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AN INTERVIEW WITH DR. ROBIN FOX
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SPECIAL REPORT

**THE ROLE OF
HAEMATOPOIETIC GROWTH FACTORS**

**PROSPECTS FOR
HIGH-DOSE CHEMOTHERAPY**



THE GILBERT METHOD
AN INTERVIEW WITH DR. WALTER GILBERT

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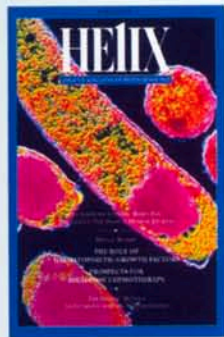
DR. JIMMIE C. HOLLAND, holder of the world's first endowed Chair of Psychiatric Oncology, has played a central role in the establishment of psycho-oncology as a recognized sub-specialty within the field of oncology. In 1989 she published, as senior editor, *Handbook of Psychooncology*, the first reference text available on the psychological aspects of cancer. Dr. Holland continues to be a strong advocate for the humanistic aspects of care of patients with cancer and AIDS.



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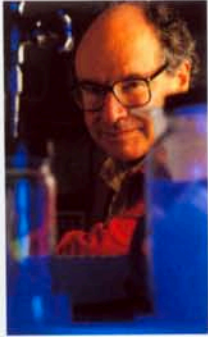
DR. ROLAND MERTELSMANN is chairman of the Department of Medicine I (Haematology/Oncology) at the Albert-Ludwigs University Medical Centre in Freiburg, Germany. From 1976 to 1985, he headed the laboratory of Molecular Hematology at Memorial Sloan-Kettering Cancer Center in New York City. From 1985 until 1989, Dr. Mertelsmann was in charge of the Department of Haematology at the University of Mainz. His main research interests include the molecular regulation of normal and neoplastic cell differentiation and the mechanisms of intercellular communication.



False-colour TEM of E. coli bacteria synthesizing human IL-2.

► PERSPECTIVES ◀

THE HUMAN FACE OF CANCER In the past, oncologists largely viewed the psychological domain of cancer treatment as not amenable to rigorous scientific study. Dr. Jimmie C. Holland describes how this attitude is beginning to change as the field of psycho-oncology matures into a recognized scientific discipline. 34



THE GILBERT METHOD Nobel Prize-winner Walter Gilbert was instrumental in the birth of both the biotechnology industry and the Human Genome Project. Dr. Gilbert reflects on the past and speculates on the future of biotechnological research in a conversation with Edward Edelson. 42



THE MARVELS OF NATURE While most official histories of anatomy begin with Vesalius in the 15th century, Robert Temple reveals how Aristotle was not only the most brilliant polymath of his time, but also the first person in history to carry out large-scale scientific dissections. 49



A PROVING GROUND FOR EUROPEAN SCIENTISTS For many, the European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany, is a model of how research institutions should be established in the future. Barbara Bachtler examines the laboratory's flexible, multi-disciplinary approach to basic research. 58



► SECTIONS ◀

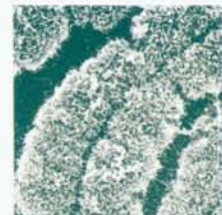
RESEARCH NEWS Edward Edelson reveals how the genetic amplification theory is teaching an old dogma new tricks. 18

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ARISTOTLE AS
ANATOMIST AND DISSECTOR

THE MARVELS OF NATURE

MOST HISTORIES OF ANATOMY BEGIN WITH VESALIUS IN THE 15TH CENTURY. HOWEVER, HUMAN DISSECTIONS WERE ALSO CARRIED OUT IN ANTIQUITY, ALTHOUGH THESE OPERATIONS WERE SURROUNDED BY SECRECY AND TABOO. ROBERT TEMPLE REVEALS HOW ARISTOTLE CAN BE CONSIDERED THE FIRST PERSON IN HISTORY TO HAVE PRACTICED LARGE-SCALE SCIENTIFIC DISSECTION.



PATRIS INSOMNIUM



GALENI DOCTORES



HEPATICI COGNITIO



CRISIS PRÆCOGNITIO



AMANTIS DIGNOTIO



PALESTRITE CVRATIO



DISCEPTATIO CVM ALEX HABITA



ARISTOTLE OF STAGIRA (384-322 BC) was born into a long-standing tradition of medical practice.

