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ENDOCRINE GENETICS AND GENETICS OF GROWTH

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Christos S. Bartsocas

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ENDOCRINE GENETICS AND GENETICS OF GROWTH

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Preface

We are pleased to present this volume with a selection of the Proceedings of the 4th International Clinical Genetics Seminar which was held in Athens, Greece, May 22–25, 1985.

The topic of this Seminar was "Endocrine Genetics and Genetics of Growth." It included lectures on a group of disorders, followed by free communications on the same subject and concluded with lively and stimulating discussions. The purpose was to delineate, classify and find answers to questions on the genetics of the endocrine disorders and growth.

This opportunity was given extensively due to the fact that participants represented several medical disciplines, a fact that makes these Seminars a unique forum for discussions between specialties.

Due to its limited number of pages this volume will give you an overall coverage of the subjects discussed. Nevertheless, we hope that it contains useful information and the present State of the Art about "Endocrine Genetics" for the geneticist, the pediatrician, the internist and the endocrinologist.

We wish to thank Mr. Alan R. Liss and his staff, particularly Ms. Paulette Cohen, for the expeditious process of this publication as well as all participants of this and the previous Seminars for making them an established Genetic event.

Costas J. Papadatos, MD
Christos S. Bartsocas, MD

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GOITERS, DWARFS, GIANTS AND HERMAPHRODITES

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INTRODUCTION

It is with great pleasure that I welcome you to this Fourth International Clinical Genetics Seminar. As with the two previous Seminars on the "Management of Genetic Disorders" in 1979 and "Skeletal Dysplasias" in 1982, this Seminar's topic was chosen by the majority of the participants in 1982 who voted for "ENDOCRINE GENETICS AND GENETICS OF GROWTH".

Endocrine and growth disorders viewed through the geneticists' eyes have not been the subject of extensive discussions and only a few diseases, such as diabetes mellitus, have been dealt with occasionally; therefore, it seems that a conference on "Endocrine Genetics and Genetics of Growth" is not just timely, but needed. The recent progress in molecular genetics, receptor function and antibody action as applied to endocrine diseases is a vast field, which requires intensive research not only by the endocrinologist, the pediatrician, the internist, the immunologist, but also by the geneticist.

We hope that the 1985 Athens Conference on Endocrine Genetics and Genetics of Growth will help define, clarify and arrange much of the new material in this exciting field and set the ground for even more exciting discoveries on the role of heredity in the cause, pathogenesis and management of Endocrine and Growth disorders.

Ancient greek art and literature are rich in information about heredity and hereditary diseases in antiquity. Investigation of ancient skeletal material complements this information with findings and observations useful to paleogenetics.

Three years ago we had the opportunity to look into ancient greek genetics and to point out Aristotle's remarkable contribution worth to call him the Father of Genetics (Bartsocas 1982b, Bartsocas 1983). As we stressed then Aristotle distinguished five forms of heredity! Important contributions to the knowledge of heredity were made also by other ancient authors, particularly Hippocrates, Embedocles and Galen. We should mention here that Origenes was the first to describe sex-linked inheritance!

The information from antiquity is vast and it is always exciting for any scientist willing to look back more than 2000 years into our cultural roots. Nevertheless, we should like to limit ourselves to endocrine disorders,principally to goiters, dwarfs, giants and hermaphrodites.

Goiters

It seems that Aristotle was the first greek writer to describe goiter, as the tumor of the neck. He thought that persons who had a thick and large neck were spirited and rash; therefore, it seems that he had in mind toxic goiter rather than nontoxic (Marketos et al. 1983). A few centuries later Galen defined goiter as a tumor of the larynx or a tumor of the pharynx. Aetius of Amida, a leading christian physician, further defined goiter as "bronchocele (hernia of the bronchus) that is a rupture of larynx and it is called tumor in the neck" (*bronchocele, id est, gutturis remex appellatus tumor in gutture)*. Aetius classified between the varieties of thyroid diseases as bronchocele glutinous, honeyed, tollowy, enormous, local aneurysm and scirrhus tumor and carcinoma of the thyroid gland (Marketos et al. 1983). Paul of Aegina, another famous byzantine physician, reported goiter as "a large round tumor (which) appears on the neck from the inner parts and, therefore, it obtains the appellation of bronchocele, of which there exist two varieties, the steatomatous and the aneurysmatic" (Adams 1846).

Aristotle also studied exophtalmos! He related this

sign to the brain and marked that persons who had exophthalmos were stupid ("Οσοι ἐξόφθαλμοι, ἐβέλτεροι ἀναφέρεται ἐπί τήν ἐπιτρέπειαν). Plato and Xenophon also describe exophthalmos. Plato the philosopher, mentions exophtalmos on Theaetetus, while Xenophon, the historian, believed that exophthalmos marks vigilance, clear and better eyesight (τό ἐξόφθαλμον εἶναι ἐγρήγορος μᾶλλον φαίνεται τοῦ κοινοφθάλμου καί ἐπί πλεῖον δ'ἄν ὁ τοιοῦτος ὁρώη).

