THE INTERNAL SECRETIONS OF THE SEX GLANDS

LONDON AGENTS:
SIMPKIN, MARSHALL, HAMILTON,
KENT AND CO., LTD.

THE INTERNAL SECRETIONS OF THE SEX GLANDS

The Problem of the "Puberty Gland"

BY

ALEXANDER LIPSCHÜTZ, M.D.

Professor of Physiology in Dorpat University (Estonia), formerly
Privatdocent of Physiology in Berne University (Switzerland)

With a Preface by

F. H. A. MARSHALL, F.R.S.

Author of *The Physiology of Reproduction*

With over 140 Illustrations in the text

ENGLAND
W. HEFFER & SONS LTD., CAMBRIDGE
AMERICA
WILLIAMS & WILKINS COMPANY, BALTIMORE
1924

PRINTED IN GREAT BRITAIN

Preface.

It has been known from very early times that castration in both man and animals, besides suppressing the sexual instincts, causes marked differences in the conformation of the body and the secondary characters of sex, and, moreover, that these results are most definite if the operation be performed before maturity has been attained. Numerous references to this subject occur in the works of Aristotle, who comments on the extensive modifications brought about in the general configuration as a consequence of the mutilation of a comparatively minute organ. The manner in which this influence is exerted, however, has only been ascertained comparatively recently, and although great progress has been made in the last few years there are still wide gaps in our knowledge.

According to Berman, the author of a work on *The Glands Regulating Personality*, the first to put forward the idea that the gonads produce their effect through substances discharged into the blood was Bordeu, court physician to Louis XV., in the eighteenth century. It would appear, however, that Berthold in 1849 was the first physiologist to base the conception on experimental investigation. Little account was taken at the time of Berthold's work, and it was not until considerably later that the idea of an endocrine organ which elaborated a secretion transmitted through the medium of the blood was revived by Claude Bernard to describe the glycogenic and sugar-producing activities of the liver. The conception of internal secretion received a great stimulus from Brown-Séquard's experiments with the injection of testicular extracts in 1889, and although the validity of this particular work soon became discredited, it served a useful purpose in directing attention to the study of the endocrine organs and the possibilities of applying it practically in medicine. Brown-Séquard's views, which he extended so as to refer to all the elements of the body, contributed largely to the adoption of organotherapy, the methods of which have been applied to all the organs of internal secretion as well as to others of problematic or unknown function. It was not until much more recently that Prof. Starling suggested the term "hormone" for the active principles of those internal secretions which act as chemical messengers and have a definite specific stimulating effect upon other and sometimes distantly situated organs. The result of such a stimulus is usually either growth or, in the case of a glandular organ, secretion, and one of the most obvious effects of the reproductive hormones is to produce growth. This, however, is far from being the only effect, since the influence of the testicular and ovarian hormones is manifested in greater or less degree throughout the whole body, and is extended to the psychical activities, as is plainly manifested in the display of sexual feeling and those associated phenomena which play so important a part in the activities of the organism.

There is one important respect in which the endocrine functions of the gonads appear to differ from those of other organs of internal secretion, and that is in being cyclical. For although the ovarian and testicular hormones are probably produced to some extent at all times, especially throughout the period of reproductive life, the secretions change in quantity, and probably also in the female in composition, with certain recurrent seasons. This periodicity is apparently partly inherent in the reproductive organs themselves, but it is also influenced by external or environmental factors such as nutrition and seasonal and climatic conditions. Numerous instances of the cyclical activity displayed by the gonads and the modes of working of their internal secretions, with many cognate matters, are given by Prof. Lipschütz in the pages of the present work.

The book was first published at Berne in 1919 under the title *Die Pubertätsdrüse und ihre Wirkungen.* The name "puberty gland" was given by Prof. Steinach, of Vienna, to denote the testicular and ovarian endocrine organs, since these glands, although they are believed to exert their influence on the organism from early stages of development onwards, show an especially accentuated activity at the phase of life when the gonads become mature. In the present edition, which contains a considerable amount of new matter, Prof. Lipschütz has thought it expedient to change the name to *The Internal Secretions of the Sex Glands,* a title that indicates more accurately and more completely the contents and character of the book.

The reader will find in these pages a comparative and connected account of the endocrine functions of the gonads, so far as these are known, in all groups of multicellular animals. The importance of such knowledge has now become generally recognised, and the subjects treated are of profound interest for zoologists and physiologists alike, as well as for medical men, psychologists and students of eugenics. As a guide to the literature of a branch of endocrinology that has grown rapidly in recent years the work should be of great value.

The manuscript has been written by the author in English, and in my capacity as editor I have confined myself for the most part to making such alterations as seemed to render Prof. Lipschütz's meaning more clearly. For the views expressed (with which I am not always necessarily in complete agreement) the author is solely responsible, and to him alone the credit is due.

F. H. A. MARSHALL.

CHRIST'S COLLEGE,
CAMBRIDGE.
April, 1924.

Author's Preface.

It is only owing to my esteemed friend, Dr. F. H. A. Marshall, who has contributed so much to our knowledge of the internal secretion of the ovary, that it was possible for me to publish this book. Dr. Marshall has kindly corrected my foreign English throughout the whole manuscript and afterwards read the proofs. May I be permitted here to express my sincere gratitude to Dr. Marshall, who has done all this hard work in the most unselfish manner.

It was originally intended to publish a revised translation only of my book *Die Pubertätsdrüse und ihre Wirkungen* (Berne, 1919). But when I began translating the book, together with my friend Dr. Karl Kautsky jun. in Vienna, who had undertaken to translate part of it, it became clear to me that the book had to be entirely rewritten. Since 1918 important experimental work has been done in this special field of physiology. To the foundation laid by Bouin and Ancel, by Steinach and by Tandler, facts have been added which have enriched our knowledge on the internal secretions of the sex glands and on their bearing on morphogenesis in an extraordinary manner. I mention only the important work done by Goodale and by Pézard in fowls and the quantitative investigations of the latter in the laboratory of Gley; the remarkable work done by Sand in mammals, especially on hermaphroditism; the experiments of Zawadowsky, who confirmed and richly enlarged the statements of Goodale and Pézard; the most interesting observations of Lillie and his pupils and those of Tandler and Keller on the freemartin; the work of Marshall and his co-workers, of Morgan, of Pearl, of Crew, of Athias, Harms and Wilhelm. Bouin and his pupils, and Champy, Guyénot and Kolmer have extended the problem to a great many species. Goldschmidt has given knowledge of unexpected facts on insects. Some of these new investigations have been shortly mentioned already in the first edition, but most of them were published only in the last five years. My point of view has been widely influenced also by the result of my own experimental work done during the last five years in this Institute. So a new book originated from the old one.

I have taken into consideration all the recent literature without distinction of language. I am indeed aware that some important papers may have been omitted without intention. There were also great intervals between writing the different parts of the English edition, and some very interesting statements from more recent literature could be introduced in Chapters II. and III. only very shortly during the reading of the proofs. But, intentionally, I have omitted some papers which, though much quoted in the current literature on the internal secretion of the testicle, are devoid of scientific value and are contrary to the real spirit of scientific discussion.

My personal relations with colleagues working in the same field have been of the greatest use to me. Many of them gave me the opportunity of seeing their patients, their experimental animals and specimens. These colleagues are too numerous to be named here, and I must confine myself to thanking them collectively. Many of them have contributed to the book by kind permission for reproducing their figures.

The book as it is now could not have been written without the help of those who have collaborated with me in the Institute of Physiology in Dorpat. To Dr. Karl Wagner, now Professor of Histology at the University of Kovno, I am highly indebted for his histological work. The collaboration of Dr. B. Ottow, Dr. H. E. V. Voss, Dr. W. Krause was also of great value to me, and likewise that of Dr. E. Blum-Sapas, Miss E. Kropman, Miss S. Brunnow, Miss A. Ibrus, Mr. F. Bormann, Dr. F. Lange, Mr. H. Fuchs✠, Dr. M. Tiitso and Mr. W. Faure.

Most of the figures which were in the first edition have been replaced by new ones from my own experimental observation. Dr. H. Kull and Mr. S. Vešnjakov did the photographic work, whilst Miss L. Lehbert and Mrs. Lipschütz made the drawings.

I have dictated almost the whole English manuscript to Mrs. Lipschütz. I thank her here also for the great patience and unselfishness she exhibited and for her linguistic help.

To Messrs. W. Heffer & Sons my warm thanks are due for the interest they have taken in the publication of the book and for the great care they have shown.

A. LIPSCHÜTZ.

INSTITUTE OF PHYSIOLOGY
OF THE UNIVERSITY OF DORPAT (TARTU, ESTONIA).
1*st July*, 1924.

Contents.

PAGE
PREFACE v
AUTHOR'S PREFACE viii
LIST OF ILLUSTRATIONS xv
EXPLANATION OF SIGNS xviii

CHAPTER I.

SEXUAL DIMORPHISM AND THE SECONDARY SEXUAL CHARACTERS 1

CHAPTER II.

THE RESULTS OF CASTRATION 5
A. The Results of Castration in Man . . . 5
Observations 6
Theoretical 15
B. The Results of Castration in Mammals . . 18
1. Morphological Signs of Castration . . . 18
2. The Psycho-sexual Behaviour of the Mammal . 33
C. The Results of Castration in Birds . . . 36
Observations 36
Theoretical 46
D. The Results of Castration in the Frog and in Fishes 51
E. The Results of Castration in Arthropoda . . 55
1. Moths 55
2. The Parasitic Castration of Crabs 59
3. The Parasitic Castration of Insects . . . 66
F. The Results of Castration in other Invertebrata 67
G. Summary 70
Bibliography 71

CHAPTER III.

THE INTERNAL SECRETIONS OF THE SEXUAL GLANDS 79
A. Transplantation 81
B. Feeding with Sexual Gland 92
C. Injection 93
D. Internal Secretion of the Sex Glands and Nervous System 97
1. Is there an Accumulation of the Internal Secretion in the Central Nervous System? 97
2. Physiology of the Clasp Reflex 98
3. The Pyscho-sexual Behaviour of Man . . 102
Bibliography 105

CHAPTER IV.

PAGE

THE SEAT OF PRODUCTION OF THE INTERNAL SECRETION OF THE TESTICLE 109
- A. MAMMALS 110
  - 1. The Interstitial Cells of the Testicle . . 110
  - 2. The Ligature of the Vas Deferens . . . 127
  - 3. The Retained Testicle 142
  - 4. The Engrafted Testicle 148
  - 5. The Influence of X-Rays on the Testicle . . 153
  - 6 The Relation between the Quantity of Interstitial Tissue and the Hormonic Effect 155
    - (*a*) Is there a compensatory hypertrophy in the Testicle? 155
    - (*b*) The Law of "All or Nothing" 166
  - 7. On Cyclic Changes in the Development of the Interstitial Tissue 170
  - 8. The Phases of Puberty in the Male . . . 175
  - 9. The "Follicular Theory" of Hormone-Production in the Testicle 176
  - 10. The Condition of the Interstitial Cells in Intoxication and Disease 178
  - Conclusions 185
- B. INTERSTITIAL CELLS IN THE TESTICLE OF OTHER SPECIES 186
  - 1. Invertebrates 186
  - 2. Fishes 186
  - 3. Amphibians 187
  - 4. Birds 191
- BIBLIOGRAPHY 200

CHAPTER V.

THE SEAT OF PRODUCTION OF THE INTERNAL SECRETION OF THE OVARY 211
- A. MAMMALS 211
  - 1. The Interstitial Cells of the Ovary . . . 211
  - 2. The Origin of the Interstitial Cells of the Ovary . 222
  - 3. The Influence of X-Rays on the Ovary . . 227
  - 4. Transplantation of the Ovary 235
  - 5. The Condition of the Ovary in Partial Castration . 243
  - 6. The Internal Secretion of the Corpus Luteum . 246
    - (*a*) Histogenesis of the Corpus Luteum . . 248
    - (*b*) The Functional Relationship between the Corpus Luteum and the Interstitial Tissue . 251
    - (*c*) Objections to the Theory of the Internal Secretion of the Corpus Luteum 263
  - 7. The Phases of Puberty in the Female . . 267
  - Conclusions 270
- B. OTHER VERTEBRATES 272
- BIBLIOGRAPHY 276

CHAPTER VI.

PAGE
THE SEX SPECIFIC ACTION OF THE TESTICULAR AND OVARIAN HORMONES 285
A. Experiments on Amphibians 285
B. Feminization and Masculinization in Mammals and Birds 287
1. Experiments on Mammals 288
(*a*) Feminization 288
(*b*) Masculinization 299
2. Experiments on Fowls 307
C. Experiments on Arthropoda 312
Bibliography 313

CHAPTER VII.

THE QUESTION AS TO THE ISOLATION OF THE SEXUAL HORMONES 319
A. Extracts of the Whole Sex Gland 319
B. Extracts of Different Parts of the Sex Gland . 322
Bibliography 330

CHAPTER VIII.

THE SEMINAL VESICLES AND THE PROSTATE GLAND IN RELATION TO THE DEVELOPMENT OF THE SEX CHARACTERS 335
A. Physiology of the Seminal Vesicles 335
1. Experiments on Frogs 335
2. Experiments on Mammals 336
B. Physiology of the Prostate Gland 338
1. The Effect of Prostatic Injections 339
2. Simultaneous Removal of the Seminal Vesicles and of the Prostate 340
3. Removal of the Prostate 341
C. The Secretion of the Genital Passages in Relation to the Vitality of the Spermatozoa . . . 343
Bibliography 346

CHAPTER IX.

INTERSEXUALITY 347
A. True Hermaphroditism and Pseudo-Hermaphroditism 347
B. Experimental Hermaphroditism 351
1. The Antagonism between Testis and Ovary . . 352
2. Somatic Characters of the Experimental Hermaphrodite 359
3. The Psycho-sexual Behaviour of Experimental Hermaphrodites 364
4. Histological 365

PAGE
C. INTERSEXUALITY IN MAN, MAMMALS, AMPHIBIANS, AND INSECTS 367
  1. Man 367
    (*a*) Homosexuality 367
    (*b*) Other forms of Intersexuality in Man . 371
    (*c*) Is Hypospadia a Symptom of Intersexuality? 378
  2. Mammals 379
    (*a*) Different forms of Intersexuality in Mammals 379
    (*b*) The Case of the Freemartin 383
  3. Birds 390
    (*a*) Different forms of Intersexuality . . 390
    (*b*) Experimental 394
  4. Amphibians 397
  5. Insects. Goldschmidt's Experiments . . . 400
D. CLASSIFICATION 403
BIBLIOGRAPHY 413

CHAPTER X.

EUNUCHOIDISM AND SEXUAL PRECOCITY . . . 423
A. EUNUCHOIDISM. 424
B. SEXUAL PRECOCITY 431
BIBLIOGRAPHY 438

CHAPTER XI.

SEXUAL HORMONES AND MORPHOGENESIS . . 441
A. THE ASEXUAL EMBRYONIC SOMA 441
B. DETERMINATION OF SEX 448
C. FIXATION OF SEX CHARACTERS 449
D. EVOLVED CHARACTERS OF THE ASEXUAL EMBRYONIC SOMA 453
E. TERMINOLOGICAL 454
F. ASEXUAL EMBRYONIC SOMA AND HEREDITY . . 456
G. CLASSIFICATION OF SEX CHARACTERS . . . 465
H. THE HORMONIC ACTIVITY OF THE SEX GLANDS WHICH IS NOT SEX SPECIFIC 473
BIBLIOGRAPHY 479

CHAPTER XII.

SOME PRACTICAL ASPECTS. THE PROBLEM OF REJUVENATION 483
BIBLIOGRAPHY 493

INDEX OF AUTHORS 495

GENERAL INDEX 501

List of Illustrations.