Both of his parents were members of the Asclepiad clan, a hereditary line of medical doctors claiming descent from Asclepius, the Greek god of medicine. Aristotle's father Michomachus had not only been the personal physician to King Amyntas III of Macedonia (grandfather of Alexander the Great, who later became Aristotle's pupil), but also the king's close friend and confidant. Aristotle began his studies in Athens at the age of 17 as a student of Isocrates, the famous rhetorician. But Aristotle found his querulous instructor annoying and later transferred to the Academy, the philosophical school founded by Plato. Plato became quickly enamoured of Aristotle's obvious brilliance, referring to him as 'the Mind of the School'.

Aristotle was by far the most astonishing polymath of his time. Although he is now chiefly known for his academic writings, Aristotle also published two volumes of poetry (of which only three poems survive) and was a well-rounded scholar. He was also the world's first true scientist. Unlike his predecessors from the pre-Socratics through Plato, Aristotle based his theories on direct observation and empirical knowledge. It was thus he who first made the quantum leap from the mythological imagination of the primitive mind to the clarity of the dispassionate observer.

Widely recognized as the 'father of zoology,' Aristotle's surviving writings on this subject constitute the first great body of scientific literature in the history of the world. His *History of Animals* alone describes some 560 named species. Nevertheless, few people still read Aristotle's zoological works. Even classical scholars, as well as the editors and translators who have published the material, have tended to ignore this facet of Aristotle's work. Zoologists themselves don't often sit

down to read Aristotle either. Despite this neglect, however, the study of Aristotle's scientific work remains a rich and rewarding field. Approximately one-fourth of Aristotle's zoological works concerned anatomy and dissection and, unfortunately, all of these have been lost. Aristotle published eight volumes entitled *Dissections*, in addition to a one volume abridgement of the work.

Although Aristotle was himself a wealthy man, the sums expended on his zoological research exceeded even what he could realistically afford. Thus, the funds provided by his illustrious patrons went towards deferring the costs of the huge filing system, the extensive and elaborate artwork and the host of scribes connected with the dissections. In addition, Aristotle also had to finance a small army of people to obtain specimens for him to dissect. As a result, he was able to establish an extensive museum of specimens at his school, the Lyceum, in Athens during the last 12 years of his life.

AN ANATOMICAL MENAGERIE

IN MID-LIFE HOWEVER, ARISTOTLE FINANCED his investigations personally, especially during the three years during which he lived on the island of Lesbos and made his most intensive study of fish. From references in his zoological works, it seems that he must have dissected over 100 types of sea creatures. Various stray remarks betray his familiarity with certain seamen's 'tricks of the trade,' thus making it clear that he sometimes went to sea with the fisher-

men. These remarks even include occasional glimpses of strange marine sights, such as Aristotle's account of a snoring dolphin asleep in the sea with its head above water.

In his surviving zoological works, Aristotle mentions his treatise the *Dissections* by name no less than 18 times, although not all of these references are indexed in the published works. On four of these occasions, it is in con-



► 'The heart is itself the source and spring of the blood, or the first receptacle of it.' ◀

Above left: Illuminated letter, from a Flemish manuscript of the late 15th century.

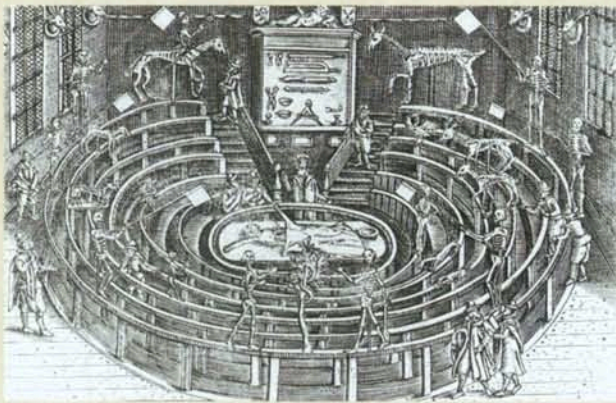
Below left: An engraving depicting Hippocrates (right) and Galen (Leipzig: Georgii Heinrichi Frommanni, 1677). Where Hippocrates touches the bush in the centre of the illustration, it is in flower; on Galen's side, there is nothing but thorns.

