumours, in the modern sense.

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Herodotus tells us that at the turn of the 6th century BC, Atossa, the wife of Darius the Great, was cured of a breast tumour (*phuma*) by a captive Greek physician, Democedes.<sup>1</sup> The readiness with which Democedes promised a cure and the ease with which he attained this, points to a benign breast tumour rather than a cancer.<sup>2</sup> The Hippocratic writings mention a woman from Abdera who had a breast tumour and a bloody discharge from the nipple; she was diagnosed as having a *karkinoma* and died of the lesion.<sup>3</sup> This was most likely a cancer as we know it today. However, the Graeco-Roman theories of tumour formation and carcinogenesis differed radically from our modern concepts, which originated as late as the 19th century. In the present study the theories of tumour formation in antiquity, and the nature of tumours reported, are reviewed.

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## THEORIES OF TUMOUR FORMATION

In antiquity all tumours were considered to be of inflammatory origin and were explained with reference to the humoural theory, in vogue since early Greek times.<sup>2</sup> According to Celsus's classical description, inflammation was characterised by pain (*dolor*), redness (*rubor*), heat (*calor*) and swelling (*tumor*).

However, pain, redness and heat were gradually restricted to 'exquisite inflammation' near a body surface, while *tumor* was accepted as indicative of nothing more than abnormal swelling or mass (still caused by *inflammatio*). This remained dogma as late as the 18th century.<sup>2</sup>

According to the humoural theory all matter originated from four universal elements: fire, air, water and earth. These elements were brought into relationship with four basic qualities (*dunameis*): hot, cold, moist and dry. The Hippocratic writers then associated these *dunameis* with their four bodily humours, namely phlegm, blood, black bile and yellow bile. The precise associations fluctuated with time, but were eventually finalised by Galen and thereafter remained unchanged for 1 500 years: blood was associated with hot and moist (air, spring), phlegm with cold and moist (water, winter), yellow bile with hot and dry (fire, summer), and black bile with cold and dry (earth, autumn). According to Galen, perfect health depended on the right mixture (*eukrasis*) of hot, moist, cold and dry, and illness was caused by an imperfect balance (*duskrasis*).

The humours originated from ingested food. Through the process of *pepsis* (or *concoctio* in Latin), facilitated by cooking, digestion and subsequent maturation in blood vessels and body tissues (under the influence of predominantly innate body heat), the humours evolved. Digested food (*chulê*) was absorbed into the portal vein and liver where yellow bile (*cholê*) was formed. The earthy, cold components of nutriment were converted to black bile (*melaina cholê*) by the spleen to strengthen the body fibres. Blood was the most important humour and phlegm was mainly a waste product.

The circulatory system (nourishing the body parts) consisted of arteries (which carried heat and *pneuma* or spirit, derived from inhaled air) and veins (which conveyed blood, as well as the other three humours in varying mixtures depending on local or systemic circumstances). Between arteries and veins were specialised anastomoses which only opened under certain abnormal conditions, e.g. fevers or trauma, pouring blood into arteries with resultant regional congestion, and interference with peripheral delivery of *pneuma*. Venesection allegedly alleviated this. Galen later showed that arteries did contain blood and not air, but this did not cause him to change his views on inflammation.

Galen postulated that moist inflammation, *inter alia* responsible for tumour formation, arose from a 'flux of humours'. This entailed an abnormal congestion and mixture of these substances in response to stimuli such as fever, injury,



THE Classical Greek theory that all materials were made up of four "elements" persisted among philosophers—and doctors—as late as the sixteenth century when this manuscript picture was drawn.

The four elements, basis of the humoural theory (from a 16th century manuscript).

fractures and over-exertion, in a localised region of the body. Depending on the humoural mixtures, the type of inflammatory response would differ, e.g. with excessive yellow bile herpes developed, erysipelas was caused by very hot bile, anthrax arose from thick hot blood, and *oidêma* from excess phlegm. A flux of blood and black bile caused scirrhus, capable of converting into cancer (*karkinos*). Black bile unmixed with blood caused *karkinos*, most often in the female breast. Galen also postulated a rare form of dry inflammation, when only heat and no humour flowed to a bodily part, in which case tumour formation was impossible.

