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Relation of Sperm Morphology to Genotypically Controlled Variations in Fertility. (19238)

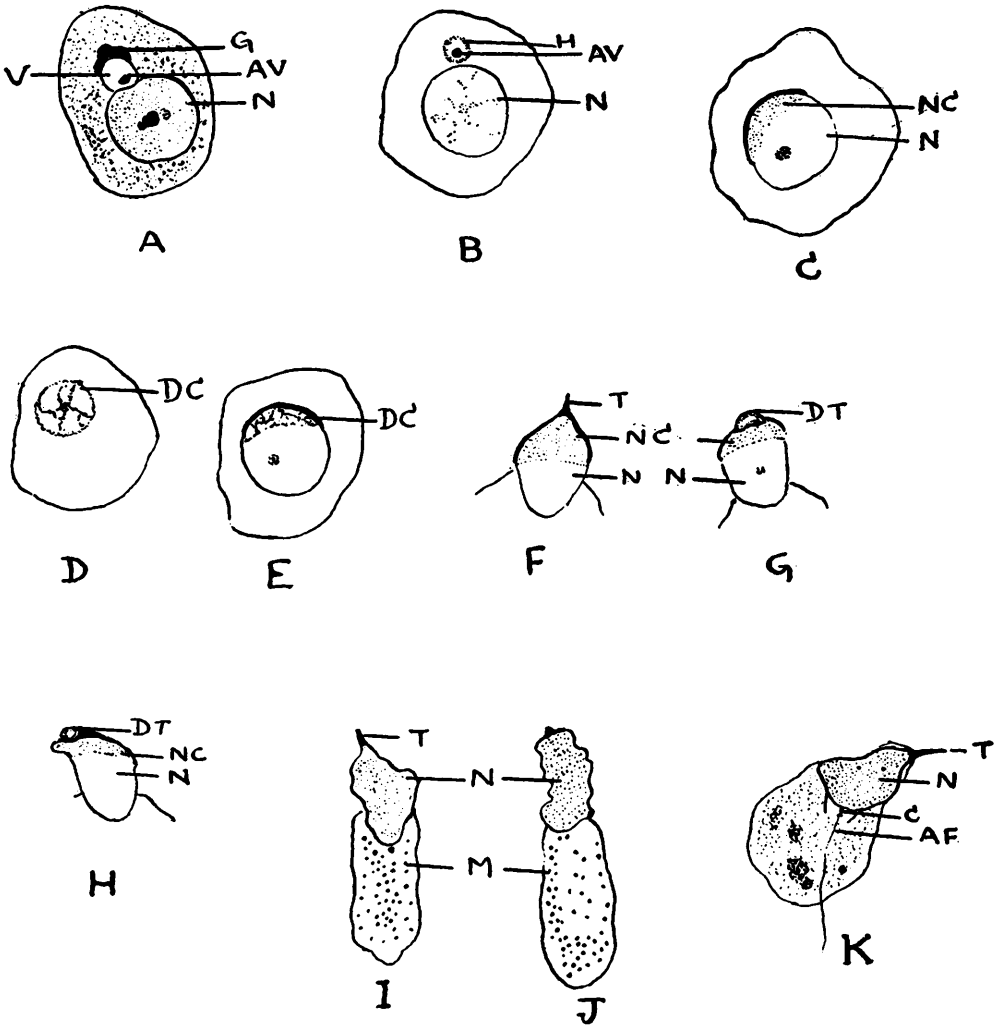
M. R. RAJASEKARASETTY. (Introduced by E. T. Engle.)
From the Department of Zoology, Columbia University, New York.

Since the classic investigations of the relation between sperm morphology and impaired fertility made by Williams and Savage(1), Moench(2), and Lagerlof(3), studies of sperm cytology have provoked great interest and some controversy.

In the laboratory mouse a number of mutations have been found, which by their interaction affect the reproductive efficiency of the male in various degrees—from almost complete sterility to almost complete fertility, while their sisters of the same genotype are normal in fertility. The factors responsible for this impairment have been described in several papers from our laboratory(4). Here it need only be recalled that these mutations belong to a series of alleles at or near the T locus in Chromosome IX. Of these alleles 7 have been studied in some detail. They have been normally maintained in balanced lethal lines in which T/t^x is tailless and T/t^u is similarly tailless, whereas crosses between these lines produce compounds $t^u t^x$ distinguished by normal tails and impaired fertility in the males. Examination by Bryson(5) of spermatozoa from males of one of these gene combinations, $t^u t^1$, which was completely sterile, revealed that, although these sterile males copulated normally and produced a large number of spermatozoa, about a quarter of the sperm had abnormally shaped heads, which were less frequently found in fertile males. He also logically concluded that the normal looking spermatozoa of these sterile males were incapable of fertilization. Recently, spermatozoa have been examined from males of 2 other gene combinations, $t^0 t^3$, and $t^1 t^3$. These males, unlike $t^0 t^1$ males, are not quite sterile. These "quasi-sterile" males produce less than 20% the number of young sired by "normal" males. Attempts to correlate percentages of morphologically abnormal spermatozoa with the breeding efficiency of such males reveal that, while one may with some caution distinguish between normal fertile males and $t^0 t^3$ males whose fertility is impaired in various degrees, any attempt to set numerical boundaries to distinguish absolute sterility from quasi-sterility would be highly misleading.