Right: Detail from *The School of Athens* (1508) by Raphael in the Stanza della Segnatura in Vatican City. The detail shows Plato (left) and Aristotle in conversation. Photograph by E. Lessing/Magnum.



nection with dissection drawings that he suggests consulting the work for particular creatures such as cuttlefish, lobsters, wild limpets, snails and certain small types of crayfish. On another occasion, he refers the reader to a comprehensive series of dissection diagrams of practically every kind of *testacea* accessible to him for study. Five references are primarily to fish, five to a wide variety of animals and two to humans. But in trying to reconstruct the contents of the lost *Dissections*, this breakdown into types of creature is not the most helpful approach. It is far more profitable to consider the contexts, since by examining them it becomes clear that the *Dissections* seems not to have been organized along taxonomic lines, [1] but according to functional anatomical parts.

These references are preoccupied with particular organs as they appear in a succession of different creatures. In the *Generation of Animals*, for example, there is a reference in Book 2 (746a16) to a series of illustrative diagrams in the *Dissections* of various mammalian uteri, foetuses, umbilici, associated blood vessels, cotyledons, placentas, membranes in the uterus and so on. The emphasis is on how these organs and tissues appear in a variety and not merely in a succession of animals. In Book 1, the same is true with regard to a large number of fish. Aristotle prepared what must have truly been a vast number of drawings, which he recommends (719a11) 'to ascertain the arrangement of the uterus of the Selachians and other kinds [of animals] as well [...]. Thus, the Selachians have their uterus high up because they are ►



Above: An engraving of the Anatomical Theatre at Leiden University. In: *Muers Athenae Batavae, Leiden, 1625.*

Below: A woodcut (Leipzig: Martin Landsberg, ca. 1493) depicting a young man receiving instruction in the dissection of a cadaver.

oviparous [...]. Animals which are viviparous from the outset all have the uterus low down [...]. The uterus of all viviparous animals is fleshy, whereas in those cases where it is near the diaphragm the uterus is membranous. This is clearly to be seen in the case of those animals which produce their young by the two-stage process [...].'

Throughout Aristotle's zoological works statements appear which imply personal inspection of large numbers of species for comparison, while the layout of the *Dissections* seems to have been one stressing comparisons and differences of parts and organs within large groups. In the *Parts of Animals* Book 2 (650a32), another long series of mammalian diagrams appears to be referred to as illustrating the differences between various digestive systems, including the human. Aristotle writes: 'These matters should be studied in the *Dissections* [...].' Similarly, in Book 3, Aristotle refers (666a9) to many diagrams describing vascular systems in many animals, including man: '[...] the blood is conveyed and conducted away from the heart into the blood-vessels, whereas none is thus conveyed into the heart from elsewhere, for the heart is itself the source and spring of the blood, or the first receptacle of it. All this, however, is more clearly

brought out in *Dissections* [...].' This is one of several indications that the *Dissections* was not simply a collection of diagrams, but a collection of commentaries as well.

There are certain passages in the enormous *History of Animals* which give an indication of what the commentary passages of the *Dissections* must have been like. In Book 2, Aristotle inserts a long and meticulous description of the chameleon because it was such a rare animal with which few readers could be expected to be familiar. This full species description includes observations during Aristotle's dissection of a chameleon, and represents the kind of remarks which probably accompanied most of the dissection diagrams. This fascinating passage (503a18-503b28) includes the following: 'When dying it becomes pale, and it retains this colour when dead. With regard to the position of the oesophagus and the windpipe, it resembles the lizards. It has no flesh anywhere except some portions on the head and jaws and the root of the tail. It has blood only around the heart, the eyes and the region above the heart, and in the small blood-vessels ramifying from them, though even in these parts there is a very small quantity. The brain is situated slightly above the eyes, but is continuous with them.'