The first association between goiter and exophthalmos was made centuries later, in the 10th century A.D. In fact these two signs, were not considered as signs of disease since patients could carry out their work, as mentioned in a legal byzantine text! Emperor Leon VI the Wise (886-910 A.D.) issued "Vasilika" a legislation distinguishing between disease and affection. He notes that "the man, who has a great walnut around the neck, and has bulging eyes,is considered as healthy" ('Υγιής ἐστίν ὁ μέγα περί τόν λαιμόν ἔχων κάρυον, καί ὁ τούς ὀφθαλμούς ἔχων προκύπτοντας) (Zepos 1910). It should be mentioned, however, that a Roman Jurist, Dometius Ulpianus (170-228 A.D.) had mentioned this association in his legislation, which was incorporated by the Corpus Juris Civilis Justiniani in the 6th century (Zepos 1910).

Ancient greek art has its share in the delineation of goiter. As goiter is still endemic in certain regions of the country, obviously it should have existed also in antiquity. In fact ancient coins produced in areas with endemic goiter, such as the greek mainland, Sicily and Asia Minor present persons with goitres. Therefore, Apollo is depicted with a goitre on coins of Myrina, Hera on coins of Elis,Artemis or Arethousa on coins of Syracuse (Fig. 1) etc. It is probable that certain coins of Cleopatra show her with a goitre (Hart 1969, 1973).

Giants and Dwarfs

Herodotus (IX, 82) reports a giant's body among the dead of the battle of Plateae, where the Greeks won the Persians in 479 B.C. According to the description of Herodotus this man ought to measure 2.30 m! Herodotus describes also a Persian giant, Artachaies, a military engineer who measured approximately 2.55 m (Grmek 1983). Giants are also present in greek mythology in their revolt against the Gods (Graves 1957).

Fig. 1. Arethousa with goiter on a tetradrachm coin of Syracuse minted in 439/435 B.C.

Greek mythology defines dwarfs as Pygmies,those of the size of a πυγμή (fist), approximately 46 cm. There are several reports about "pygmies" in the ancient greek literature and art (Fig. 2). The most well-known representations of a dwarf in art is of the achondroplastic dwarf on an aryballus of the Vth century now in the Louvre (Fig. 3).

Hermaphrodites

Every deviation of the human body from normal was considered as a supernatural or an evil sign from the depth of centuries until the 17th century. Hermaphroditism was an example of this deviation. It is well known that in many cultures hermaphrodites were killed. The ancient Spartans disposed them into the Kaiadas chasm, where all abnormal infants were thrown, and many ancient greek cities disposed hermaphrodites into the sea. Infanticide of the hermaphrodites was practiced also in ancient Rome as hermaphrodites were considered the causes of major catastrophs.

Fig. 2. A Pygmy fighting a crane.

Fig. 3. Achondroplastic dwarf painted on the Peytel arybal-lus (Musée du Louvre, Inv. CA 2183).

The myth about the hermaphrodites is of oriental origin. They were considered deities of conception and expressed the idea of an archetypal, superior and most perfect subject. A subject that included both male and female qualities; therefore, hermaphrodites were considered to be self-fertilized.Their cult was introduced to Greece through Cyprus. After all Aphrodite (Venus) was called "arsenothelys" (male-female) and was somehow related to the phrygian Cybele in Paphos and Amathous (Cyprus). In fact Aphrodite Cybele was divided into two deities, Aphrodite, the godess of beauty, and Aphroditos. The cult of Aphroditos reached the greek mainland around the latter part of the 5th century B.C. He was considered less as a god and more as a hero of a poetic myth. With his heroic identity he was artistically represented by Hermes steles,which were named Hermaphrodites. Little by little a myth was developed which considered him the child of Hermes (the god of Commerce) and

Aphrodite. The myth wants Aphrodite flattered by Hermes' love confession, to have spent a night with him, after which she gave birth to a child Hermaphroditos.

According to the tradition Hermaphroditos was a young man with female breasts and long hair. It seems possible that the transition of metriarchy to patriarchy was symbolized in antiquity by the "androgyne" or the bearded woman. Androgyne was the mother-godess of pre-hellenic tribes which refused to adopt patriarchy (Graves 1957).

Another myth reports Hermaphroditos, the son of Hermes and Aphrodite, a youth of extreme beauty to bathe in the Salmakis fountain near Halicarnassus. Nymph Salmakis fell in love with him, embraced him and asked the gods not to separate them. According to Ovid who reports this myth the two bodies formed one thus maintaining both male and female genitalia.

Later two types of hermaphrodites were established. One with female body proportions and male genitalia and another with a united appearance of the two sexes. It is obvious that ancient artists found an impressive subject to represent. Hermaphrodite statues were found in abundance and enrich the Louvre (Fig. 4,5) and the Vatican Museum, the museums of Rome (Fig. 6), Florence, Naples, Dresden (Fig. 7), Dion (in No.Greece) (Fig. 8) and naturally the National Archeological Museum in Athens. Several statues of hermaphrodites belong to private collections (Fig. 9).

Congenital Adrenal Hyperplasia

Two reports of masculinization of girls may be found in ancient texts. One relates to Galateia, the daughter of Evrytius, who gave birth to a girl in Phaestos. As her husband had threatened to kill the baby if it were a girl, Galateia hide the true sex of her child and named her Lefkippos. As Lefkippos was growing up there was great risk that Galateia's lie might be revealed. The unfortunate mother took refuge in the temple of Leto and asked her to protect her little girl. Leto accepted her pray and changed Lefkippos' sex from female to male.

Ovid is credited with the second report during the 1st century B.C. He describes with admiration the progres-