Fig. *Page*

1. Section through the penis of a eunuch 28 years old . 6
2. Section through the middle of the penis of a normal adult 7
3. Scopec of 28, castrated at the age of 16 8
4. Man of Central Europe with well developed body hair 9
5. Scopec of 24, castrated at the age of 5 10
6. Adult European woman 11
7. Normal male rat, 1 month old 19
8. Normal adult male rat 19
9. Male rat, 8 months old, castrated at the age of 1 month . 20
10. The penis and intromittent sac of guinea pig, castrated at different ages 21
11. Penis of guinea pig castrated at the age of 4½ months, drawn 2 months later 22
12. Seminal vesicles of a normal guinea pig 1½ years old . 22
13. Seminal vesicles of a guinea pig 21 months old castrated at the age of 2 weeks 23
14. Seminal vesicles of guinea pig castrated at the age of 4½ months, drawn 11 months later 23
15. Influence of castration on the rabbit's penis . . 24
16. Influence of prepuberal castration on the uterus of rabbit 25

17 a, b, c. Histological features of the uterus of normal and castrated rabbits 26, 27

18. Profile of normal and castrated cows 29
19. Pelvis of a new-born male lamb 30
20. Pelvis of a new-born female lamb 30
21. Pelvis of an adult ram 30
22. Pelvis of an adult sheep 31
23. Pelvis of a ram castrated at an early age . . . 31
24. Pelvis of a sheep castrated at an early age . . 31
25. Growth of comb and spurs in the normal and in the castrated cock 37
26. Comb of normal and castrated animals in Brown Leghorn 38
27. A Brown Leghorn capon, 3 years old 39
28. Head apparel in the cock castrated when one year old . 41
29. Ovariotomized Pullet 42
30. Hen castrated four months previously 43
31. Normal Rouen duck 44
32. Normal Rouen drake 45
33. An ovariotomized duck 45

34a. Normal Sebright cock 48

34b. Castrated Sebright cock 49

35. Pad of male Rana temporaria in July, after period of heat 52
36. Pad of male Rana temporaria in April, at time of heat . 53

37–45. Transformation of Inachus by Sacculina . . . 60

46. Male rat, 8 months old, with testicular autotransplantation at an age of 1 month 83

Fig. *Page*

47. Section through uterus of a normal rat 89
48. Section through the uterus of a castrated rat . . 90
49. Section through the uterus of a rat with ovarian autotransplantation 91
50. Brain of frog 99
51A. Section through testicle of normal guinea pig, aged about 4½ months 110
51B. Section through testicle of normal guinea pig, aged about 4½ months 111
52. Section through testicle of normal rabbit, 14 months old 112
53. Group of interstitial cells in testicle of adult cat . 113
54. Section through testicle of man 26 years old . . 114
54A. Section through testicle of human embryo of fifth month 115
55. Section through testicle of adult cat, stained with Sudan 116
56. Interstitial cells of different animals 117
57A. Development of interstitial tissue in guinea pig . . 118
57B. Development of interstitial tissue in guinea pig . . 119
57C. Development of interstitial tissue in guinea pig . . 120
57D. Development of interstitial tissue in guinea pig . . 121
58. Section through testicle of guinea pig, 2 to 3 weeks old 123
59. Section through testicle of rabbit, 2 months old . . 124
60. Section through testicle of adult guinea pig . . 127
61. Section through testicle of guinea pig 78 days after ligature of vas deferens 128
62. Testicle of adult guinea pig 131
63. Testicle of adult guinea pig, about 18 months old . 132
64. Diagram of different operations performed on the testicle of mammal 132
65. Section through testicle of rabbit 8 months old, with eunuchoid penis 134
66. Section through testicle of rabbit about 8 months old, with normal sex characters 135
67. Section through testicle of rabbit 6½ months old, with eunuchoid penis 136
68. Section through testicle of rabbit 6½ months old, with normal sex characters 137
69. Interstitial cells of rabbits with normal and eunuchoid penis 138
70. Section through testicle of rabbit 6 months old, with normal penis 139
71. Section through testicle of rabbit 6 months old with eunuchoid penis 140
72. Another section 141
73. Seminal vesicles of guinea pig (4 states) 144
74. Retained testicle of pig (bilateral cryptorchism) . . 146
75. Retained testicle of pig (unilateral cryptorchism) . 147
76. Section through testicle which 8 months previously had been subjected to autotransplantation (rat) . 149
77. Section through normal testicle of a rat about 9 months old 149
78. Section through testicle of normal adult guinea pig . 151
79. Upper testicular fragment of a partial "castrate" (guinea pig) 151

Fig. *Page*
80. A similar section 156
81. Interstitial cells of a normal adult guinea pig . . 157
82. Section through upper testicular fragment of guinea pig subjected to "complex" testicular section . . 158
83. Section through testicle of guinea pig subjected to operation V. of Fig. 64 159
84. Section through upper testicular fragment (guinea pig) 160
85. Diagram to illustrate the hypothesis that the so-called compensatory hypertrophy of the remaining testicle is only an accelerated growth 161
86. Section through testicle of rabbit 14 months old, unilaterally castrated when 1½ months old . . 162
87. Section through testicle of rabbit, 8 months old, with eunuchoid penis 164
88. Section through upper testicular fragment (guinea pig) . 165
89. Diagram: Dependence of hormonic effect upon the quantity of testicular hormones 167
90. Diagram to illustrate the law of "All or Nothing" . 168
91. Cyclic development of generative and interstitial tissue of the testicle of hibernating mammals . . . 171
92. Section through testicle cut horizontally . . . 182
93. Diagram: Cyclic development of generative and interstitial tissue of the testicle of amphibians . . 189
94. Ovary of rabbit 18 months old 212
95. Section through ovary of rabbit 213
96. Interstitial tissue in the ovary of Phascolomys . . 214
97. Lutear and interstitial cells 215
98. Section through ovary of pregnant rabbit . . . 216
99A. Development of interstitial tissue of the ovary in rabbit 217
99B. Another section 218
99C. Another section 219
100. Section through ovary of rabbit 2½ weeks old . . 220
101. Section through ovary of adult cat 221
102. Growing primary follicle in rabbit 7 months old . . 223
103. Young Graafian follicle in rabbit 11½ months old . . 224
104. Section through ovary of white rat, 62 days old . . 225
105. Influence of X-rays on sex characters in virginal female guinea pig 229
106. Other sections 232
107. Section through ovary engrafted six months previously into a castrated male 236
108. Section through ovary engrafted a year previously on a castrated male 237
109A. Disappearance of primary ova in highly hypertrophied minute ovarian fragments 240
109B. Another section, after treatment 241
110A. Decrease of number of oocytes in ovarian fragment . 244
110B. Another section 245
111. Section through ovary of pregnant cat . . . 247
112. Section through fresh corpus luteum of rabbit . . 252
113. Influence of the corpus luteum on the mammary gland of the rabbit 254

Fig. Page

114. INFLUENCE OF OVARIAN TRANSPLANTATION ON THE TEATS OF THE CASTRATED MALE GUINEA PIG .
 A. NORMAL MALE 290
 B. FEMINIZED MALE (DURING LACTATION) . . . 291
115. FEMINIZED MALE GUINEA PIG SUCKLING YOUNG . . . 292
116. BODY WEIGHT OF NORMAL AND FEMINIZED MALE RATS . . 294
117. BODY WEIGHT OF CASTRATED AND FEMINIZED MALE RATS. . 295
118. LITTER OF NORMAL GUINEA PIGS, ABOUT 7 MONTHS OLD . . 296
119. INFLUENCE OF OVARIUM TRANSPLANTATION ON SIZE OF MALE GUINEA PIG 296
120. INFLUENCE OF TESTICULAR TRANSPLANTATION ON THE CLITORIS OF THE GUINEA PIG 301
121. INFLUENCE OF TESTICULAR TRANSPLANTATION ON SIZE OF FEMALE GUINEA PIG 304
122. FEMINIZED COCKEREL 308
123 A, B, C. INFLUENCE OF EXTRACTS OF CORPUS LUTEUM ON THE UTERUS 326–7
124. INFLUENCE OF EXTRACTS OF CORPUS LUTEUM ON THE OVARY . 328
125. ARTIFICIAL OVARIOTESTIS IN THE GUINEA PIG . . . 353
126. ARTIFICIAL OVARIOTESTIS IN THE RAT 354
127. EXPERIMENTAL HERMAPHRODITISM IN GUINEA PIGS (6 STATES) . 360–1
128. SAME DRAWN FROM NATURE. 362
129. SECTION OF OVARIOTESTIS (SEE TEXT) 374
130. TWINS IN CATTLE 385
131. TWINS IN SHEEP 386
132. PROSTATE AND SEMINAL VESICLES OF A EUNUCHOID OF 28 AND OF A NORMAL ADULT MAN 425
133. TESTICLE AND EPIDIDYMIS OF EUNUCHOID OF 28 . . . 426
134. DIAGRAMS TO ILLUSTRATE HOW A CHANGED CAPACITY ON THE PART OF THE CENTRAL NERVOUS SYSTEM TO RESPOND TO SEX HORMONES INTERFERES WITH EROTIZATION, WITHOUT THE HORMONE PRODUCTION BEING DISTURBED . . . 429
135. PUBERTAS PRAECOX IN A BOY OF THREE 432
136. X-RAY PICTURE OF THE HAND OF A GIRL OF 13½ WITH SEXUAL PRECOCITY 433
137. DIAGRAM: ORIGIN OF THE DIFFERENT PARTS OF THE MALE AND FEMALE SEX APPARATUS 457
138. UNILATERAL UNDERDEVELOPMENT OF SEMINAL VESICLES IN CASE OF UNILATERAL CASTRATION IN GUINEA PIG 6½ MONTHS OLD 477
139–142. "REJUVENATION" OF SENILE DOG, 18 YEARS OLD . . 486–9

EXPLANATION OF SIGNS.

♂ = male
♀ = female
⚦ = castrated male
∞⚦ = partially castrated male
♀̸ = castrated female
t♂ = male with transplantation

t ⚦ = castrated male with transplantation
t ♀̸ = castrated female with transplantation
f ⚦ = feminized male
m ♀̸ = masculinized female

Chapter I.

Sexual Dimorphism and the Secondary Sexual Characters.

When we speak of sexual dimorphism we refer to the morphological and physiological differences between the two sexes, differences which relate to other characters *besides* the dimorphism of the generative cells. In so doing we recognise two different groups of sexual characters: first, the generative cells or the primary sexual characters, and, secondly, the so-called secondary characters. But the term "secondary sexual characters" is not always used in the same sense. By "secondary sexual characters" one often means those morphological and physiological characters which are directly connected with the sexual functions (the actual generative cells being the primary sexual characters), all the other differences between the sexes being called "tertiary" characters. On the other hand all the morphological and physiological differences between the sexes, other than the generative cells, are sometimes designated secondary sexual characters. Disputes about the boundary lines between the characters designated primary or secondary sexual characters have bulked largely in scientific literature. These terminological polemics merely show an insufficiency of knowledge of the facts. The standpoints taken up by those who have been engaged in controversy as to the meaning of the terms primary, secondary and tertiary sexual characters reflect individual opinions on the value or importance of the different characters in relation to the sexual and reproductive functions. Some authors assess a higher value and some a lower to a particular character according to their opinions as to its precise functions. And as our knowledge is still very incomplete, it is easy to understand that the opinions of various authorities as to what are primary, secondary and tertiary characters differ widely from one another.

The distinction between primary and secondary sexual characters might be based also on another wholly different view. In drawing a definite distinction between primary and secondary sexual characters one might intend to express the idea of an ontogenetic dependence of the second upon the first. One might imply that the formation and full development of the morphological and physiological sexual characters —and under the latter we have to reckon also the psychical differences between the two sexes—depend upon the sexual gland or the primary sexual characters. One would then understand that the terms in question are not used merely as more or less conventional definitions necessary for mutual understanding, but that they in reality involve a kind of explanation of the ontogenetic origin of certain characters. There is implied in this distinction of primary and secondary characters something of the nature of a genetic system of sexual differences.

Certain questions should be answered before one is in a position to group the sexual characters in such a genetic system. These questions may now be formulated.

(1) Is it possible to show that certain sexual characters are in a genetic dependence upon the sexual glands, i.e., to show that the ontogenetic development of these sexual characters is influenced by the sexual glands, and that the further persistence of these characters depends on the presence of the sexual glands?

(2) Does the formative and preserving influence of the sexual glands concern all the sexual characters, or, in other words, are all or only some of the sexual characters in a genetic dependence upon the sexual glands? In the latter case only a certain number of the sexual characters could be described as genetically secondary in comparison with the sexual glands.

(3) If it be shown that only certain sexual characters are in a genetic dependence upon the sexual glands, there arises the question whether the formative and preserving influence of the sexual glands relates only to characters necessary for the performance of the sexual function, or whether the influence of the sexual glands concerns also other sexual characters which are in a more distant relation to the sexual function, or are in no relation to them at all.

(4) How far does this genetic dependence on the sexual glands go, i.e., is a development of sexual characters for the full differentiation of which the sexual glands are necessary,

also possible to any degree at all in the absence of the sexual glands?

It will be our task in the following chapters of this book to supply answers to all these questions, basing our statements on the known data, and only after this has been done shall we have the material necessary for a genetic system. Until these questions have been answered, there can be no object gained in discussing whether or in what way we should distinguish between "secondary" and "primary" sexual characters.

Nevertheless it is desirable at the outset that we should have a clear idea as to what we mean by a "sexual character." In the present work we propose to use the term so as to include all morphological, physiological and psychological features by which the individuals of one sex of a given species differ from the individuals of the other sex of the same species. It will not matter whether these distinguishing features are related to the sexual function or not. That certain features are different in the two sexes suffices to designate them as sexual characters. For us the generative cells will be sexual characters in the same sense as the penis, the clitoris, the uterus and the prostate, as the hairiness, size and proportions of the body, as voice, temperament and sexual behaviour. The problem we have to solve is the genetic systematization of the sexual characters.

From what has just been said it follows that at the base of our attempt to erect a genetic system of the sexual characters we shall put the sexual glands. The justification for doing so will be apparent when we have dealt with the facts described in the following pages. These will show to how great an extent the sexual characters depend upon the sexual glands. But one realizes also at the outset, as has been clearly shown, that the sexual glands themselves depend in their development and function upon other internal factors. The thyroid gland, the adrenals, the hypophysis, the pineal body, are in functional relation with the sexual glands and consequently with the sexual characters also. These relationships must be taken into consideration, if we are to understand the formation and persistence of the sexual characters. Now, before we are in a position to erect a scientific superstructure we require a relatively fixed point or basis on which we may start to build. This relatively quiescent basis is afforded by the sexual gland.

Not until we have built up a genetic system of sexual characters on this basis will it be possible for us to approach the second great problem, the investigation of the manner in which the other parts of the organism influence the sexual gland and through them the sexual characters. Meanwhile we must also leave the question open as to whether the other endocrine glands and parts of the organism influence the development of the sexual characters directly, and if so, how this is effected.

We have so far tacitly assumed that the two sexes are definitely distinguishable by morphological, physiological and psychical characters, that male and female are, as it were, like two opposite poles within the same species. But we know that there are in reality transitions between "male" and "female," and what is still more important, that "male" and "female" organs are not mutually exclusive even in the same individual. Moreover, these matters must be taken into consideration in discussing a genetic system of sexual characters.

Chapter II.

The Results of Castration.

It is not our purpose in this book to give a full description of the results of castration. We shall describe these only in so far as is necessary for the purpose of discussing and answering the questions formulated above. So far as possible we shall base our position on investigations made in recent years, since the older observations were often made at random, and from an unsatisfactory standpoint. We shall include also our own observations in setting out the evidence.

A. THE RESULTS OF CASTRATION IN MAN.[1]

It is probable that the castration of bulls was universally practised wherever agriculture was sufficiently developed as to be based on the employment of animal labour. And it is at the same time very probable that the castration of animals was preceded by the castration of man himself. In any case there can be scarcely any doubt that castration of man was done in very ancient times. But what we know about the results of castration in man comes almost exclusively from observations collected in the last few decades. The older observations were made mostly on men who were castrated on account of religious beliefs. On the other hand castration has been performed frequently in recent times for therapeutic reasons; for instance, in cases of tuberculosis of the testes, and for osteomalacia and different affections of the abdominal organs in women. Sometimes cases have been observed where the testes were lost by an accident, as during the late war, or owing to criminal injury. Finally, the senile atrophy of the sexual gland in both sexes may be considered as a sort of physiological castration. On the other hand, the various cases in which the testicles or ovaries are described as being

---

[1] For references see *Biedl* (1913), pp. 258-279; *Hofstätter*, pp. 246-267; *Kammerer* (1912), pp. 62-91; *Tandler and Gross* (1913); *Hirschfeld* (1917), Chapter I.; *Koch* (1921).

congenitally absent are very problematic, as Tandler and Gross have shown in a critical analysis. But a deficient development of the testicles and ovaries has often been observed; this is a matter which we shall discuss later.

OBSERVATIONS.

The morphological and physiological changes which follow castration vary according to the age at which the organism is castrated.

FIG. 1.—*Section through the penis of a eunuch 28 years old.* × 3. c.c.p. = corp. cav. pen.; c.c.ur. = corp. cav. urethrae. The c. cav. ur. almost normally developed; c. cav. pen. much reduced.—From Tandler and Gross. (To be compared with Fig. 2.)

(*a*) After prepuberal castration in man (*Tandler and Gross*, 1909, 1910), i.e., after castration in the first decade of life, as for instance in the Russian religious sect known as Skopecs, the genital organs do not develop in a normal manner. In the adult prepuberally castrated man we find the penis, the vesiculae seminales and the prostate underdeveloped. They are abnormally small. Tandler and Gross made the interesting statement that the corpus cavernosum urethrae of such a penis attains a normal development, and that only the corpora cavernosa penis are underdeveloped (*Figs.* 1 *and* 2). The histological examination of the prostate shows a scarcity of glandular tissue. The vas deferens is relatively thin, with an even mucosa.