During a discussion of stomachs in the *Parts of Animals*, Aristotle casually mentions his familiarity with the stomachs of men, dogs, lions, horses, mules, asses, pigs, camels, sheep, oxen, goats, deer, birds and fishes. It is also known that he dissected seals, bears, wolves, stoats, cats, weasels, turtles, tortoises and many other mammals, and had information about such exotica as the crocodile and the elephant. Another relevant passage in the *History of Animals* is the account (524a3-525a13) of dis-



► 'In all natural things there is somewhat of the marvellous.' ◀

sections of octopi and other cephalopods: 'From this [the stomach] there leads back upwards towards the mouth a fine gut: It is thicker than the oesophagus.' These observations were meticulous, and many specimens must have been unsatisfactory, so much so that repeated dissections must have taken place.

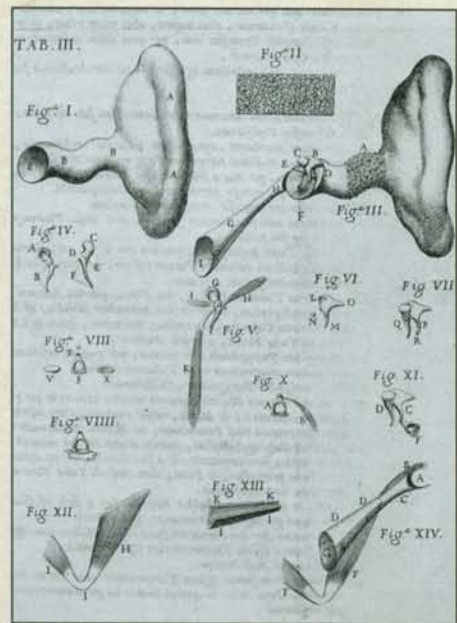
HUMAN DISSECTIONS

THE ENORMOUS NUMBER OF DISSECTIONS CARRIED out by Aristotle is also indicated by the way in which he speaks of them in this passage from the *Generation of Animals* (764a34): 'Further, male and female twins are often formed together in the same part of the uterus. This has been amply observed by us from dissections in all the Vivipara, both in the land-animals and in the fishes.' Elsewhere in the same work (746a19), Aristotle gives a further indication of his numerous dissections of the foetuses of many creatures: 'Those people who say that children are nourished in the uterus by means of sucking a bit of flesh are mistaken. If this were true, the same would occur in the other animals, but it is not found to do so, as can easily be observed by means of dissections. Also, all embryos alike, whether they be of animals that fly or swim or walk, have around them fine membranes which separate them from the uterus and from the fluids which are formed there and there is nothing of the sort in these membranes nor can the embryos get the benefit of anything whatever through them.'

One of the most intriguing questions raised by these references is whether Aristotle actually dissected human corpses himself. On several occasions, he makes rather unconvincing and coy remarks about how one cannot dissect human bodies. He then proceeds to provide the most minute details of human anatomy and refers to diagrams of human organs. It is therefore certain that he either dissected human foetuses himself or saw the results of dissections done by others. Aristotle was very friendly with the Athenian midwives, and derived much information from them. It appears that these midwives cut up the foetuses without a qualm. Book 10 of the *History of Animals* has only recently been published in English. It is not part of that original work, but is a separate treatise tacked on to the original long ago

by scribes. The work has been identified with Aristotle's lost treatise entitled *On Failure to Generate*, and it concerns human beings. This treatise relates midwives' lore and, in the course of so doing, Aristotle speaks of moles (uterine masses arising from a poorly developed or degenerating ovum) which have been delivered of women: '[...] it becomes so hard that they cannot cut it up with an axe.' Notice the use of the pronoun 'they.' Doubtless, a great deal of investigation into moles and miscarried foetuses was common among the midwives, and Aristotle availed himself of this knowledge.

Aristotle carried out a series of dissections on monkeys, which he describes in the *History of Animals*. In Book 1 (502a17-502b27), he observes: 'In all animals of this sort the internal parts, when dissected, resemble those of man.' Such a remark elicits the question: how could Aristotle have known that the innards of monkeys so closely resembled those of man? In fact, the great extent of detailed knowledge of human internal anatomy shown by Aristotle must have come from dissection. He seems to have dissected the corpses of both men and women on various occasions. In the course of this work, he made a number of surprising discoveries, many of which were generally considered unknown in ancient times. For instance, Aristotle leaves the first record of the existence of the Eustachian tubes in the *History of* ▶



The Eustachian tube as depicted in A.M. Valsalva's Opera, (Venice, 1740). Valsalva notes that Aristotle was familiar with the structure of the inner ear.