Tumours therefore arose from localised inflammation when flux caused exudation of fluid from the veins into the fleshy (*sarks*) or parenchymal components of the body part (*parenchuma*). This happened because the tissues had acquired an abnormal ability to extract fluid, or because an abnormal mix of intravascular humours facilitated the extravasation of fluid. Accumulated extravascular fluid could be broken down (*diaphtheretai*) to form a fully concocted mixture (*materia peccans*) that was either gradually absorbed, discharged as septic residue (abscess), or remained indefinitely as a tumour which could have various characteristics. Galen and Soranus<sup>4</sup> used the word *onkos* to cover all tumours, whatever the nature.

In the Hippocratic writings there is reference to various kinds of tumours:

1. *Karkinos*, *karkinôma*<sup>35</sup> (Latin: *cancreum*, *carcinoma*). Although not always indicative of cancer as we know it, many of the





reported cases probably do represent cancer. The name is derived from the Greek for 'crab' because of a fancied resemblance of the tumour to this animal with its hard, rough exterior, and its long projections (feet and claws) into the tissues, onto which it adheres tenaciously.<sup>2</sup> The verb *karkinoō* refers to the process of converting to cancer and was used with reference to cancerous change in certain lesions of the female genitalia.<sup>2</sup>

2. *Phuma*.<sup>2,3,5</sup> An inclusive term which encompassed a great variety of predominantly non-malignant and inflammatory tumours.

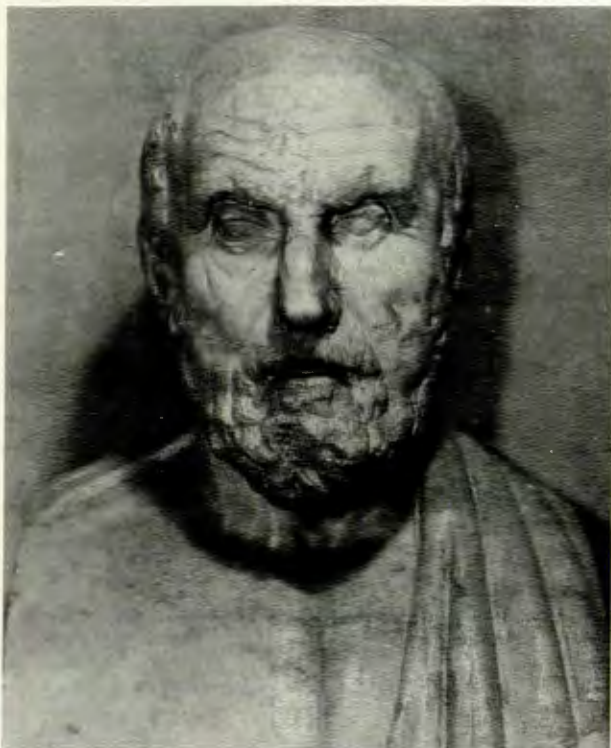
3. *Oidēma*.<sup>2,6,7</sup> A soft, usually non-tender tumour, sometimes pitting on pressure. It probably included gross oedema of the body.

Other terms less often used in ancient literature included *scirrhus*,<sup>8</sup> *struma*,<sup>6,8</sup> *melicerides*,<sup>6</sup> *condyloma*,<sup>6</sup> *tuberculum*,<sup>6</sup> *occalescit*,<sup>6</sup> and *carcinode*.<sup>6,9</sup>

## TUMOURS DESCRIBED IN LITERATURE

### *Karkinos, karkinōma*

When Hippocrates (5th century BC) states in the *Aphorisms*<sup>5</sup> that it is better not to treat internal cancers as this shortens life, the term *karkinos* is used. As mentioned above, this term is also used regarding the woman from Abdera who died of a breast tumour which presented with a bloody discharge from the