In the distribution and the development of the hair of the body characteristic abnormalities may be observed. The beard does not develop (*Fig.* 3). Only lanugo is present on the face. But in old age there may be, according to Tandler, a development of the beard like that present in old women. Diagnostically very important is the abnormal distribution of hair in the regio pubis. In the normal man (*Fig.* 4) the hair in this region is limited by a convex line, and in individuals with much hair there is a triangle of hair, having this convex line as the base and the navel as the apex. On the contrary, in the prepuberally castrated man we find, as in the normal woman, an horizontal, or even a slightly concave limit of the hair in the regio pubis (*Figs.* 5 *and* 6). The rest of the body, the axillae, and the extremities are deprived of the hair normally present in the male.

The skin is pale, and often swollen and creased.

The subcutaneous fat of the prepuberally castrated man is more developed than normally. The localisation of the fat is very characteristic, as was stated by Tandler and Gross and Hirschfeld. One finds much fat in the gluteal region, under the breasts, in the trochanters, in the abdominal wall, especially on the mons veneris and on the lateral sides of the upper eyelids (*Fig.* 3). Hirschfeld speaks of the "characteristic slippery and fatty face of the castrated man."[1] But it seems

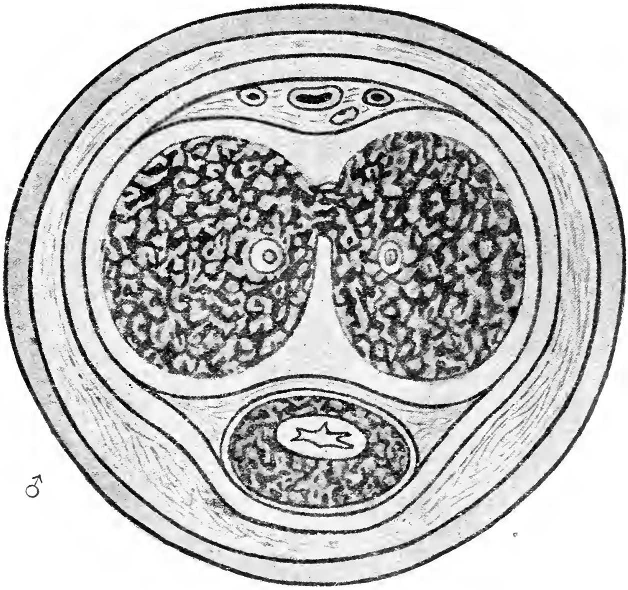


FIG. 2.—*Section through the middle of the penis of a normal adult.* x 3. Corp. cavernosa pen. above; corp. cav. ur. below.—Adaptation from Toldt.

---

[1] Gorki gives in his memoirs ("With Strange People") the following description of the Skopec: "At Sarapul (on the Volga) a strange passenger came on board; a fat man with a flabby womanish face; the long warm kaftan resembling a dressing gown and the fox fur cap with ear lapels made him still more womanlike. . . Before Jacob (the stoker on board) went again to work I asked him what kind of a man that was. But *one sees that on the spot*, my dear, he answered smiling, he is a Skopec. From far away, from Siberia! a diligent man, he has a plan of life. . . He has

that there are two different types of "castrates," the fatty and the thin one. It suffices to compare the two figures (3 *and* 5).

The skeleton of the castrated individual shows also some characteristic changes. The zone of proliferation of the epiphyses in the extremities remains longer than normally. Tandler and Gross observed by X-rays the persistence of the zone of proliferation in the proximal epiphysis of the humerus in a 35-years-old Skopec, of whom it was said that he had been castrated at the age of 8; the same observation was made on a 26-years-old Skopec. As the growth of the long bones is continued beyond the usual time, the castrated individual attains a greater height, caused by the longer growth of the under extremities. Owing to this there is a disproportion, the under part of the body being too long as compared with the upper part. In ten Skopecs who had an average height of 178 cm. Pittard found a length of 101.9 cm. for the leg, whereas the average length of the leg in Frenchmen of the same height was 91.8 cm. (*Martin*, 1914).

FIG. 3.—*Scopec of* 28, *castrated at the age of* 16. Hair of head thick, but face hairless. Fat deposits in the lateral part of the eyelids. Short neck. The larynx was found to be not prominent. — From Tandler and Gross.

The pelvis of the castrated man has a juvenile form.

The larynx of the castrated man is in its shape like a slightly enlarged infantile larynx, and the voice remains for the whole of life the same as in the normal boy before puberty. It is well known that the Church of Rome formerly made use of castration systematically to obtain 'soprani' for singing.

All examined Skopecs were found to have an extremely small thyroid gland. We have no exact knowledge on this point. In regard to the hypophysis we have direct knowledge only from

taken me as his servant. . . Will you come with me? He will take you also if I only say a word to him. . . . They will cut away from you what you do not need and will give you money. For them it is a matter of great rejoicing if they can maim a man, they reward him richly. . . . The Skopec stood on board with a white bundle under his arm, awkward and swollen like one drowned, staring fixedly at Jacob. . ."

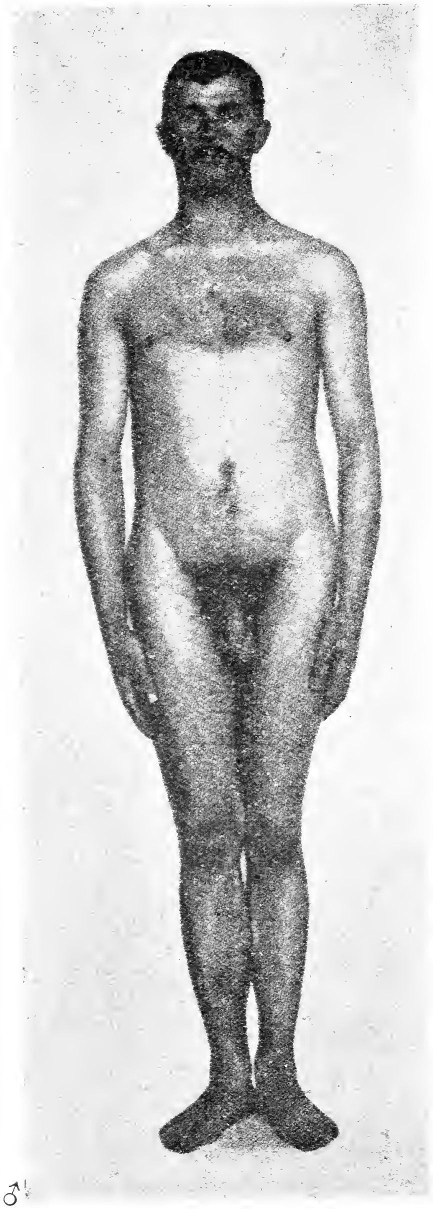


FIG. 4.—*Man of Central Europe with well developed body hair.* Compare the hairiness of the regio pubis with that of the "castrate" (Fig. 5).—From Martin.

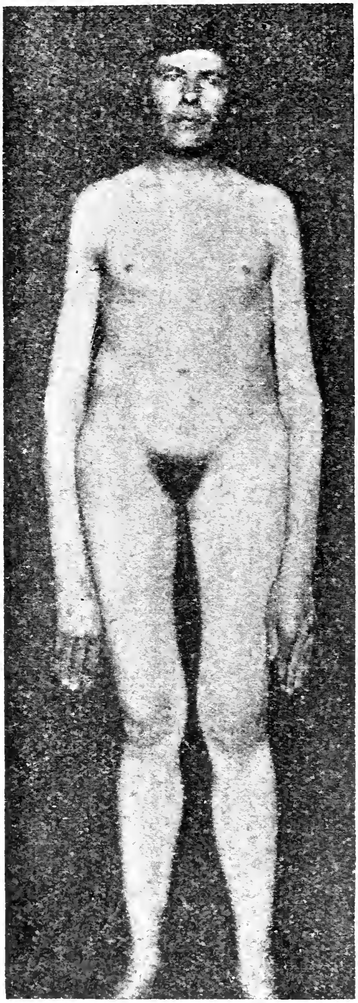


FIG. 5.—*Scopec of 24, castrated at the age of* 5. Body length 184 cm. Thin and tall. Insufficient hair on the face; no prominentia laryngea. Extraordinarily short torso without any hairiness. More developed pubic hair with a concave line above. —From Tandler and Gross.

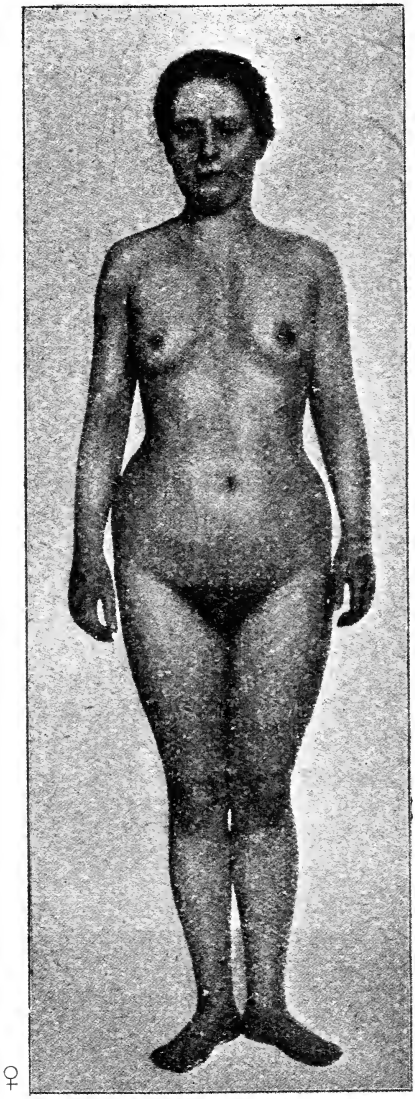


Fig. 6.—*Adult European woman.* Compare the shape of pubic hairiness with that of the castrate.—From Martin.

castrated women in whom the hypophysis was found to be greater and heavier than normally (*Kon*, 1908, *Rössle*, 1914). Tandler and Gross state that in the castrated individual the sella turcica of the base of the skull is correspondingly enlarged.

It is often said that an hypertrophy of the mammae takes place after castration in man; but it is very probable that only an accumulation of fat occurs without any hypertrophy of glandular tissue.

With reference to the psycho-sexual behaviour of the prepuberally castrated man one often reads that erection and cohabitation are still sometimes possible. Tandler and Gross observed erection in a prepuberally castrated Skopec during the examination. But on the other hand one cannot take all statements on the potentia coeundi after prepuberal castration very seriously, as every practitioner will understand; thus it is stated by some writers with absolute certainty that even after postpuberal castration erection and cohabitation do not take place as a rule after a certain time.

The general intelligence does not seem to be influenced by prepuberal castration, but a certain apathy is a characteristic feature, and sometimes psychical disturbances of a not very serious character occur.

Koch (1921) has re-examined the question of the condition of the Scopecs, and he has confirmed the statements of Tandler and Gross. For details the original paper must be referred to.

(*b*) On the results of postpuberal castration we have new observations by *Tandler and Gross* (1913), *Magnus Hirschfeld* (1916), and *Lichtenstern* (1916) on individuals between 21 and 46 years of age. These cases were carefully observed. An almost complete disappearance of the beard and a great change in the distribution of hair on the body are described. In Lichtenstern's two cases, which were men of 28 and 29 years of age, these changes were already visible after four months and three weeks respectively. In all the four cases there was superabundance of fat tissue characteristically localized in the hips, in the abdominal wall, on the breasts and on the face. Hirschfeld relates of his two cases, which were men of 21 and 46 years when castrated, and were observed by him ten and three years after the operation, that the larynx was small and the voice high. The sexual libido was completely absent in all the four cases of Hirschfeld and Lichtenstern. In the case where castration was done at the age of 46, erections still occurred, but they were not accompanied by sexual sensations. On the other hand the man castrated at the age of 21 said that he cohabited every day, but that the erections did not persist for long; the orgasm took place very quickly. Some other authors also relate that erection and cohabitation are still possible after postpuberal castration (*Busquet*, 1910, p. 250; *Oberholzer*, 1912, two very careful observations from the standpoint of a psychoanalyst). It seems that in regard to sexual libido and sexual activity after postpuberal castration, great individual variation may occur. But, nevertheless, the desirability of resorting to castration should always be considered in cases of criminal sexual behaviour. I saw myself a case of this kind with good results after castration in Hirschfeld's "Institut für Sexualwissenschaft."

In regard to the results of castration in women the available observations almost exclusively concern postpuberal castration. The data are much less uniform than in the case of the male. It is very probable that this lack of precision is due to the fact that castration in women is performed, as a rule, very late, and the external changes are of course less marked. But in all cases an atrophy of the genital organs takes place; an atrophy of the vagina and especially of the uterus. In general, menstruation ceases, although some authors relate having observed menstruation after castration. I think that they were misled by an accidental hæmorrhage. A very marked accumulation of fat takes place, and we find therefore a marked augmentation of weight. The accumulation of fat, however, is not present in all cases. The data on the distribution of the hair after castration are also very conflicting. In general it is agreed that the increased hair growth on the face (the beard of old women) is a characteristic feature of the castrated woman. But Tandler and Gross found also in old Skopecs a fair growth of beard on the chin and above the corners of the mouth, whereas the middle of the upper lip, the skin under the chin, the cheek and the upper part of the neck, which in normal men have a rich growth of hair, were hairless. Such an abnormally localized beard corresponds more to the beard so often found in old women (*Tandler and Gross*, 1910 a, p. 249). So one might suppose that the hair-growth of the aged woman after the climacteric is nothing else than a phenomenon common to the aged female and male "castrate." Some authors relate having observed an augmented growth and changed localization of hair also in other parts of the skin of castrated women, such as near the breasts and over the sternum. According to other observers, in the castrated woman, as in the castrated man, the hair of the body disappears.

As regards the breasts, a diminution and also an augmentation after castration have been described by different authors. The statements about the sexual libido are also conflicting, but it seems that it is generally diminished.

As in men, a certain psychical disturbance is sometimes observed in women after postpuberal castration, whereas the intelligence, as a rule, remains unchanged.

In many cases changes in the general metabolism occur in women after castration. The most remarkable phenomenon is the diminution in the oxygen used, and this results in the accumulation of fat. Sometimes one may observe changes in the calcium and phosphorus metabolism probably correlated with changes in the skeleton; but the data are very contradictory. Only when castration is performed on account of osteomalacia can one state with certainty that the metabolism of calcium and phosphorus depends upon the ovary. In general, the data quoted to show the influence of castration on the different metabolic processes are so contradictory that it is impossible to give a precise description of these influences.

As we said above, the cessation of function in the sexual glands in old age can also be regarded as a castration effect. In men commonly about the age of 60 or later one observes nervous troubles of an undecided nature. Much more definite are the phenomena occurring at the climacteric in women; the cessation of menstruation, the accumulation of fat, and sometimes an increase of hair on the face or the appearance of a beard. But it must not be forgotten that we have no direct evidence that these phenomena are caused by the sexual glands ceasing to function, and it is impossible to base definite conclusions as to the influence of the sexual glands in modifying the morphological and physiological characters of the organism upon this kind of observation.

THEORETICAL.

The different observations referred to above on the results of castration in man are discussed here from a more general point of view.

There can be no doubt that the formation of the morphological, physiological, and psychical characters of man depends on the sexual glands. There may be different opinions as to the extent of this dependence, and one cannot deny that the data relating to the results of castration are sometimes very uncertain, but on the other hand we are absolutely certain that this dependence exists.

Basing his position on clinical observations, *Blair Bell* (1920, p. 152), takes the view that "the gonads . . . especially in the absence of active genital cells may be described as more or less indifferent organs in the matter of sex-characterisation." A similar view was recently expressed by *Robert Meyer* (1921), who declares that "for the development of secondary female characters, both physical and psychical, ovaries are not necessary"; this statement of Meyer is based on observations on pseudo-hermaphrodite individuals. We shall discuss this question more fully in Chapter IX. Here it may be said that in any discussion *experimental evidence must take the first place*, because the conditions of experiment are more or less known to us, whereas in clinical cases the conditions are unknown.

We have seen that the sexual glands influence not only the genital organs, but also sexual characters which have nothing to do with the sexual function, such as the growth of the hair, the accumulation of fat, and the proportions of the body.

If castration is done at a time when sexual characters are already fully developed, the results of castration are not so marked as after prepuberal castration. But the influence of the sexual glands on the sexual characters may be observed even when castration is done very late. We see that the sexual gland does not only influence the development of the sexual characters by initiating and stimulating their growth but also by keeping them in a state of maximal development.

Taking into consideration the changes in some of the measurements of the skeleton, the accumulation of fat and the high voice in the prepuberally castrated man, and on the other hand the beard as one of the marked signs of the woman after the climacteric, the possibility suggests itself that castration leads not only to the disappearance or partial atrophy of the homologous sexual characters, but also to the appearance of heterologous sexual characters. In support of this view it may be pointed out that in castrated men, even when the operation is done postpuberally, the breasts may develop in a very striking manner. But, as we have said already, modern authors seem to agree that there is only an accumulation of fat in the breasts and not a development of glandular tissue. Also certain measurements of the skeleton as observed in castrated men, as for instance, those of the pelvis, which appeared to resemble those of the female, are in reality infantile; it is the same with the voice and the sexual libido. Moreover, the accumulation of fat is not a female sexual character, because it is not the fact that fat is accumulated, but rather the localization of the fat, which characterizes the castrated man. This is very different in a castrated man from what it is in a normal woman, and one cannot designate it as a female character. The only facts one might make use of in support of the suggestion that heterologous sexual characters appear after castration, are the beard and the low voice of the woman after the climacteric. But as already remarked, Tandler and Gross observed a similar beard in the castrated man. In view of these facts there can be no question of the appearance of heterologous sexual characters after castration. A similar statement may be made about animals.