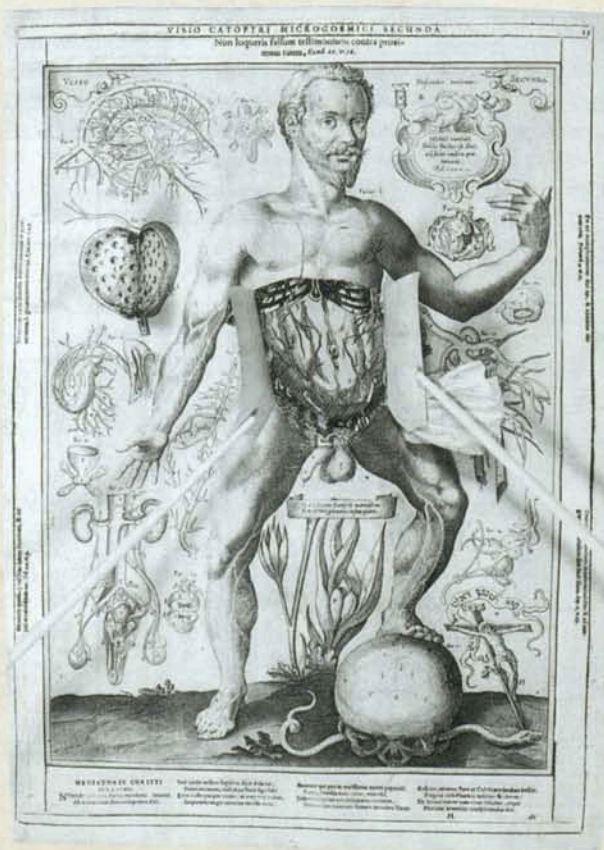
Animals, Book 1 (492a20): 'The natural structure of the interior of the ear is like the spiral-shells: the innermost part is a bone similar to the ear, and into this ultimately the sound penetrates, as into a vessel. There is no passage from this to the brain, but there is a passage to the roof of the mouth, and a blood-vessel passes to it from the brain. The eyes too are connected with the brain, and each eye is situated upon a small blood-vessel.' The Eustachian tubes were supposed to have been discovered by Bartolomeo Eustachi, whose work was published in 1714. It is now clear that Aristotle anticipated him by more than 2,050 years.

THE EYE OF SCIENCE

IN THE *PARTS OF ANIMALS*, ARISTOTLE DESCRIBES the shape of the human spleen (674a2), and describes human kidneys in a manner which apparently reflects the kidneys of foetuses rather than adults (671b7). At another point (653a28), he writes: 'Of all the animals, man has the largest brain for his size; and men have a larger brain than women.' In fact, in the *History of Animals*, he has a great deal to say about the human brain (494b28-495a18): '[...] for his size man has the largest

brain and the most fluid one. The brain is surrounded by two membranes: the one round the bone is the stronger, the one round the brain itself less so. In all animals the brain is double. Beyond this, at the far end, is the cerebellum as it is called; its form is different from that of the brain, as can be both felt and seen. [...] In all animals the brain is bloodless; there is not a single blood-vessel in it, and it feels cold to the touch. In most animals it has a small hollow in the middle. The membrane which surrounds it is patterned with blood-vessels: this is the skin-like one that surrounds the brain. [...] From the eye three passages lead to the brain: the largest and second-largest to the cerebellum, the smallest to the brain itself: this last is the one nearest to the nostril. So the two largest run side by side and do not coalesce [...] Elsewhere (514a15), he discusses the blood vessel that 'run[s] on its own side from the region round the ear to the brain, and divides up into a number of small delicate blood-vessels into the meninx (as it is called) which surrounds the brain. The brain is bloodless in all animals; no blood-vessel, large or small, terminates there. Of the remaining blood-vessels which divide off from the one