The average percentage of abnormal sperm in fertile controls is 8.18 ± 0.98, in quasi-steriles 32.20 ± 1.14, and in steriles 43.16 ± 3.69. While the difference in the average percentages of abnormals, between quasi-steriles and steriles, is significant, there is an overlap in their ranges. There is the further evidence that there is no correlation between percentages of abnormal sperms and degree of sterility. All one could safely say is that a higher incidence of abnormal sperms indicates lowered fertility, and there is no justification for treating morphology of spermatozoa as the only diagnostic factor for impaired fertility. The source of the alterations in the sperm pathology was sought by the study of spermatogenesis in quasi-sterile and sterile males. No major cytological aberrations were found.

It has become apparent of late that several different anatomic components of the spermatozoon are significant in evaluating fertility. With improved staining technics, it is becoming clear that nuclear and acrosomal ab-



All figures were drawn with the aid of camera lucida, × 1500. Lettering: AC, acrosome; ACS, space in the acrosome; AF, axial filament; AV, acrosome vesicle; C, centrioles; DC, degenerating cap of the acrosome; DT, degenerating tassel of the acrosome; G, Golgi material; GR, Golgi remnant; H, halo of acrosome; MS, mitochondrial sheath; N, nucleus; NC, normal cap of the acrosome; R, refractive body in the sperm head; SH, sperm head; T, normal tassel of the acrosome; V, vacuole surrounding the developing acrosome. A, K, L, M, N, S from Flemming (without acetic acid), haematoxylin and Fastgreen preparations. B, C, D, E, F, G, H, O, P, Q, R from San Felice and periodic acid Schiff preparations. I, J from Champy-Kull preparations. T, U, V, W, X from basic Fuchsin Fastgreen (Slizinsky's) preparations.

FIG. 1. Comparison of normal and abnormal, early and mid-spermatic stages. A, B, C, normal young spermatids; D, polar view of degenerating cap of a young spermatid; E, side view of same; F, normal sperm head at mid-spermatid stage; G, the same with a degenerated tassel; H, I, J, K, mid-spermatid stages showing abnormalities of nucleus and acrosome.

normalities are more common than abnormalities of the posterior extremity which are comparatively rare(6). After a detailed study of spermiogenesis and mature sperm in quasisteriles it was clear that in the spermatozoa of t^3t^0 males only the nucleus and acrosome were affected. The abnormalities of the nucleus are indicated by the shape and size. (Fig. 2, M, N, U, V, W, X) The axes of the sperm-head are affected. The nucleus assumes a variety of shapes ranging from almost normal to highly distorted. Microsperms, megalo-