As stated above, the prepuberally castrated man shows a disproportion in the growth of the different parts of the skeleton, since the growth of the bones does not stop at the normal time. It may be that the influence of the sexual glands on the skeleton is not a direct one. It is very probable that they exert their influence by the intermediation of other internally secreting glands, and this is rendered probable in view of the fact that the sexual glands react upon almost all the other glands which elaborate internal secretions (see especially *Bell*, 1920), and these in their turn influence the growth of the organism in manifold ways. *Koch* (1921), when examining the Scopecs, has especially insisted on this question. He postulates, like Tandler, different types of "castrates," the one being "hypophyseal-adipose," the other "acromegalic." According to Koch it depends upon the age at the time of castration which type will develop. I think that possibly the individual endocrine condition in general is of great influence on the results of castration. Unfortunately the mutual relations of the organs producing internal secretions are not yet sufficiently known, and at present it is only possible to discuss this question superficially. The complete elucidation of the problems involved in the study of these interrelations implies the solution of all the problems of biochemistry.

Taking into consideration the fact that some sexual characters remain after castration ever after in an infantile stage, and especially that the skeleton is longer than normally in that stage, Tandler made the suggestion that some of the phenomena observed in the castrated individual are merely symptoms of a prolonged prepuberal stage ("protrahierte Unreife"), the result being that the sexual divergence is less marked in the castrated than in the normal individual. The castrated man and woman tend more or less towards a common type, that is, to a juvenile form common to both sexes, or to a form in which sexual divergence has not yet taken place (*Tandler and Gross*, 1913, p. 58). One might object that there are in the castrated man some features, as, for instance, the larger pelvis and the hairless face, the female character of which cannot be denied; but these features are only apparently female. Although it is illegitimate to explain all differences in body shape between man and woman by the woman remaining always in an infantile stage, or by the growth of the woman's body stopping earlier than that of the man, it seems certain, as *Martin* (1914, pp. 33 and 205) points out, that the body shape in the woman is nearer to the infantile form than that of the man. Under these circumstances one can understand that the castrated man must have some characters which seem to be more or less female, but are in reality not necessarily female characters; they should be regarded rather as infantile, and common to both sexes.

The facts recognised by Tandler and related above, compel us to believe that in the ontogenetic development of the soma there is in the beginning an *asexual* stage, the subsequent differentiation of which is caused afterwards by the formative influence of the sexual glands (*Steinach*, 1912, *Lipschütz*, 1917 and 1918 a). It is true that the results of castration in man might be interpreted differently. One might point out that some sexual characters, as for instance, the penis, the beard, and the sexual libido can continue their development to a certain degree after prepuberal castration. And after postpuberal castration the sexual characters, both physical and psychical, persist to some extent. So the sexual characters are in a certain degree independent of the sexual gland, and the influence of the latter on the former may be understood as of the nature merely of a "protection" necessary for the development of the sexual characters. This view was put forward notably by *Halban* (1903). But on the other hand we must not forget that castration, even when done as early as possible, is always performed on an organism with sexual characters already partly developed, and we cannot exclude the possibility that the sexual glands before removal were already able to fix, in a sexual sense, the embryonic soma. Thus the fact that some sexual characters persist after castration is no real evidence against the conception of an asexual stage in the ontogenetic development of the soma.

But we must confess that the observations made on the castrated man do not supply the proof we would like to have in dealing with the question whether and how far the "castrate" approaches to a type common to both sexes, although it must be said that our conception that every sexually differentiated soma goes through an asexual stage during ontogenetic development, is not incompatible with the facts observed in man. Now the experimental investigations made with castration in mammals, and still more those in birds, give a very strong support to this conception. We shall see that for birds the existence of a common type after castration is a well-established fact, at least in regard to external appearance.

B. THE RESULTS OF CASTRATION IN MAMMALS.

1. Morphological Signs of Castration.

Although castration was performed on mammals, such as on the bull and the horse, even in ancient times, our knowledge of the influence of the sexual glands on the development of the sexual characters of this class was not much advanced thereby. Not until lately have systematic scientific observations been made on the bull and the cow. Important data upon the question as to the results of castration have been obtained from experiments made on the rat, guinea pig, rabbit, dog, and hedgehog.

If we perform castration on young male rats about four or six weeks old we observe very striking results on the genital organs (*Steinach*, 1894, 1910). These organs are very slightly developed (*Fig*. 7) in the young rat. The vesiculae seminales are very small. Of the prostate macroscopically very little is to be seen. The penis is short and thin. The corpora cavernosa have not yet formed the characteristic proximal part of the penis. In the full grown animal (*Fig*. 8) the vesiculae are enormous sacs filled by a coagulable secretion; the prostate is a great lobular organ; the penis is long and wide and can be easily protruded; the corpora cavernosa form the proximal

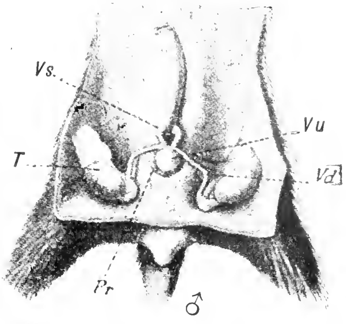


FIG. 7.—*Normal male rat*, 1 *month old*. T. = testis; Pr. = prostate (macroscopically almost invisible); Vd. = vas deferens; Vs. = seminal vesicles (infantile stage); Vu. = bladder.—From Steinach.

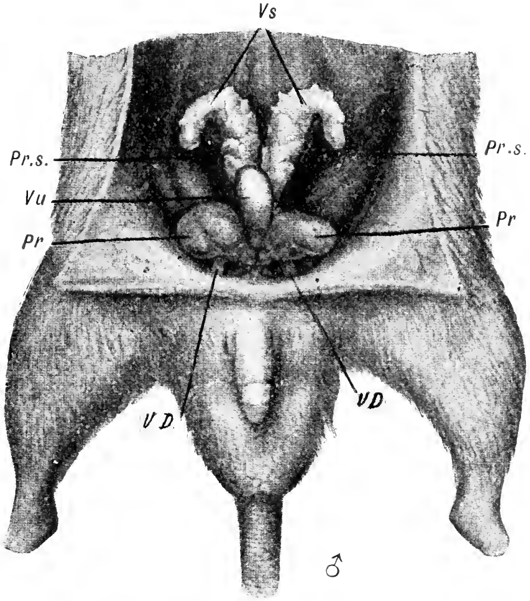


FIG. 8.—*Normal adult male rat*. Testis in the scrotal sac. Explan. signs as in Fig. 7; Pr s. = prostatic tissue around the sem. vesicles.—From Lichtenstern.

part of the penis. Wholly different is the copulatory apparatus of a full grown "castrate" (*Fig.* 9). The vesiculae and the prostate are here in the same stage of development as in a four or five weeks old animal, and the penis has grown but little. I observed an underdevelopment of the genital apparatus also in white mice which were castrated by Ottow and myself, when weighing about 4.5 gr. We observed a very marked underdevelopment of the vesiculae and of the penis.

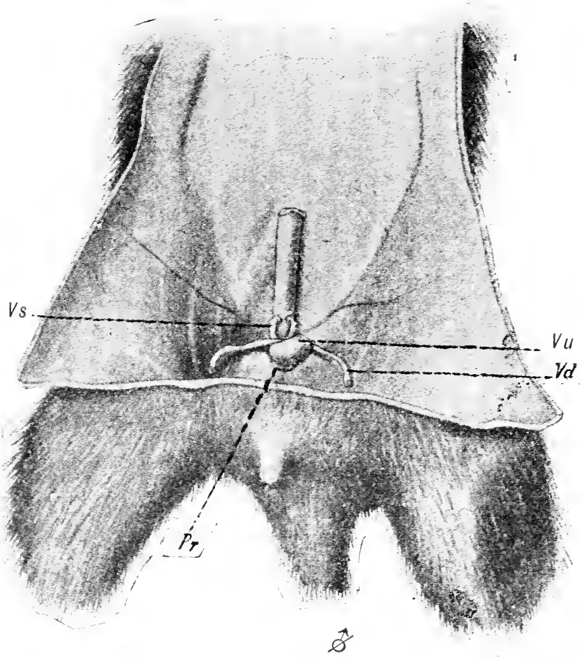


FIG. 9.—*Male rat, 8 months old, castrated at the age of* 1 *month.* Vd.=sectioned vasa deferentia. Prostate and seminal vesicles remain at the same infantile stage as in Fig. 7.—From Steinach.

I made detailed observations on guinea pigs. The penis of an adult guinea pig, castrated when about two weeks old, is smaller than in the normal animal, but externally it has the characteristic features of the normal penis (*Fig.* 10). We see that the distal part of the corpora cavernosa penis, not yet formed at the time of prepuberal castration, can develop however to a certain degree (*Fig.* 10, D *and* E). This is of great interest, as the development of this part of the penis really depends on the testicle; it never attains the same size after prepuberal castration as it does during normal postpuberal development, for in the normal animal it continues to grow for more than a year after the attainment of puberty at an age of about 2½ months. The influence exerted by the testicle before castration may suffice in some instances to maintain the growth for a certain time after prepuberal removal of both testicles, contrary to what we see with the vesiculae seminales, or to what Marshall observed with the horns of sheep, which also stop their growth immediately after castration. The

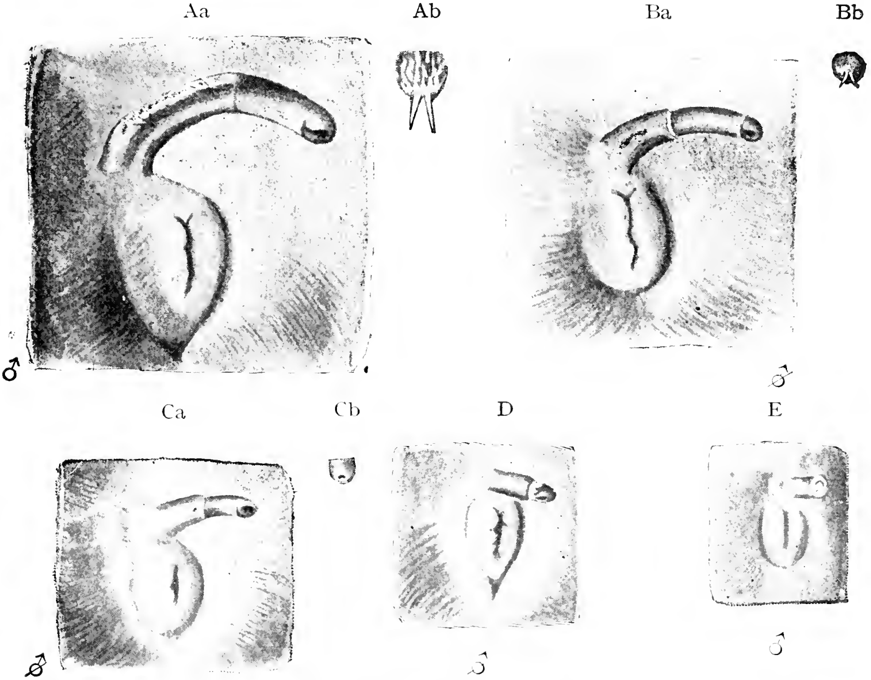


FIG. 10.—*The penis and intromittent sac of guinea pig, castrated at different ages.* Nat. size. Aa, Ba, Ca, D, E = penis. Ab, Bb, Cb = intromittent sac.

A. Normal, 12 months old.
B. Castrated at 6 months, drawn at 12 months (Prot. Nr. 25). Penis shorter. Mucosa of intromittent sac smooth; horny styles very shortened.
C. Castrated at 1½ months, drawn 7½ months later (Prot. Nr. 15). Penis shorter than in B; horny styles invisible.
D. Castrated at ½ month, drawn 6½ months later (Prot. Nr. 23). Penis very short, but more developed than the juvenile penis (E).
E. Normal penis at age of ½ month.

age at the time of castration is of great importance. A series of observations carried out with *Bormann* (1922) showed this very strikingly. In the corpora cavernosa urethrae of the guinea pig there is a blind sac on the bottom of which two horny styles may be seen; in erection this blind sac is turned back like a finger of a glove (*Fig.* 10, Ab); the horny styles are protruded and moved rhythmically. I showed that the horny styles may regenerate to a certain degree in the normal animal; if in an animal a year old we cut away a horny style 5 or 6 mm. long, leaving only a little stump of less than 1 mm., we shall observe a regeneration of the latter to a length of about 3 mm. If now we castrate a guinea pig with horny styles of about 5 mm. the latter diminish in a few weeks forming finally only thin stumps of about 1 to 2 mm. (*Fig.* 10, Bb). If the

FIG. 11.—*Penis of guinea pig castrated at the age of 4½ months, drawn 2 months later* (Phot. Nr. 27). Great quantity of preputial secretion.

FIG. 12.—*Seminal vesicles of a normal guinea pig 1½ years old* (Prot. Nr. 80). Nat. size. Below the vasa deferentia are to be seen.

castration is performed on a younger animal with horny styles about 2 mm. long, the latter diminish as far as the bottom of the blind sac, and no horny styles can be seen with the naked eye or magnifying glass (*Fig.* 10, Cb). In how striking a manner the result varies according to the age at which castration was performed, is also shown by our observations on the penis in general (*Figs.* 10 *and* 11) and on the vesiculae seminales (*Figs.* 12, 13, 14). A detailed histological examination of the changes the vesiculae seminales undergo in the guinea pig after castration was made by *Gley and Pézard* (1921). The epithelium, normally cylindrical, becomes cubical, and loses its granulation. By this fact the changes in the secretory activity of the vesiculae seminales after castration can be explained. Similar observations were made by *N. F. Fisher* (1923) in the rat. As was stated by Gley and Pézard and by myself, the secretion of the vesiculae seminales, which normally coagulates under the influence of the prostatic juice, does not coagulate after castration.

FIG. 13.—*Seminal vesicles of a guinea pig* 21 *months old castrated at the age of* 2 *weeks* (Prot. Nr. 23). Nat. size.

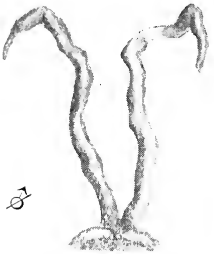


FIG. 14.—*Seminal vesicles of guinea pig castrated at the age of* 4½ *months, drawn* 11 *months later* (Prot. Nr. 27).

A characteristic feature in the castrated guinea pig is the accumulation of preputial secretion on the penis (*Fig.* 11).

The penis remains undeveloped or infantile after prepuberal castration also in the rabbit, as was stated by *Richon and Jeandelize* (1903). They castrated rabbits of one to two months old, and observed them during one year. The difference between the penis of a normal adult rabbit and that of a prepuberally castrated animal of the same age is extraordinarily striking (*Fig.* 15, B *and* C). The distal part of the corpora cavernosa penis, designated as a glans penis, is absent after prepuberal castration. Although the penis continues to grow after prepuberal castration, it does not acquire the characteristic shape of the normal penis.

A careful investigation of the relations between the testicle and the activity of the prostatic gland in the dog has been made by *Amantea* (1919).

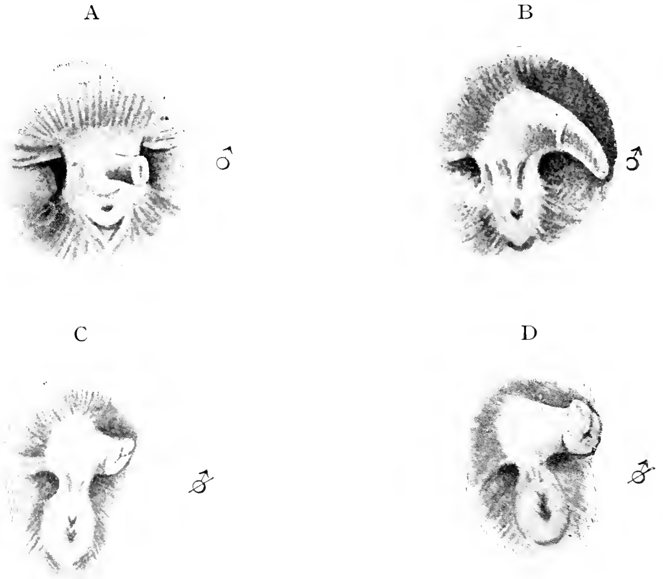


Fig. 15.—*Influence of castration on the rabbit's penis.*

A. Normal, 2 months old.
B. Normal, 12 months old. (Prot. Nr. 42).
C. 12 months old, castrated when 2 months old (Prot. Nr. 43).
D. 12 months old, castrated when 6 months old (Prot. Nr. 56).