Hippocratic writers first identified tumours (5th century BC).

nipple. In the *Epidemics*<sup>3</sup> a patient is described with a *karkinōma* of the pharynx that was cured by cautery.<sup>3</sup> This is perhaps less likely to have been a true cancer in the modern sense. Retsas claims that a Hippocratic work, *On carcinosis*, was mentioned by Bacchius in the 2nd century BC, but it no longer survives.<sup>10</sup>

Cato the Elder (234 - 149 BC), the inveterate proponent of cabbage as a panacea for illnesses, claimed that a cabbage poultice will heal all kinds of ulcers and swellings, and in particular a *carcinoma* of the breast.<sup>11</sup> Celsus (1st century AD) also used the term *carcinoma* to describe a strange ulcerating and incurable lesion of the upper part of the body, but which also involved the spleen. He mentions that the Greeks called it malignant (*kakoēthes*), but that it was impossible to distinguish between those lesions associated with rapid death and those with a long survival. In describing a progressive ulceration of the penis, Celsus uses the word *cancrem*. This might well have represented a true cancer, but he goes on to say that unless rapidly cauterised, it developed into *phagedaena*, a necrotising condition associated with blackening of the skin and total destruction of the organ. Elsewhere, when dealing with surgical removal of urinary stones, he uses the word *cancrem* or *cancer* to describe a very serious complication of this procedure. However, this almost certainly represents a rapidly spreading sepsis, even gangrene, rather than a malignant tumour. Similarly his *therioma* resembles necrotising ulceration rather than *carcinoma*.<sup>6</sup>

Galen (2nd century AD) recognised incipient cancers (*karkinoi genomenoi*) and applied deadly nightshade (*solanum nigrum*) in the treatment of ulcerated cancers (*hēlkēkoi karkinoi*).<sup>2</sup> He recognises a variety of hard ulcerating and non-ulcerating nodular lesions (*karkinoi*) of the breast, uterus, male and female genitalia and elsewhere that carried a bad prognosis unless properly treated. His treatment consisted of initial 'emptying of melancholic humours' (through venesection) followed by surgery (complete resection of all vestiges of the tumours) and supplementary topical and systemic remedies. He echoes Hippocrates in stating that only superficial cancers should be treated this way. Leonides, a contemporary of Galen, described total mastectomy for those cancers not attached to the thoracic wall. Retsas also lists Rufus (2nd century AD), Philumenis (2nd century), Oribasius (4th century), Aetius (6th century) and Paul of Aegina (7th century) as physicians of antiquity who described lesions that could have been cancers.<sup>10</sup> Dioscorides (1st century AD) recommended specific ointments for a *karkinos*, e.g. of the nose. He used cantharidin against a tumour called *karkinōdē*, but Celsus refers to *carcinode* as a benign variety of *phuma*.<sup>5,6,9</sup>

### *Phumalphumata*

Under this heading were included a vast array of tumours ranging from minor skin nodules to large pelvic tumours obstructing labour. In the Hippocratic writings many of these tumours were quite nonspecific and ill-defined. However, the





urethral *phuma* mentioned in *Aphorisms* iv.28 and internal *phuma* of *Aphorisms* vii. 8 probably refer to infective tumours, even abscesses.<sup>3</sup> Scrofulous tumours referred to in *Prorrhetic* ii.11<sup>5</sup> and *Epidemics* ii.1.7<sup>3</sup> were almost certainly of infective nature, as were the para-aortic tumours (possibly renal cysts or abscesses) associated with kidney stones in *Nature of Man*.<sup>5</sup> The abscesses and tumours (*phumata*) of *Traditions in Medicine* are of quite uncertain nature, as are the growths referred to in *Physician*.<sup>5</sup> The small mammary tumours (also called tubercles) associated with lactation, mentioned in *Glands* 17, could have been fibro-adenosis or innocent retention cysts<sup>5</sup> — and one might speculate that Atossa's breast tumour (*phuma*, mentioned above) could well have been an abscess or tumour of this nature.<sup>1</sup>