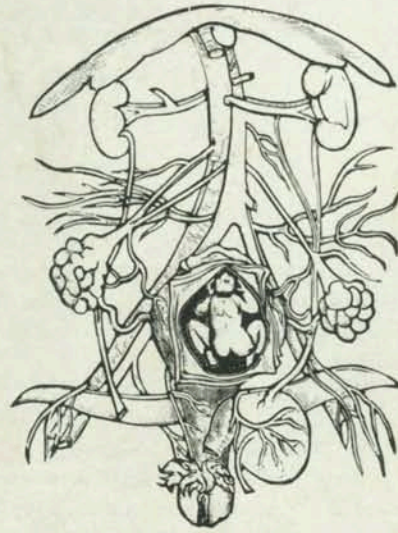
Captoprium Microcosmicum, an ingenious 16th century booklet consisting of two fold-out plates that provide interior views of human physiology. Courtesy Leiden University Library and B.M. Israels, Amsterdam.



just mentioned, some encircle the head, others find their terminus in the sense-organs and the teeth in extremely fine blood-vessels.'

In the first book of the *Parts of Animals*, Aristotle wrote a ringing defence of his practice of studying and dissecting living things. He writes (644b28) that plants and animals deserve our attention 'because we live among them; and anyone who will but take enough trouble can learn much concerning every one of their kinds. [...] So far as it in us lies, we will not leave out any one of them, be it never so mean; for though there are animals which have no attractiveness for the senses, yet for the eye of science, for the student who is naturally of a philosophical spirit and can discern the causes of things, Nature which fashioned them provides joys which cannot be measured. [...] we must not betake ourselves to the consideration of the meaner animals with a bad grace, as though we were children; since in all natural things there is somewhat of the marvellous. [...] we ought not to hesitate nor to be abashed, but boldly to enter upon our researches concerning animals of every sort and kind, knowing that in not one of them is Nature or Beauty lacking. [...] If, however, there is anyone who holds that the study of the animals is an unworthy pursuit, he ought to go further and hold the same opinion about the study of himself, for it is not possible without considerable disgust to look upon blood, flesh, bones, blood-vessels and such-like parts of which the human body is constructed.'

Aristotle did more than master his 'considerable disgust' in investigating animals and man. He carried out the first great investigation into living things. He must have dissected well over 200, perhaps more than 300, different species, considering the fact that he dissected just about every type of Mediterranean fish, insect, reptile, mammal and bird he could find. Although Aristotle's eight volumes of dissection diagrams have been lost for over two millennia, enough can be gleaned about his anatomical studies and dissections to appreciate the magnitude of his achievements. His pupil Diocles of Carystus, who seems also to have been Aristotle's chief assistant during dissections, built upon them to write the first theoretical treatise on anatomy, and the great physician Galen (2nd century AD) was the



Woodcut (ca. 1642) depicting a normal child in utero and showing its relationship to its mother's organs. By courtesy of the Bettmann Archive, New York.

chief disciple of Aristotle's work, admitting that one of his favourite books was Aristotle's *Parts of Animals*.

Galen carried out many dissections, and most historians of science are not aware that Aristotle had preceded and inspired him in this. Galen's work, as a continuation of Aristotle's, greatly influenced Europe during the Middle Ages and also spread throughout the Muslim world. Although one cannot say that Aristotle's dissection work had much other influence in the end, we must pay tribute to him for being the pioneer of anatomical studies, and attempt to resurrect the forgotten glories of his immense labours and inspired observational genius. It seems all the more fitting now to reflect on Aristotle's ground-breaking work in the field of dissection and human anatomy, during a time when the Human Genome Project seems poised to supply what may very well be the final piece in the mystery that Aristotle began to unravel some 2,300 years ago.

Notes

1. Aristotle had, in fact, no taxonomy and did not use the words usually translated as 'genus' and 'species' in a taxonomic sense.

BY ROBERT TEMPLE

FILM AND TELEVISION PRODUCER AND SCIENCE WRITER BASED IN THE UK.

The illustration on page 49 is a partial title page of Galen's *Opera Omnia*, published in Venice in 1556. The title page depicts some of the many illnesses that Galen, one of the chief disciples of Aristotle's work, was able to diagnose.