All these experiments show that normal development of the genital organs is possible only when the sexual glands are present in the organism. But I have mentioned already that there is a diminution of the length of the horny styles also after postpuberal castration in the guinea pig. An even more striking instance of this kind is presented by observations made on the penis of rabbits postpuberally castrated. At the time of the operation the penis was fully developed, having attained the characteristic shape of the normal adult animal;

about three months later the degeneration of the penis proceeded so far that it more or less resembled that of a prepuberally castrated rabbit (*Fig.* 15, D). It is of great interest to notice that the penis remains sometimes almost unaltered during one or two months after castration to undergo afterwards a more or less rapid and almost complete atrophy of the distal part of the corpora cavernosa penis. We see how different are the reactions of the various parts of the organism to the removal of the testicles.

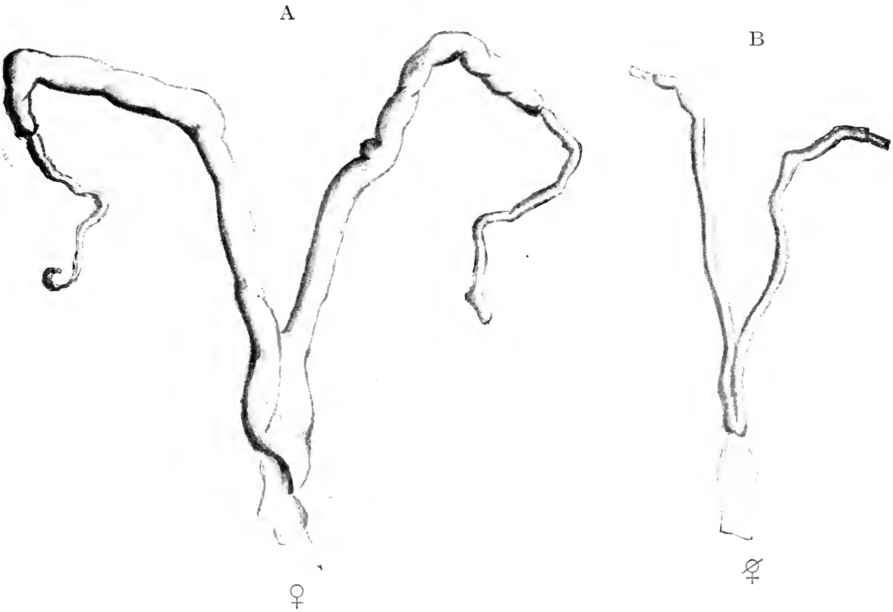


FIG. 16.—*Influence of prepuberal castration on the uterus of rabbit.*
A. Uterus and tubes of normal rabbit (Prot. Nr. 129) 8 months old.
B. Uterus of rabbit of the same litter castrated at an age of 2 months and 10 days (Prot. Nr. 127).

Observations made on female mammals[1] also showed that after prepuberal castration the genital organs cease to develop. The difference between the uterus of a normal and that of a prepuberally castrated rabbit is very striking, both macroscopically and microscopically (*Figs.* 16 *and* 17). There is an underdevelopment both of the mucosa and of the muscle

---

[1] See the books of *Biedl*, *Kammerer*, *Tandler and Gross*, especially *Carmichael and Marshall* (1907) and *Marshall* (1910), Ch. IX.

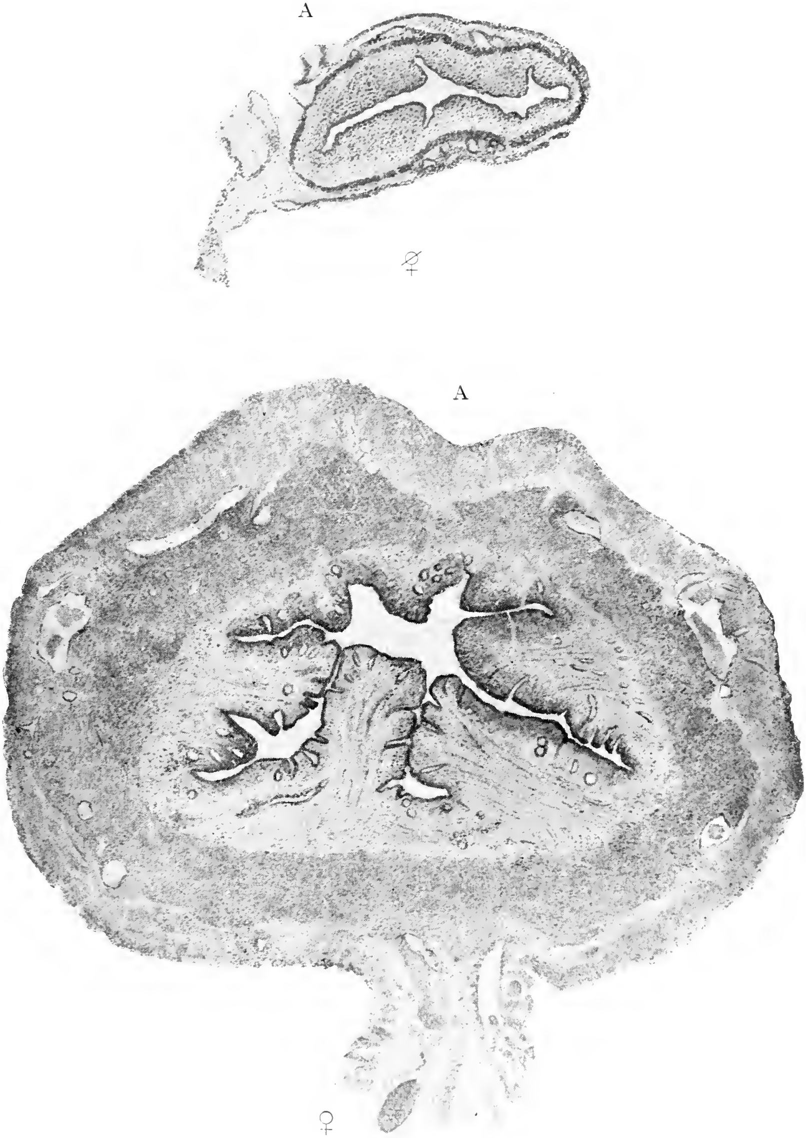


Fig. 17.—*Histological features of the uterus of normal and castrated rabbits* (Prot. Nr. 129 and Nr. 126, both of same litter).

A. Section through uterus; low magnification. All layers of the uterine wall (mucosa, muscularis) are highly reduced in the castrated animal.

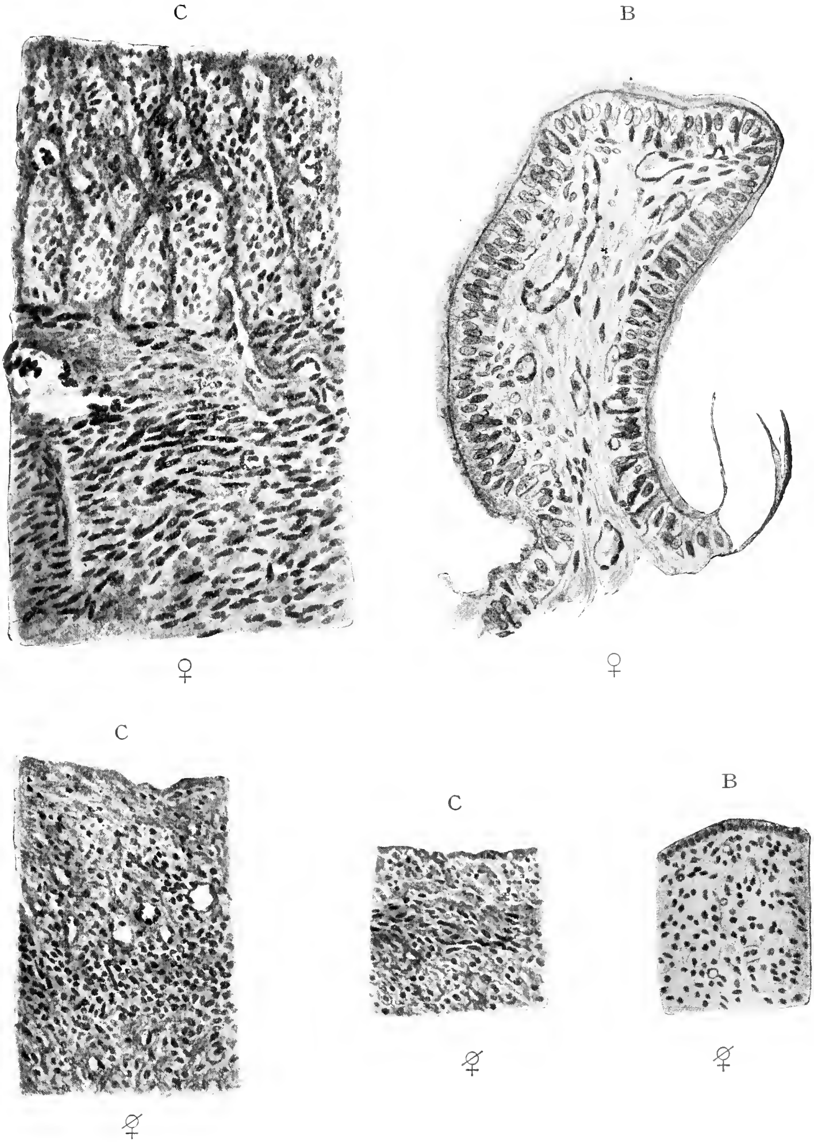


FIG. 17.—*Histological features of the uterus of normal and castrated rabbits* (Prot. Nr. 129 and Nr. 126, both of same litter).

B. The uterine mucosa; high magnification. No folds of mucosa in the castrated animal.

C. Muscular wall; high magnification.—Prepar. of Wagner; design of Lehbert.

layers. Glands are absent in the mucosa and the epithelium is flattened. The muscle layers are several times thinner than in a normal uterus. The vascularization of the uterus is also diminished. Similar observations have been made on guinea pigs, on rats, and on the cow. *Athias* (1919) has shown in experiments on the isolated uterus of guinea pigs that the uterus after castration is functionally different from the normal one; the intensity of the spontaneous contractions of the uterus decreases after castration or they may even disappear.

What is stated about the features of the mammary glands of animals after castration is just as contradictory as in the case of man. *Sellheim* (1901) described in calves castrated at six or eight weeks of age an augmented growth of the mammary glands, both nipple and glandular tissue. The older the ox is the more striking is the difference between it and the bull, the nipples of the ox being longer and broader, the glandular tissue showing microscopically a richer development in the ox than in the bull. Even milk secretion after castration is reported. In male guinea pigs and rabbits prepuberally castrated, I never could observe an increased growth of the nipples; but the question is worth further investigation in regard to the microscopical character of the glandular tissue. Very contradictory, also, are the statements made on the mammary gland after castration in the female mammal. Halban and Steinach found that the mammary gland of prepuberally castrated guinea pigs remained undeveloped. But some authors seem to have observed that after postpuberal castration the mammary gland not only persists, but can even increase and secrete colostrum (*Kammerer*, 1912, pp. 108 and 109). I think that a mistake may have occurred here, as small particles of ovarian tissue left unintentionally in the body can replace functionally the whole ovary, and they can grow and even undergo a very marked hypertrophy, as was stated by *Carmichael and Marshall* (1908) and confirmed by myself (1922).

In prepuberally castrated animals heat never occurs; the genital organs not being fully developed cannot undergo the characteristic cyclical changes. With postpuberally castrated animals the data are contradictory, as they are with those on menstruation in women. But in general it seems that investigators have not directed their attention in a sufficient manner to this question in mammals. Marshall affirmed definitely that heat does not occur in the hedgehog when postpuberally castrated.

A great number of observations have been made on the growth of the skeleton in the castrated mammal. These observations have shown that different parts of the skeleton react to castration in a different manner. This explains why the skeleton as a whole has other proportions than normally. and even each single bone. As in man, so also in certain mammals the bones of the extremities are longer, this having been shown by measurements on guinea pigs and rabbits, though the differences may not be very significant, as in the experiments of *Moore* (1922) on guinea pigs. As in man this phenomenon is presumably caused by the more prolonged persistence of the zone of proliferation. Observations on the skeleton after castration have been made also on the dog, sheep and ox. The observations of Tandler and Keller, who measured a great number of normal and castrated cows and bulls, are very important. They found striking differences in the height of the normal and of the castrated cow. Out of eleven castrated cows ten attained a height of 140 cm. or more; out of 250 normal animals only four attained this height (*Fig.* 18). The greater height is due to the longer extremities.

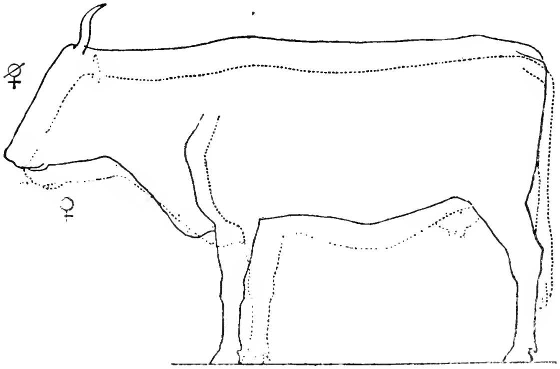


FIG. 18.—*Profile of normal and castrated cows.* Normal, average of 100 animals; castrated, average of eleven animals.—From Tandler and Keller.

Very careful investigations have been made also on the skull of the castrated mammal. *Tandler and Keller* (1910) stated that the very striking sexual divergences in the size

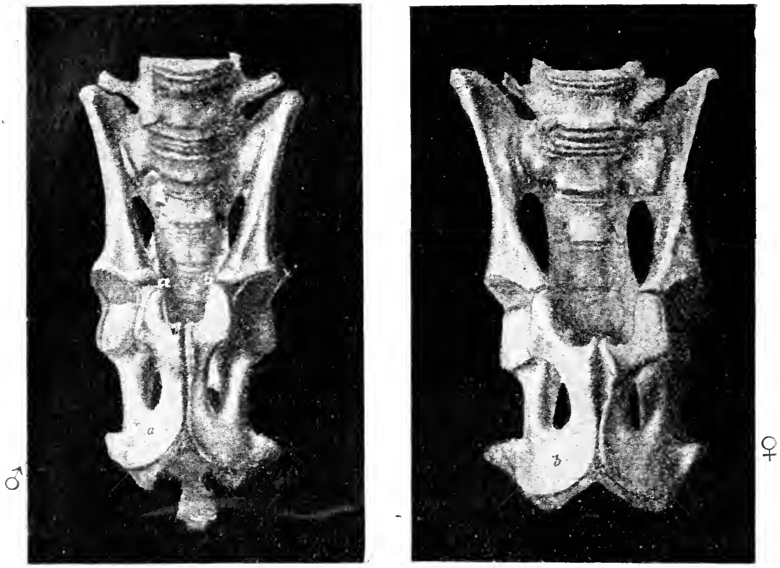


FIG. 19.—*Pelvis of a new-born male lamb.*

FIG. 20.—*Pelvis of a new-born female lamb.*

Great similarity between male and female. The female pelvis somewhat bigger, but relative proportions identical.—From Franz.

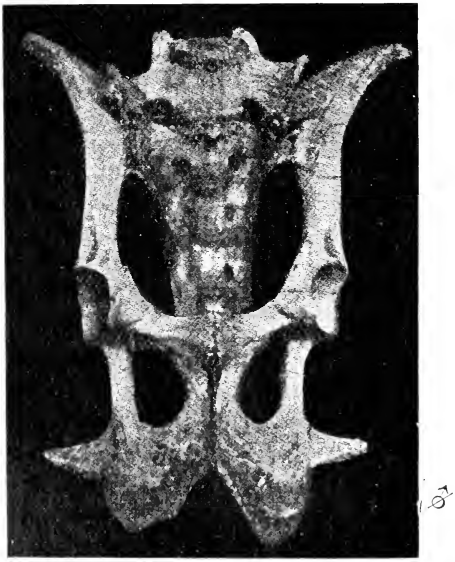


FIG. 23.—*Pelvis of a ram castrated at an early age.*

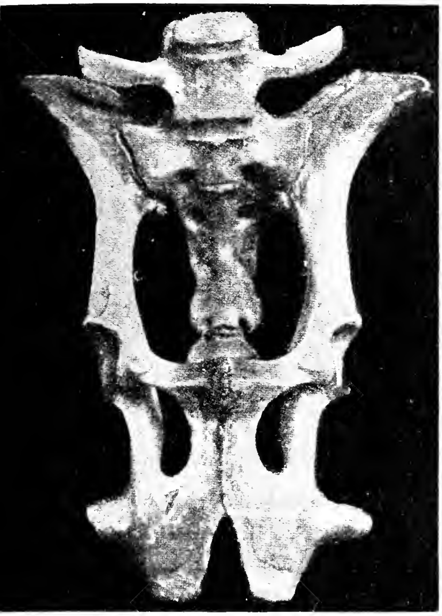


FIG. 21.—*Pelvis of an adult ram.*

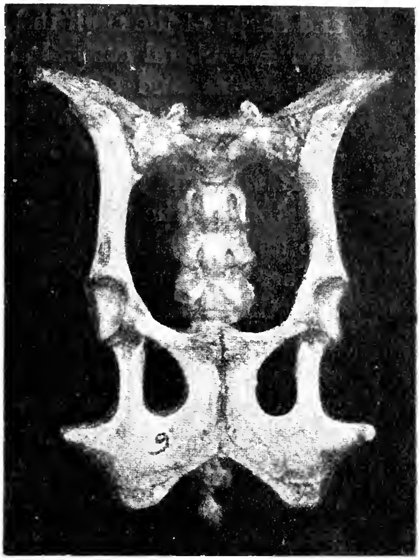


FIG. 22.—*Pelvis of an adult sheep.* Very pronounced differences between both sexes. From Franz.