In his description of penile disease, Celsus refers to excrescences (*phumata*) appearing on the glans before *cancrem* sets in. He also described a variety of small skin tumours. Many would seem to be minor infective lesions, and apparently easily cured by local applications — among them *meliceridis* (*favi*) and *carcinode*.<sup>6</sup> Dioscorides suggested colchicine applications for *phumata* not yet producing pus.<sup>9</sup> *Phumata empua* were suppurating lesions (possibly even tuberculous lymph nodes). *Phumata sklêra* were hard tumours in the breast which did not suppurate, but became increasingly harder and could develop into *karkinoi kruptoi* (occult cancers).<sup>2</sup>

Soranus (2nd century AD) quotes Herophilus (3rd century BC) when he states that abscesses and tumours in the pelvis may obstruct labour. These nonspecific tumours are also referred to as *phumata*.<sup>12</sup>

### Oidêma

When Hippocrates writes about swelling of the hypochondrium he refers to a lesion which is soft, painless and pits on finger pressure, as *oidêma* — with a better prognosis than hard swellings, but nevertheless indicative of protracted illness.<sup>7</sup> Elsewhere, dropsy appearing in undernourished persons is referred to as *oidêma*, as well as pelvic tumours causing leucorrhoea in women. When the causes of abdominal swelling (*oidêma*) are discussed in the *Aphorisms*, abdominal wall swellings are said to have a better prognosis than deep swellings.<sup>5</sup>

Dioscorides recommends cabbage, colchicine in wine, or cucumber for soft swellings (*oidêmata*), without defining them.<sup>9</sup> Galen is also vague about the exact nature of *oidêma*, and seems to accept generalised dropsy as a manifestation of it, but does include it in the category of tumours that could well have been malignant growths.<sup>8</sup> He prescribed three specific herbs for the treatment of *oidêma*.<sup>28</sup>

### Other

Galen defines *skiros* (scirrhous) as a hard and painless swelling which might arise spontaneously, develop in an area of



Galen's postulates (2nd century AD) regarding tumourogenesis remained dogma for 1 500 years.

inflammation (like erysipelas), or originate from *oidêma* 'when excessively cooled'.<sup>8</sup> It could give rise to *karkinos*.<sup>2</sup> The word *struma* according to Galen refers to a hardening of lymph nodes,<sup>8</sup> while Celsus uses the same word for scrofulous tumours (Latin: swollen neck glands), which might well have represented tuberculous lymphadenopathy).<sup>6</sup> Anal *kondulômata* (condylomata) (Greek for callous lump) were considered of infective origin, although some *kondulômata* could well have been malignant neoplasms.<sup>6</sup> Celsus uses the Latin word *occalescit* (a hardening of the skin) to refer to a callosity of the penis; nasal polyps are described as *carunculae* (Latin: fleshy protuberances), and gingival gumboils as *parulides*, while the term *tuberculum* simply signified a very small tumour.<sup>6</sup> The word *kêria*, occurring in the Hippocratic writings, has been translated as a malignant (Greek: *deina*) cyst. However, 'malignant' does not necessarily carry the modern connotation, as in malignant neoplasm. The original Greek words were *deina* ('fearful', 'terrible' in the sense of something which is to be regarded with awe because it surpasses human understanding) and *kakoêthês* ('malicious', 'abominable'), and referred to both infective and neoplastic lesions (in modern jargon). The Latin word *vitiosa* (meaning corrupt, vicious), used by Celsus, is also





translated as malignant.<sup>6</sup> The Hippocratic *Aphorism* vi.4 is usually translated as stating that an ulcer with a peeling edge is malignant (Greek: *kakoëthês*).<sup>5</sup> *Therionia* is often considered synonymous with malignancy, but Celsus's original description fits in better with a very severe, spreading infection.