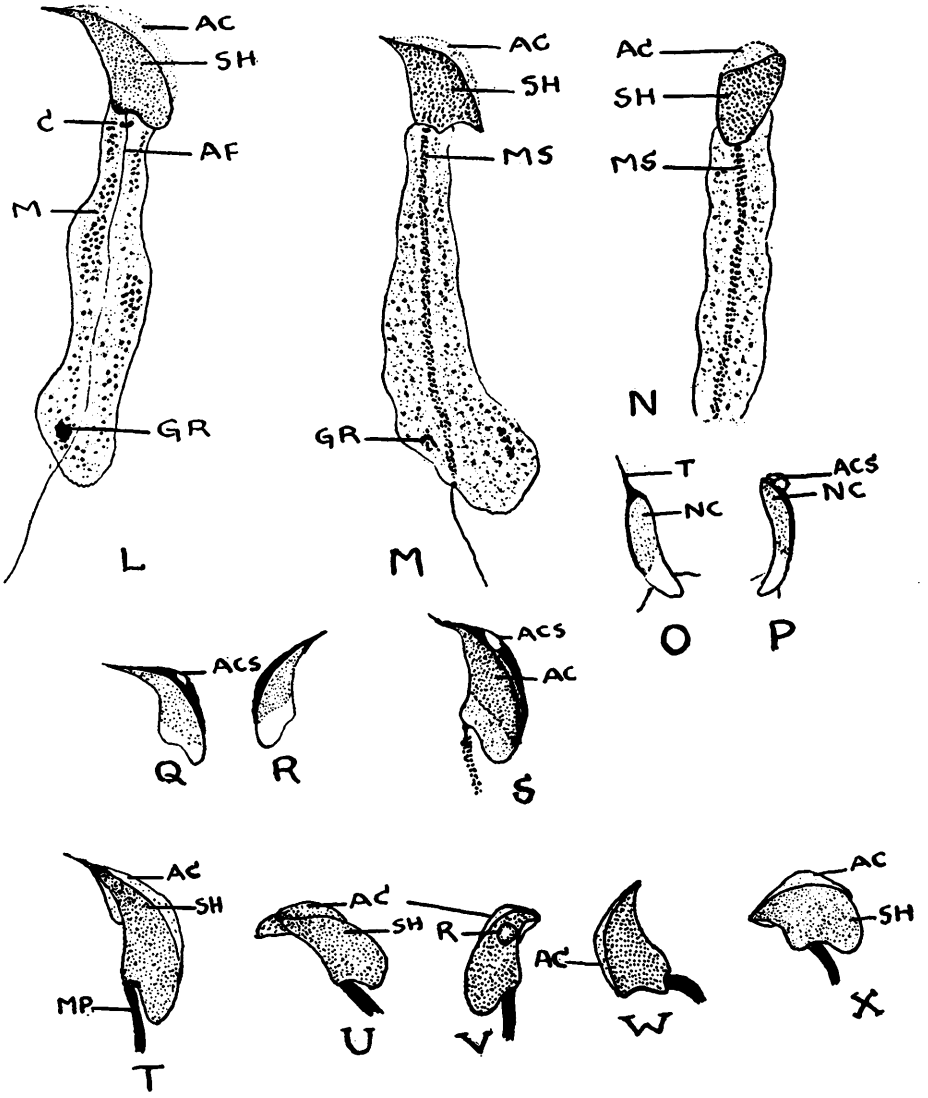


FIG. 2. Comparison of normal and abnormal late spermatid stages and mature sperms. L, a normal late spermatid; M, N, late spermatids showing abnormalities in the shape of the nucleus and acrosome; O, A normal elongating nucleus of late spermatid stage with a normal tassel and cap; P, a normal elongating nucleus with acrosomal spaces; Q, S, normal mature sperm heads with acrosomal spaces (vacuoles); R, T, normal mature sperm heads; U, V, W, X, abnormal sperm heads with abnormal acrosomes.

sperms, and sperms with twin heads are comparatively rare. The nuclear abnormality sets in at a stage when the nucleus of the spermatid has started elongating. (Fig. 1, H, I, J, K).

Studies on the acrosomal changes in spermiogenesis were facilitated by using Periodic-Acid Schiff Reaction(7). Changes in the acrosome consist of the loss of typical sickle shape and of deficiencies in development which lessen in various degrees its visible surface area (Fig. 2, U, V, W, X). In some only a thin fringe of acrosome overlies the flattened anterior nuclear pole (Fig. 2, M, W). The onset of acrosomal abnormality appears to occur in two ways. First, it may set in very early in spermiogenesis, when the acrosome vesicle and the halo around it start spreading

on the anterior pole of the nucleus (Fig. 1, D, E, G); secondly, the abnormality may set in during the midspermatid stage when its topography is disturbed mechanically by the changing nucleus (Fig. 1, H, I, J, K). It was also noted that in some of the apparently normal looking spermatozoa, the acrosome, while it had the typical sickle shape, had one, and rarely two, vacuoles (Fig. 2, P, Q, S) comparable to those of human spermatozoa(8) and those of the bull(9). While these vacuoles were rarely seen, and then with difficulty, using ordinary technics, P.-A.S. technic made it possible to count them in sections of testis.

Conclusions. Most of the sperms in the sterile individuals of these genotypes were normal looking and presumably physiologically inefficient. I agree with Chang(10) in stating that a morphologically normal sperm may be physiologically incapable of effecting fertilization. The fact that the acrosome alterations as revealed by P.-A.S. technic may easily be overlooked when treated by usual methods suggests that differences in such non-chromosomal elements may be of considerable importance in evaluating morphological normality of a spermatozoon.

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Effect of Cortisone on Histamine Liberation Induced by Tween in the Dog.* (19239)

ANDRES GOTH, ROBERT M. ALLMAN, BEN C. MERRITT, AND JAMES HOLMAN.

From the Department of Pharmacology, Southwestern Medical School of the University of Texas, Dallas.

The inhibitory effect of cortisone on certain experimental hypersensitivity reactions has been shown by several investigators. Anaphylaxis in the mouse(1,2), the Arthus phenomenon in the rabbit(3,4), the tuberculin reaction in the guinea pig(5,6), and the Shwartzman reaction in the rabbit(7) represent hypersensitivity reactions which are influenced by cortisone. In addition, clinical studies too numerous to mention indicate that improvement may follow the administration of cortisone in a variety of human diseases in which hypersensitivity appears to play a part. Somewhat paradoxically, anaphylactic shock cannot be prevented in the guinea pig(8,9) with cortisone administration, although certain features of passive anaphylaxis in this species may be modified *in vitro*(10). Also, passive anaphylaxis in the dog(11) is uninfluenced by

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