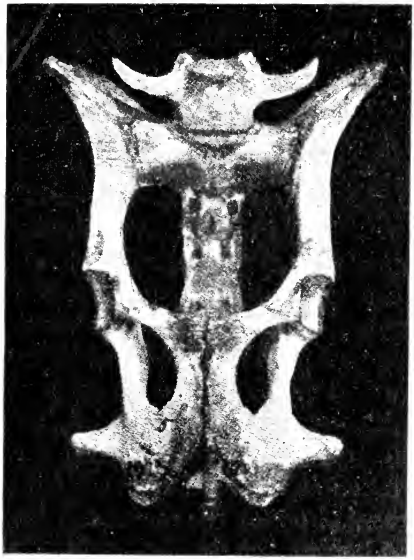


FIG. 24.—*Pelvis of a sheep castrated at an early age.* The castrated animals were of the same age (2 years) as the normal ones in Figs. 21 and 22. Great similarity between the male and female castrate.—From Franz.

and shape of the skull in horned cattle are much less marked after prepuberal castration, there being a great resemblance in the size and shape of the skull in the castrated cow and the ox. The ox and the castrated cow are very similar also in the proportions of the body. Castration leads, according to Tandler and Keller, to a convergence of both sexes. The skeletons of the castrated cow and bull represent something like an asexual type.

These statements of Tandler and Keller are in accordance with those made previously by *Franz* (1909) on the pelvis of the sheep. Franz examined the pelves of new-born lambs and of fully grown male and female sheep; he found no striking sexual differences in new-born lambs, whereas the pelvis in fully grown sheep was very different in both sexes (*Figs.* 19-22). These differences are due to variation in the size and shape of the bones which compose it. But in male and female sheep which were castrated soon after birth, Franz found the pelvis two years after the operation, i.e., at a time when the growth of the animal is completed, very similar in castrated animals of both sexes (*Figs.* 23 *and* 24). The figures leave no doubt about the tendency of the pelvis of the castrated male and female to approach a common form or an asexual type. If a small particle of the ovary remained in the body the pelvis developed normally.

There can be no doubt that in mammals there is no development of characters characteristic of the other sex after castration. On the contrary, what we see in mammals gives us new and important evidence that castration, performed at an age when sexual characters are not yet very marked, leads the organism to a form common to both sexes. The observations of Franz on the pelvis, and of Tandler and Keller on the skull, are very important in this connection.[1] It may be also that the observations made on the mammary gland of the ox where an increased growth was recorded, and those on the mammary gland of the cow where an underdevelopment occurs, can be taken as further evidence for the conclusion of Tandler and Gross. But for the mammary gland the question would appear to be not yet decided. (For the castrated deer see *Tandler and Gross*, 1913, pp. 31-40).

---

[1] New important data as to this were given by *Zawadowsky* (1922).

As in man changes in the hypophysis after castration have been found in the rat, guinea pig, rabbit, horned cattle and buffalo. An increased volume and weight and characteristic histological changes have been recorded. (See especially *Schoenberg and Sakaguchi*, 1917).

For the changes occurring after castration in the other glands of internal secretion, such as the thyroid, the pineal, the suprarenals, the thymus, *Bell's* book (1920, pp. 38-46) may be referred to. According to *Ocaranza* (1921, 1922) a diminution of the number of the red corpuscles occurs after castration. Transplantation of testicle induces an increase in the number of red corpuscles. But these changes are transitory.

As already said, the changes in the skeleton as observed after prepuberal castration, and characterized by Tandler and Gross as a prolonged infantile stage, are probably caused through the intermediation of the internally secreting glands. The question of the mutual relations between the sexual and other endocrine glands is of great importance in relation to the physiology of growth.

A great many observations have been made on the metabolism of the castrated animal, but little definite knowledge exists on this subject. The accumulation of fat, however, may be mentioned. In prepuberally and postpuberally castrated male rabbits I found six to sixteen months later enormous quantities of fat in the abdominal cavity such as I never saw in normal males; the quantity of the fat in the abdominal cavity represented as much as 10 % of the body weight, whereas in the control animal of the same litter less than 3 % of fat was found. The greater weight of the "castrate" seems to be due according to my weighing, especially, if not exclusively, to the accumulation of fat. *Moore's* papers (1919, 1922) may be referred to, but further data are needed on this point.

2. THE PSYCHO-SEXUAL BEHAVIOUR OF THE MAMMAL.

Besides the morphological changes a series of changes in the psycho-sexual behaviour also has been recorded in the castrated mammal.[1] As far as I know the first systematic

---

[1] To simplify matters we will call all morphological and physiological characters alike physical or somatic. By "psycho-sexual behaviour" we mean all the reactions brought about by the intermediation of the nervous system.

observations on the psycho-sexual behaviour of the castrated mammal were made by *Steinach* (1894; see also *Exner*, 1903, p. 221). He records that male rats castrated at an age of 45 days first showed signs of sexual activity at the ninetieth day, i.e., at the same time as a normal control animal. They recognised a female "on heat," followed her in the same manner as a normal male would, and even made some attempts at coitus. But erection was only rarely to be observed. With a normal strange male the "castrates" fought less vigorously. After a space of a year even these traces of a diminished sexual activity disappeared.

I have made some observations, but not very systematically, on prepuberally castrated guinea pigs. If a female is put into a cage with a normal male, the latter recognises her by smelling her body in the neighbourhood of the vulva; a similar behaviour on the part of the normal male may be observed even when the other animal is also a male. If the strange animal is recognised as a female, she will be followed by the male, who makes attempts at coitus. The normal male shows great tenacity in following the female guinea pig and making these attempts. The prepuberally castrated male, on the other hand, shows no such tendency. Sometimes the "castrate" will fight with the female, but often he will display no excitement whatever. I once witnessed the following scene. A female, probably on heat, was followed by a normal male with great tenacity. When the normal male was taken away, and replaced by a castrated male, the latter remained quietly in a corner. The female approached him, and even bit his fur, but without any result; the "castrate" remained as quiet as before. A "castrate," if put with a female together with a normal male, will be recognised sooner or later by his want of sexual interest. If attempts are made by the castrated male to follow the female, the normal male will interfere, and the "castrate" will soon become quiet. He will only fight if attacked. Nevertheless, castrated animals sometimes fight together in the presence of a female.

There can be no doubt that postpuberally castrated males may show sexual behaviour for a considerable time. Steinach records normal sexual libido in rats four, or even six, months after castration; *Lichtenstern* (1916 a) confirmed these observations. Faure in our Institute observed sexual activity in postpuberally castrated rabbits about two months after the operation. But eventually the postpuberally castrated animal also will lose its sexual activity; about three months after the operation adult castrated male rabbits can be distinguished from normal males.

All these experimental observations are in accordance with those upon male domestic animals, in which after prepuberal castration sexual activity disappears after a certain time. Horses postpuberally castrated lose sexual activity after about two or three years. According to French military veterinarians about 2 or 3 % of castrated horses continue to show sexual activity, and even undergo coitus with sterile ejaculations. *Busquet* (1910) whom I quote, thinks that possibly another organ replaces the sexual glands in these cases; but this suggestion is not supported by evidence. The psycho-sexual behaviour of man and mammals is very different according to the age at which castration was performed and according to the period of time after castration. The older the animal at the time of castration and the shorter the period after the operation, the greater the probability that some signs of sexual activity may continue. There can, however, be little doubt that castration generally leads to disappearance of sexual activity in the horse as in other mammals.

It now seems certain that the sexual glands not only are responsible for the development of the psycho-sexual behaviour, but also for its continuance after full puberty is attained. Prepuberal castration admits of the existence of a rudimentary sexual behaviour; when castration is done after the psycho-sexual behaviour has been fully developed, the influence of the sexual glands exerted hitherto evidently suffices for its continuance for some time; possibly because certain reflex actions which lay at the root of the sexual behaviour are more or less fixed under the influence of the sexual glands. But, as already said, sexual activity eventually ceases soon after postpuberal castration. There seems to be some difference between man and animals in this respect, sexual activity continuing longer and being more frequently displayed in the former than in the latter. I think that this is to be explained by the reflex actions responsible for erection and coitus being fixed and brought into play in the normal man by more manifold external factors than in the lower mammal. These external factors seem to be very uniform in the latter, and olfactory stimuli play an important part. Steinach records an experiment in which he smeared the labia of a female rat with a mixture of cod liver oil and paraffin, with the result that this female was not followed, and coitus was not attempted with her by a blind male until the labia were cleaned with soap, when the male once more showed sexual excitement in her presence. On the other hand the sexual reflexes in man are put in action by many different stimuli. It seems that in man any external stimulus may excite the sexual reflexes. This is due to the high psychical development of man. Sexual fetishism finds its roots therein, being some kind of a "conditional reflex" in the sense of Pavlov. So it is not difficult to understand that sexual activity may persist some time in man after postpuberal castration, and *a priori* one would expect to find sexual activity even in the postpuberally castrated man more often and more markedly than actually is the case. Persistence of some signs of the sexual activity which diminish very slowly after postpuberal castration is by no means incompatible with the contention that the *erotization* of the nervous system (*Steinach*, 1910) depends upon the sexual glands.

What we said about the influence of the sexual glands on the development and the maintenance of the sexual reflexes in animals and in man is also true for the heat of mammals so far as it concerns changes in the psycho-sexual behaviour during this period. In experiments with female hares *Bucura* (1913, p. 22) showed that after castration heat never occurred. In experiments made with normal male rabbits and females castrated prepuberally *Lacassagne* (1913, p. 218) never saw signs of heat. As already mentioned, Marshall could prevent heat in the male hedgehog by removal of the testicles.

C. THE RESULTS OF CASTRATION IN BIRDS.

Observations.

Castration has been performed for a long while on the cock for economic reasons. Systematic experiments on the cock have been made by Sellheim, Foges, Poll and others. But nevertheless there has never been complete unanimity concerning the results of castration. As *Goodale* (1916, p. 27) pointed out, this is probably due to the fact that the various authors have not always taken into consideration the differences between the races and the variation present among normal birds of the same race. It is also very probable that in the older experiments the sexual glands were not always removed completely. In recent years *Pézard* (1911, 1918) and *Goodale* (1913, 1916) have recorded successful experiments in which cocks were completely castrated. The interest of those who made the experiments on birds was directed especially to the external sexual characters.

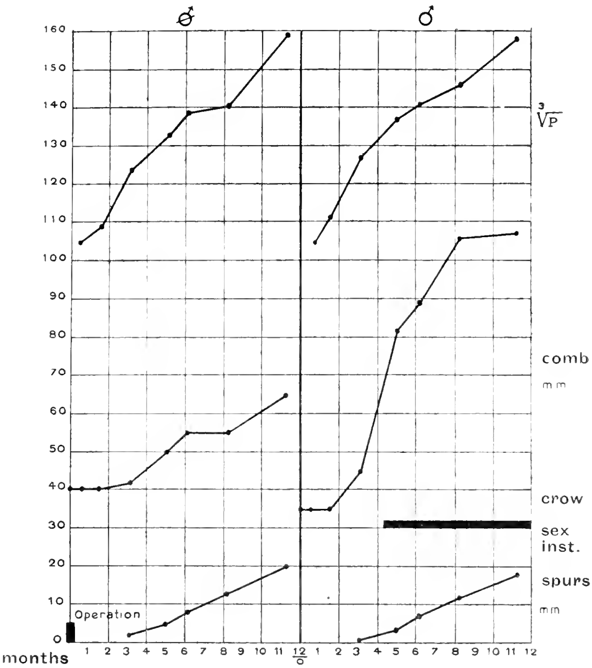


FIG. 25.—*Growth of comb and spurs in the normal and in the castrated cock.* No difference in body growth expressed in increase of $\sqrt[3]{}$ of the body weight P. The growth of the comb in the normal cock does not accord with the body growth, but it does so in the capon. No influence of castration on the growth of spurs. Crow and sexual instincts absent in the capon.—From Pézard (changed).

Pézard castrated cocks at the age of three months, when the external sexual characters, the comb, wattle and barbles, spurs and male plumage are not fully developed (Leghorn and

Orpington). Pézard showed that the comb grows after prepuberal castration, but that the curve of growth is very different from that of the normal animal. He compared the curve of comb-length at different ages with the curve of the cubic root of the body weight, so as to have a linear measure for comparison, and stated that these two curves are different. On the contrary, the growth of the comb of the castrated animal accords with that of the body as a whole (*Fig.* 25). This being so, the relation of the length of the comb l to the cubic root of the body weight P, or $\frac{l}{\sqrt[3]{P}}$ will remain unchanged during the whole development in the "castrate," whereas in the normal animal it will increase very markedly. The characteristic divergence begins at the time when the sexual differentiation in the normal bird commences. This applies also to wattles and barbles. Comb, wattles and barbles are not only smaller in the capon, but also bloodless and thin. Very detailed observations on the head apparel of the castrated cock were made by Goodale, especially on Brown Leghorns castrated at an age of about three or four weeks. Goodale also found that the comb increases in length in the same proportion as the head as a whole; he points out that the growing comb of the capon is not feminine but infantile, and does not attain the measurements of the comb of the female of this race (*Fig.* 26). However, by comparing the comb of a Brown Leghorn capon with that of a Plymouth Rock female, which

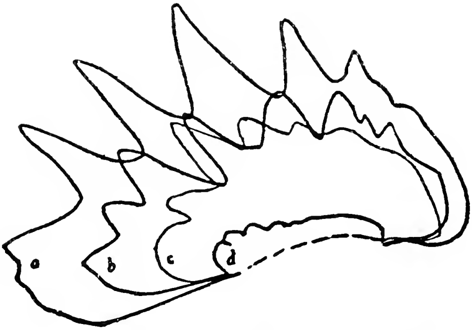


FIG. 26.—*Comb of normal and castrated animals in Brown Leghorn.* a=adult cock; b and c=adult hens; d=adult capon.—From Goodale.

has a comb much smaller than that of a Leghorn female, one might erroneously suppose that the capon had a "female" comb.

Unlike the head apparel, the spurs of the cock are not influenced by castration. All the animals castrated by Pézard and Goodale had spurs of the same length as those of a normal animal. Some authors report having observed an underdevelopment of spurs in the capon. But, as Goodale points out, this has nothing to do with castration, as underdevelopment of spurs sometimes occurs in uncastrated cocks, especially in the Brahma and related breeds.

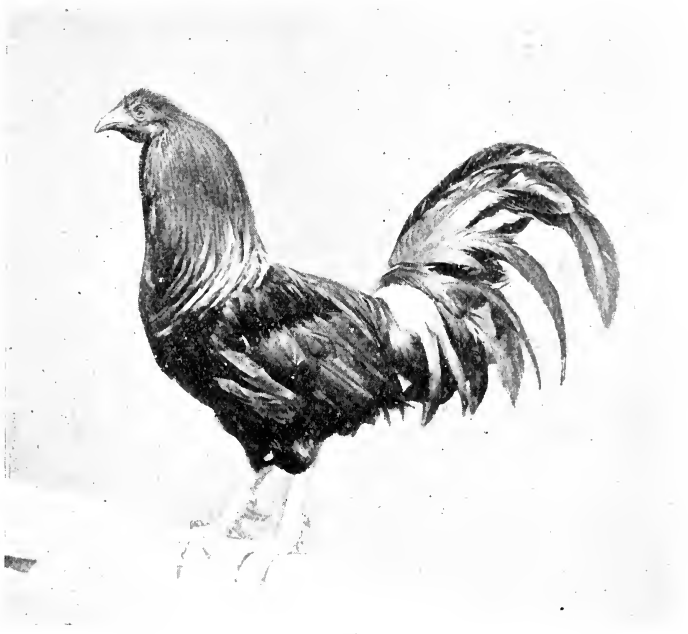


Fig. 27.—*A Brown Leghorn capon, 3 years old.* He is known to be completely castrated. Undeveloped head apparel, but normal spurs, and brilliant male plumage.—After Castle (photo kindly lent by Goodale).

The plumage of the castrated cock is in its general appearance unchanged, or it may be even more richly developed than in the normal cock. This fact has been recorded more or less definitely by *Sellheim* (1898) and *Foges* (1903, p. 42 and 1914, p. 378). Pézard and Goodale showed that the castrated cock always keeps the male plumage. Pézard found the tail feathers of the capon to be sometimes better developed, shinier, and brighter in colour than in the normal male. Similar observations were made on the other feathers of the capon by Goodale. From his own observations Goodale says that if it were not for the narrow comb and barbles the capon would have the appearance of a normal cock (*Fig. 27*). Pézard records a further observation illustrating in a striking manner the absence of dependence of the male plumage upon the sexual glands; his capons moulted a year after castration, and again acquired a male plumage.