## DISCUSSION

In Graeco-Roman times the concept of a tumour (*onkos* in Galen's terminology) embraced all abnormal swellings of the human body, and was explained on the basis of inflammation as understood within the humoural theory.<sup>2</sup> Abscesses and neoplasms (in the modern sense) therefore simply represented different phases of the same inflammatory process. Tumours resulted from accumulation of extravascular fluid and not from overgrowth of body tissues (neoplasia, as first described in the 19th century), and the concept of benign or malignant tumours was therefore non-existent. As blood-letting (venesection) was considered beneficial to relieve inflammatory congestion, it was considered efficacious for the treatment of all tumours. Similarly, cautery, application of caustic substances and excision constituted random therapy for all superficial tumours, even severe ulceration. Extensive lists of local tumour applications are given by Dioscorides and others.<sup>13</sup>

However, while *phuma* and *oidêma* applied to tumours which apparently were predominantly benign in the contemporary sense, it is clear that *karkinos karkinôma* (forerunner of our own word 'cancer') was recognised by the ancients as having a bad prognosis, often causing death. We cited reported cases of these lesions affecting the female breast and genitalia, the pharynx, penis, nose, 'chronic ulcers', 'the upper part of the body', and internal organs. Chapter 10 of Soranus' *Gynaecia* Book V was devoted to tumours of the uterus, but is unfortunately lost to us.<sup>14</sup>

Galen warned that while it was possible to excise some superficial cancers fully, Hippocrates had said that cancers of internal organs should not be treated as this shortened life,<sup>2</sup> and Celsus wrote that his *carcinoma* was incurable.<sup>6</sup> He also found it impossible to predetermine which growths would respond to therapy.<sup>2</sup> Dioscorides and Celsus's *carcinode* was probably a benign skin condition. The concept that a 'benign' lesion could turn into a cancer is embodied in what Galen called 'incipient cancer' (*karkinos genomenos*) and the Hippocratic views that hard mammary growths (*phumata sklêra*) which did not suppurate turned into occult cancers (*karkinoi kryptoi*), and that ulcers of the female genitalia, wrongly treated, became cancerous (*karkinothenai ta helkea*).<sup>2</sup> The ancients were therefore aware of premalignant conditions.

Celsus's description of what possibly represents a penile cancer obviously includes severe associated septic balanitis, infectious *phumata* of the glans and spreading *phagedaena* (a 'tissue eating' process). Celsus considered this part of the cancerous lesion, but it could as well have been a necrotising,

gangrenous infection we know as phagedena (usually seen in neglected or malnourished patients).<sup>6</sup> His *therionia* could likewise have been a phagedenic ulcer.

The word 'scirrhous' which today appears in the description of hard, sclerosing cancers, was also used by Galen to denote hard, painless swellings, some with malignant potential. Struma, today restricted to benign thyroid lesions, originally denoted indurated lymph nodes (possibly mainly tuberculous in origin), and condylomata were very much what they are today — benign perineal polyps usually of infective nature. Tubercle, denoting a small nodule, is today virtually restricted to lesions caused by the tubercle bacillus, and *oidêma*/oedema is the only major term for tumours that truly retained its original meaning, namely an extravascular accumulation of fluid, either localised as in inflammatory oedema, or generalised as in dropsy or anasarca. The concept *phuma* has virtually disappeared, except for its rare retention in words such as rhinophyma for nasal enlargement in rosacea.

The ancients therefore recognised that *karkinômata* had a much worse prognosis than *phumata* or *oidêmata*, but they did not differentiate between malignant and benign tumours in the modern sense. They certainly had no concept of a malignant tumour metastasising to the rest of the body. When the word 'malignant' appears in English translations of works of this period, it refers to Greek (e.g. *deina*, *kakoëthês*) and Latin (e.g. *vittiosa*) words which simply meant 'terrible' or 'vicious' with reference to both infective and true tumours that proved resistant to therapy. But it is likely that they were often describing tumours that we would indeed consider malignant.

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