As regards the growth of the skeleton, Sellheim found that it is influenced by castration in many ways. Pézard found the neck and the body of the capon to be longer than in the normal cock. Goodale also records that the capon is larger than the normal animal. Sellheim states that the body weight of the full grown capon is about 25 % more than that of the cock. But the greater weight of the capon is due mainly to the greater accumulation of fat, which explains the fact that in relation to the weight of the body as a whole that of the internal organs, such as brain and heart, is smaller than normally. The accumulation of fat is recorded also by Foges, and especially by Pézard, who stated that the quantity of fat is very great. Whereas the fat in the abdominal wall, i.e., the fat remaining after the abdominal organs have been taken away, in a normal animal weighs about 10 to 60 gr., the capon's fat weighs about 90 to 250 gr.

The hypophysis of the castrated cock was found by Fichera to be twice as large as in the normal animal.

The vas deferens seems to undergo a marked atrophy. As a rule Goodale could not find it in the capon; sometimes it is represented by a thin streak of tissue.

The changes in the psycho-sexual behaviour caused by prepuberal castration of the cock are evidently more marked than in mammals, although the statements of different authors are sometimes conflicting. As a rule the capon does not crow, and he does not fight with cocks; he shows no interest in the hens and does not tread them. So one may say that the capon in a general way loses the psycho-sexual behaviour of the cock. But Sellheim says that the crow of the capon is hoarser, and shorter than that of the cock, but that he fights like the cock. Pézard's records are more definite; according to him the capon does not even crow like a cockerel at the time of the sexual metamorphosis; the cry of the capon is rather like the monosyllabic clucking of the hen; the capon is tame, peaceful and apathetic. Pézard never observed a cock fighting with a capon, as the latter retreated when the cock approached. The behaviour of the capon is, in a general way, a neutral one, as Pézard says. He does not seek the hen, and never shows sexual interest. Pézard also found no evidence for the statement that the capon sometimes shows female instincts. In view of all these observations of Pézard we may conclude that in the prepuberally castrated cock a male psycho-sexual behaviour does not develop. It is probable that the differences in the statements of the various authors as to the psycho-sexual behaviour of the capon are to be explained by castration not always being complete. Some experiments of Foges, Pézard, and Goodale support this suggestion; consequently the results of castration may be partly counteracted. But Foges points out that the amount of testicular substance must not be too small if they are to produce a visible effect; his observations in regard to quantity, however, are not very definite. Similar observations have been made by *Shattock and Seligmann* (1904), and lately by Pézard; we shall deal with this question of the relation existing between the quantity of the sexual gland and its effect in another chapter, where we shall describe also our own observations on mammals.

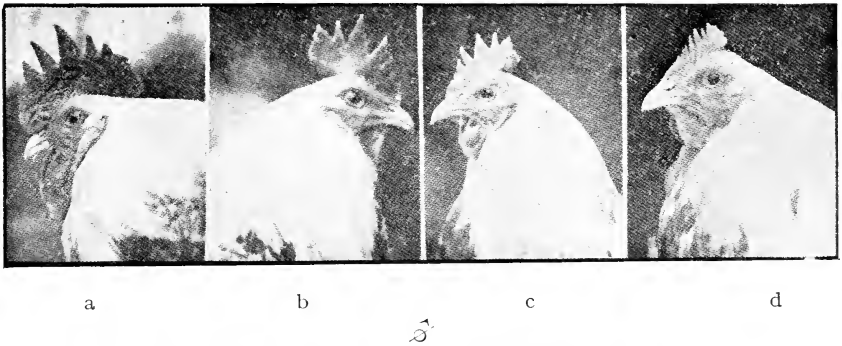


FIG. 28.—*Head apparel in the cock castrated when one year old.* a=at time of operation; b=26 days after operation; c=36 days after operation; d=$3\frac{1}{2}$ months after operation.—From Pézard.

As concerns postpuberal castration of cocks, *Poll* (1909) described an atrophy of the comb and wattles, but no change in plumage. *Pézard* (1912, 1918, pp. 57–82) made similar statements (*Fig.* 28) and studied the atrophy of the comb in the postpuberally castrated cock from an exact quantitative point of view. If the castration is a complete one, the results of the operation may be observed after a few days. For details the original papers of *Pézard* may be referred to (1919, 1920, 1921). Besides the atrophy of the erectile organs, the capon ceases to crow and loses its sexual instincts. As with the plumage, there are also no changes in the spurs. If the castration was an incomplete one, atrophy of the sexual characters does not occur.

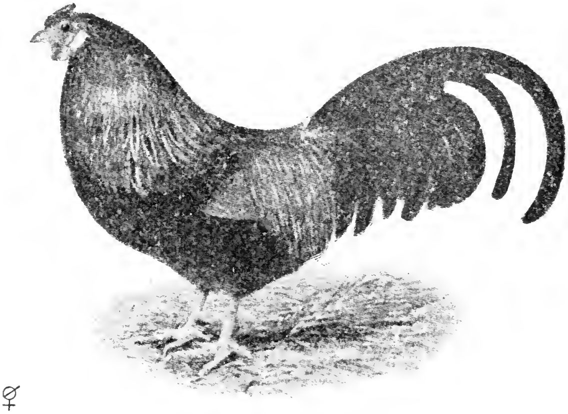


FIG. 29.—*Ovariotomized pullet.* Male plumage and spurs. Compare with Fig. 27; great similarity between castrated cock and castrated hen.—Reproduced from a coloured plate of Goodale's.

In view of the intimate relation between the sexual characters and the sexual glands in mammals it may seem difficult to explain why some of the sexual characters such as the plumage and the spurs develop independently of the sexual glands. But this can be understood if we compare the castrated cock with the castrated hen.

Goodale (1913, 1916) castrated Brown Leghorn hens at an age of four weeks to four months. These hens acquired a male plumage. The plumage was more like that of a capon than that of a normal cock, the feathers being longer. Spurs were developed. So the castrated hen is in her external appearance mistakably similar to a castrated cock (*Fig.* 29). A more or less marked change to apparent maleness was observed by Goodale in 25 castrated hens. Similar results were obtained by *Pézard* (1914, 1915, 1918) in hens castrated when a few months old. The spurs of these birds about a year after the operations were 2.3 cm. long, i.e., they grew with the same rapidity as in a normal cock. At the time of moulting a change in plumage occurred, the castrated hen acquiring the plumage of a cock (Fig. 30). The characteristic feathers of the neck, the back and the tail were present. And as Goodale and Pézard point out, a castrated hen differs externally from a normal cock only in the smaller comb and in the wattles and barbles. If one does not know the history of such a bird, one cannot decide upon its external appearance whether it is a castrated hen or a castrated cock. Goodale quotes also experiments of *Guthrie* (1910), in which the castrated hen likewise acquired a male plumage. The oviduct was always found by Goodale in the castrated hen. He stated that the oviduct was larger than in the young chick, corresponding in its dimensions to the increased size of the bird, but was otherwise

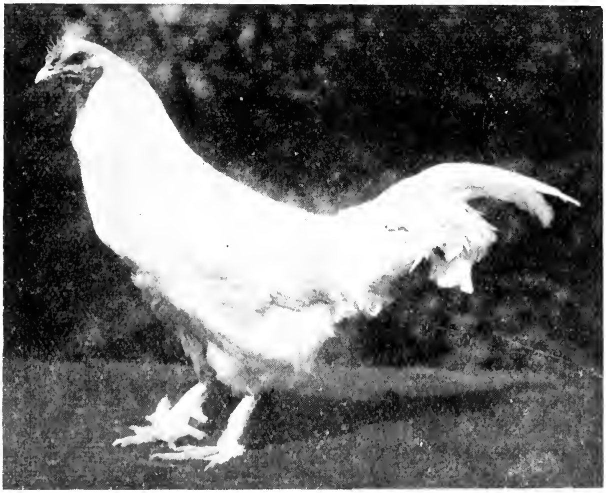


FIG. 30.—*Hen castrated four months previously.* Male plumage (feathers of neck, back and tail) and spurs.—From a photo of Pézard's.

entirely infantile. As regards sexual instincts Goodale and Pézard agree that they are absent in the castrated hen.

After partial resection of the ovary no castration results occur if the remaining particle is not too small. It seems that small particles of ovarian tissue left in the abdominal cavity can hypertrophy and counteract the results of castration.

Similar observations to those on domestic fowls were made on other birds with very marked sexual differences. *Pézard* (1911, 1918, ch. v.) castrated golden and silver pheasants at an age at which male sexual characters were not yet developed. The growth of the spurs was not inhibited by castration; after moulting the animals acquired a male plumage. The erectile head apparel did not develop in the silver pheasant, and sexual instincts were absent. *Fitzsimons* (1912) has described an ostrich hen with male plumage after castration.

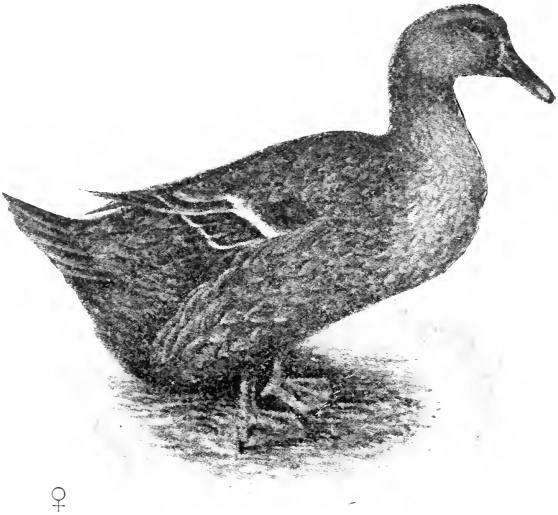
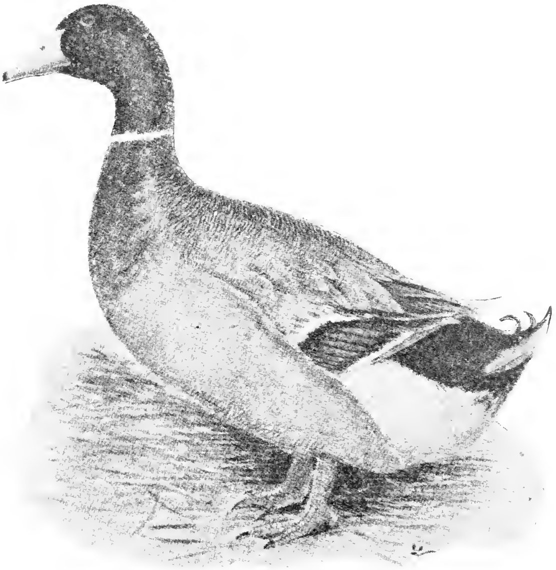


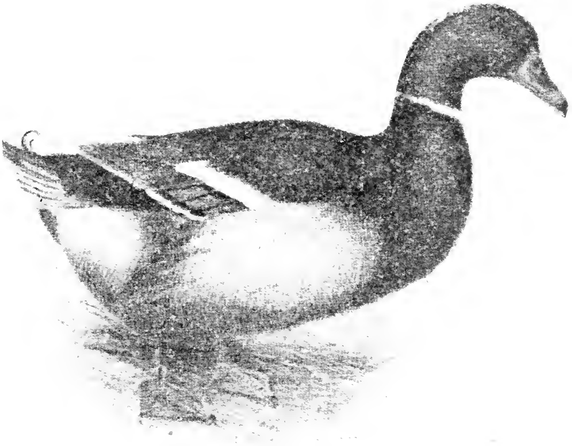
FIG. 31.—*Normal Rouen duck.*—From a coloured plate of Goodale's.

Somewhat more complicated is the case of the duck, on which *Goodale* (1910, 1916) made very extensive experiments. Female Rouen ducks castrated when a few weeks old acquired a male plumage (*Figs.* 31-33), and after moulting invariably assumed a fresh male plumage. In one experiment the female duck acquired even a voice that was more or less like that of a male. On the other hand the drake keeps his male plumage after



♂

FIG. 32.—*Normal Rouen drake.*—From a coloured plate of Goodale's.



♀

FIG. 33.—*An ovariotomized duck.* Male plumage; even curled tail feathers present.—From a coloured plate of Goodale's.

castration, but at the summer moult does not acquire the characteristic summer plumage.[1] If the removal of the sexual glands is incomplete the female duck preserves the female plumage, whereas the drake continues to assume the summer plumage, The voices of castrated ducks of both sexes underwent no changes (with one exception noted above). Sexual behaviour was lacking. The penis was found sometimes rather smaller and more flaccid than normally, but otherwise essentially the same. In experiments undertaken some years previously Poll observed castrated adult drakes assume the summer plumage; there can scarcely be a doubt that the result was due to incomplete castration ; Goodale stated that in those cases in which the castrated drake assumed the summer plumage, remains of the testicle were to be found. *Zawadowsky* (1922) has confirmed the statements of Goodale and Pézard in domestic fowls, pheasants and ducks.

THEORETICAL.

We have seen that castration leads in mammals, not to an assumption of the other sex, but to a common form in which some of the sexual characters are absent. The sexual differences in birds are intelligible in the same kind of way. The castrated cock and hen are very similar in their external appearance; so also are the castrated drake and duck. It is true that some of the results of castration in female birds might be interpreted as due to an assumption of characters of the male type. But the castrated hen does not show the sexual behaviour of the cock, and a male head apparel is not assumed. Thus the facts justify the suggestion that the cock and the hen converge after castration to a common sexual type which is externally more like the male than the female form. It is possible to hold the view that the plumage and the spurs of the cock, or the plumage of the drake are characters which developed in a common asexual embryonic soma without being influenced, excepting possibly very slightly, by the male

---

[1] The moult of ducks and drakes takes place in summer, as a rule in June and July. The drake assumes at this time its special summer plumage. In the early autumn male and female moult a second time. The drake now loses its summer plumage, which is thus worn only a few months. After castration the moult becomes irregular.

sexual glands; and further that the development of the sexual characters in the asexual embryonic soma may be influenced very considerably by the female gonad. *Pézard* (1917, 1918) points out that one can distinguish two different groups of sexual characters; those the development of which depends upon the sexual gland, and those which develop independently of the latter. The comb, wattles, barbles, and voice in the cock, and the sexual behaviour, are characters of the first kind, while the plumage and the spurs belong to the second. On the other hand, the plumage of the hen belongs to the first group, as it results, in the hen, from the influence of the sexual gland on the asexual type of plumage. The same point is mentioned by *Goodale* (1916, p. 46): "It is apparent," he says, "that the inherited base for the secondary sexual characters in each sex is the same," and that "the genetic factors that are transmitted, if expressed in terms of their somatic results in the absence of the ovary, are the male characters." The somatic basis common to both sexes is influenced and changed by the sexual glands.

As is shown especially by Goodale in the case of drakes, the plumage also of the male depends to a certain degree upon the sexual glands; the castrated drake does not assume the summer plumage. By analogy one might suggest that all the characteristic changes which occur in the plumage and in the sexual behaviour of the male bird during heat are caused by changes in the male sexual gland. In the domestic fowl the male plumage does not show this dependence upon the male sexual gland. But, nevertheless, there are a few feathers which in the capon are longer than in the normal cock. The experiments of Morgan made on the Sebright breed are of great interest here. In the Sebright the cock and the hen have a more or less similar plumage, the plumage of the cock being like that of the hen. *Morgan* (1915, 1919) states that the Sebright cock assumes after castration a plumage which is like that of our domestic cock (*Figs.* 34A, 34B). Similar observations were made by *Morgan* (1920 a) on hen-feathered Campines, castrated at an age of 3½ months. After the experiments recorded by Morgan there can be no doubt that in the Sebright cock the testicle influences the development of the plumage in the same kind of way as the ovary does. It may be that the same is true for other species, as, for instance, for the partridge, where the male and the female have a very similar plumage. On the other hand certain facts may be explained on the assumption that the ovary does not always inhibit the development of the plumage and the spurs of the asexual type. There are some birds in which the females have fully developed male plumage, as for instance, in the cases of the pheasant known as *Crossoptilum auritum* and the thistle-finch.[1] There are

♂

FIG. 34A. *Normal Sebright Cock.*
—From T. H. Morgan.

---

[1] In the thistle-finch or goldfinch "both sexes are similar; only a very practised eye can distinguish the female from the male by the somewhat greater size, by the slightly larger quantity of red on the front of the head, and by the darker black on purer white on the back of the head" (*Brehm*, Vol. IX., p. 423). Mrs. L. told me that in her youth she often wondered at seeing two "male" thistle-finches constantly together. The female was mistaken for a male! An almost complete similarity between the plumage of the two sexes seems to occur in the finch of Turkestan (*Cardualis caniceps*), as I learned from the specimen in the natural history museum in Berne. Of *Crossoptilum auritum*, *Brehm* (Tierleben, vol. VII., 4th ed., Leipzig, 1911 p. 77) says: "Both sexes are of the same colour."

also some breeds of fowl in which the female possesses spurs. *Hesse* (1910) refers to this as an inheritance of male characters by the female. But the facts recorded above show that this phenomenon can be explained in another manner (see especially Chapter XI.). The relation between the sexes in the Turnicidae and in *Phalaropus* is very different from what is usual in birds

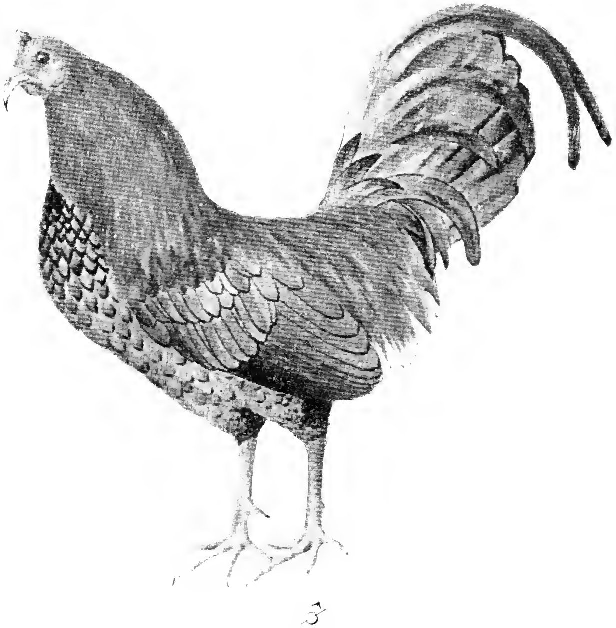


FIG. 34B. *Castrated Sebright Cock.*
—From T. H. Morgan.

In the Turnicidae, living in southern Europe, Africa, Asia and Australia, the female has a brighter plumage than the male, the female is also of a greater size and stronger; the females play the more active rôle in the relation between the two sexes, and utter the mating call and engage in sexual play, and fight one another (*Brehm*, vol. VII., p. 5). This is true also for the Phalaropes (*Brehm*, vol. VII., p. 268), living in the northern countries, the Hebrides, the Faröes, Iceland, Lapland, and the northern coasts. Also in the golden snipe (*Rostratula capensis*) which lives in Africa and southern Asia, the male apparently sits on the eggs (*Brehm*, vol. VII., p. 273). Lately

Van Oordt (1921) has recorded similar facts about the purple sandpiper (*Limicola*) of Spitzbergen: the male is much less conspicuously coloured than the female, the male becomes broody, protects the young, and keeps them warm; the male "behaves like the female of other birds."

All these details, which at first seem so be of no general interest, are of a great theoretical significance in connection with the problem of the influence of the sexual glands on the organism. Here we have instances which show the relation of this problem to genetics and evolutionary history. Some of the questions might be studied experimentally by means of castration, as has already been done in so successful a manner by Morgan on the Sebright breed, and by the implantation of the sexual glands of other species. How many problems arise in connection with the experiments of Morgan on the Sebright race! Darwin's theory of sexual selection loses much in the light of these experiments. It is possible and even probable that the subdued plumage of the female is genetically more recent than the bright plumage of the male!

Two different questions now arise in any discussion on the genetics of sexual characters: how far the somatic psycho-sexual reactions are due to a difference in the sexual gland, and how far are they due to a difference in the somatic substratum itself. In this connection it may be observed that for the Sebright race Morgan showed that the hen-feathering of the male is due to dominant inherited factors phenotypically localized in the sexual gland.

In discussing such problems one must not forget that the plumage is not an indivisible unity. We have seen that the different parts of the skeleton are not all influenced in the same manner by the sexual glands; a similar statement may be made about the different feathers in birds. We have seen further that the sexual glands can act in different ways; they can act by furthering and also by inhibiting growth, or, as Pézard says, their actions may be either positive or negative ones. It seems fair to suggest that the type of an adult male or female is the result of an harmonious development of the different parts of an asexual soma, which have been stimulated or inhibited by the sexual glands, or else have not been influenced by the sexual glands at all. In Chapter XI. we shall discuss some of these questions more fully. It should be observed, however, that Goodale has recorded a fact which at first sight is not conformable with the theory of an asexual embryonic soma. He found that in some cases the castrated duck not only assumed the ordinary male plumage but at moulting time changed it for the male summer plumage. We shall discuss in Chapter IX. what factors could have been at work here.

D. THE RESULTS OF CASTRATION IN THE FROG AND IN FISHES.

We have already referred to the relations existing between the sexual glands and the phenomena of heat or oestrus. These relations have been studied with full particulars in the frog, and by the investigations of Nussbaum, Steinach, Meisenheimer and Harms results of a general interest have been obtained. In the spring, at the time of copulation, quite characteristic morphological and functional changes take place in the male and female frog. In the male the pad on the skin of the first digit of the fore limb enlarges. The pad is histologically characterized by a thickening of the epidermal epithelium, by an augmentation of the glandular tissue, and by an accumulation of pigment (see especially *Harms*, 1914, pp. 230-231) (*Figs.* 35 *and* 36). Also the muscles of the fore arm hypertrophy (*Nussbaum*, 1912). Amongst the changes in the sexual organs the increase of the vesiculae seminales must be mentioned. Functional signs of the oestrus are the characteristic sound of the male and the clasping movement or reflex. This reflex of the male in heat is highly developed; in the breeding season males may be often found embracing dead fishes or pieces of wood. The clasping movement can be evoked at once when the skin of the chest is touched by the finger. The male presses the tuberculate pads on to the chest of the female, and the skin of the latter will be often found rubbed through to the muscles.

All the above-mentioned characteristic signs of the oestrus fail to develop if the animal has been castrated some time or other after the last oestrus. The vesiculae seminales remain small, the pad does not develop to the normal size, and the clasping reflex does not develop to the normal degree (*Nussbaum*, 1909, pp. 530, 532, 534; *Meisenheimer*, 1912). *Steinach* (1894, pp. 313, 314) castrated a number of specimens of *Rana temporaria* in the first days of January, whereas the control animals were dealt with by a simple laparotomy, the testicles remaining intact. Early in March the control animals began to embrace spontaneously. On the other hand, not one of the castrated frogs embraced spontaneously. *Harms* (1914, pp. 175, 176) stated that the castrated male makes the oestral sound only after artificial irritation of the skin; then a dull, hoarse noise can be heard.

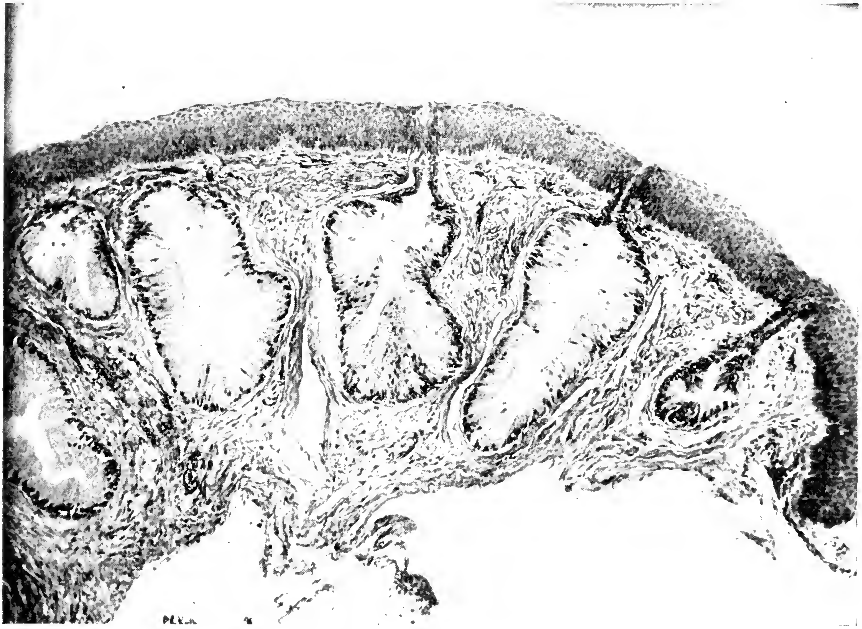


FIG. 35.—*Pad of male Rana temporaria in July, after period of heat.* x 80.—Prepar. of Wagner; photo. of Kull.

A dependence of the oestral characteristics on the sexual glands has been observed also in other Amphibia. *Bresca* (1910) has shown that the atrophy of the nuptial apparel of the triton can be accelerated if both testicles are removed. Recently *Aron* (1921, a, b) has investigated this question in a more detailed manner. He performed bilateral castration just at the beginning of the breeding season; the development of the nuptial apparel was stopped, and it atrophied rapidly. If castration is done when the nuptial apparel is already fully developed, the atrophy is completed in about three weeks. There can be no doubt that here cyclical oestral changes are caused by the testicle.

We have seen that man and mammal can be deprived of certain sexual characters by means of castration, but that other sexual characters may be preserved after castration, at least to a certain degree. It is the same with the frog, as shown by observations of Goltz, Nussbaum, Steinach and Harms. *Goltz* (1869) mentions that copulation does not cease after castration. *Nussbaum* (1912, p. 47) stated that males castrated during the breeding season embrace immediately if placed on top of the female. *Steinach* (1910) found that the clasping reflex disappears in the course of days or weeks, but returns later, though to a decreased extent; spontaneous embracing in the "castrate" seems no longer to occur at all. Also the pads of the "castrate," according to *Harms* (1910, p. 35) and Steinach, show an enlargement, which reappears periodically in the breeding season. But this enlargement of the

FIG. 36.—*Pad of male Rana temporaria in April, at time of heat.* x 80. Epidermis thickened, glands increased.—Prepar. of Wagner; photo. of Kull.

pads, though microscopically easily visible, is not to be compared to that observed in the normal animal during oestrus.

Speaking generally then, we see that in amphibians the development and the maintenance of oestrus depend on the sexual gland. Though the cyclical changes take place to a certain degree after castration, whether carried out before or during the oestrus, a normal oestrus will never recur. According to *Kammerer* (1919, p. 341) it is not the same with the male of *Alytes,* in which a pad on the fore limb was produced under conditions of experimental breeding. When Kammerer forced the frog to spawn in the water, the males of the next generation got pads. If male *Alytes* bred in that way are castrated, the oestral pad reappears nevertheless at every oestral season. Kammerer concludes from his experiments that in *Alytes* the regeneration of the pad does not depend on the sexual gland. But I think that the question of the inheritance of acquired characters is such a complicated one that it would be unwise to draw from Kammerer's experiments any definite conclusions concerning the dependence or independence of oestral changes in relation to the sexual glands in amphibians.

If we compare these data upon the dependence of the oestral phenomena on the sexual glands in Amphibia with what we learned as to the significance of the sexual glands in relation to the development and the preservation of the sexual characters in man, mammals and birds, we find a parallelism in the behaviour of the different species. In some cases the sexual characters are dependent on the sexual glands, but in others the sexual characters may continue to exist or even develop further after castration. Also one might suppose that these apparently independent sexual characters—the cyclically reappearing weakened embracing-reflex, the formation of the pad—were already established by the formative function of the sexual glands at the time when the castration was done.

Observations on *fishes* have been made by *Kopeč* (1918). He castrated the common fish *Phoxinus laevis,* which exhibits in the spring a red nuptial colouring in the back, both in the male and female. The animals survived the operation only for three weeks, but results of castration were obvious. In two series of experiments out of 30 animals castrated in April and March only 7 exhibited the nuptial colour, whereas out of 18 partially castrated animals (half a testicle on each side having been removed) 16 developed normal colouring. Likewise out of 18 normal control animals kept under the same external conditions, 16 developed normal colouring. In a series operated upon in March, there was no nuptial colouring either in the castrated, or in the partially castrated and control animals; Kopeć explains the failure of this series by the assumption that in these animals caught so early, the gonads did not attain maturity in confinement. That some castrated animals of the April and March series exhibited nuptial colour, may be due according to Kopeć to the fact that at time of catching there was already a beginning of nuptial colouring, or, in other words, that at that time the gonads were already more or less developed physiologically. There can be scarcely any doubt that nuptial colouring in fishes depends upon the sex glands.

E. THE RESULTS OF CASTRATION IN ARTHROPODA.

1. MOTHS.[1]

Castration experiments in moths have been made by Oudemans, Kellogg, Meisenheimer and Kopeć on *Lymantria dispar*, the silk-moth (*Bombyx mori*) and other species in which the sexual dimorphism is well marked. Both caterpillars and moths were castrated; the sexual glands were removed with scissors or burned out with a hot needle or a galvanocautery such as is used for medical purposes.

All the investigators agree that the formation and persistence of the sexual characters in moths are quite independent of the sexual glands. The internal and external copulatory organs developed normally in "castrates," although the differentiation of the copulatory apparatus and of the excretory ducts occurred long after the operation (*Meisenheimer*). The colour, size and form of the wings were normal, even when the caterpillars were castrated immediately after the first desquamation. If together with the sexual glands the wing rudiments on one side are removed, as was done by Meisenheimer, a more or less complete regeneration of the wings occurs. The regenerated wings are of the normal appearance,

---

[1] *Kopeć*, 1912; *Meisenheimer*, 1909; *Harms*, 1914, pp. 139-155; *Kammerer*, 1912, pp. 109-115.

characteristic of the sex, although they develop in an organism deprived of the sexual gland. Also the antennae and the shape of the abdomen are normal in the "castrate." It is the same with the sexual instinct and the instinct for progeny rearing. Copulation is performed by the male in a normal manner, and both normal and castrated males copulate also with castrated females. The castrated female of *Lymantria dispar* prepares for the reception of the eggs in the usual manner after copulation, although no eggs can be laid.

From these results the authors unanimously concluded, as already mentioned, that the sexual characters in butterflies do not depend upon the sexual glands, and from these results they drew conclusions also upon the Vertebrata. We have seen that some sexual characters in man and mammals remain more or less unaltered after castration, and this fact suggests the possibility that the sexual characters may be to some extent independent of the sexual glands, as was suggested more particularly by Halban. It is possible, however, to raise objections to the conclusions reached about insects, and these we may now consider.

Firstly, one might object that the castration was done too late, at a time when the sexual characters were already fixed by the influence of the sexual glands; further, such a fixation might be a latent one. We know from the experiments with man and mammals that the sexual characters show more independence of the sexual glands both in regard to their formation and their preservation, the later the castration is performed. *Herbst* (1901, p. 80) has raised this objection against the experiments of Oudemans. Meisenheimer and Kopeć, however, castrated their caterpillars at a very early stage of development. Furthermore, the objection is weakened also by the experiments of Meisenheimer mentioned above, in which together with the sexual glands the wing rudiments were removed. The regenerating wings were not subjected at all to the influence of the sexual glands during their development; nevertheless they showed the characteristic features of normal male and female wings.

A second objection has been discussed by Kammerer. He argues that the castration was possibly not a complete one. We shall see later on how important such an objection might be when considering the question of the formative action of the sexual gland from a quantitative point of view. But this objection is scarcely valid against the conclusions of Meisenheimer and Kopeć, as they carefully examined the internal organs of their experimental animals. The same objection was made by Kammerer to the experiments of Regen on crickets. The grubs developed into animals with fully developed sexual characters.

Still a third objection remains to be considered, and this is one which was pointed out by Kammerer, and which might be much more weighty than the previous ones if it were based on definite facts. The zoologists who experimented on moths have described certain somatic changes after castration. One might be tempted to explain these changes which do occur as due to a lack of a specific influence on the part of the sexual glands. In *Lymantria dispar* castrated by Meisenheimer, there were changes in different parts of the internal sexual apparatus such as the oviduct, the receptaculum seminis, and the vas deferens. It is, however, impossible to conclude from these changes that the formation of the respective organs is influenced in a specific manner by the sexual glands. These changes do not occur constantly. Kopeć found further that they are present after unilateral castration only on the operated side. Kopeć explains all these changes as due to the modified mechanical relations after castration. According to Kopeć this is particularly clear in the female, in which a good deal of space is set free in the abdomen by the removal of the ovaries. Lesions of the internal sex-apparatus, made during the operation, may also be of importance. Meisenheimer found further changes in the colouring of the wings after castration. A darkening of the wings which are normally white could often be observed in castrated females of *Lymantria dispar*. In the castrated males the wings, which are normally dark, became lighter. Meisenheimer, however, could bring about this change in the wings of the male by starving the normal caterpillar. These peculiarities of the wing colouring, therefore, are to be explained as due to external factors. Kopeć came to the same conclusion. After all there can be no doubt that in moths the sexual characters are by no means dependent upon the sexual glands. The external appearance, the internal and external sex-apparatus, the regenerating wings and antennae, and the psycho-sexual behaviour are not influenced in their formation by the sexual glands.

We have seen that in many species the sexual characters are fixed during ontogenetic development by the action of the sexual glands, so as to acquire finally a relative independence of the sexual glands. One might suppose that such a fixation of sexual characters takes place also during phylogenesis; the sex characters in such cases would be wholly independent of the sexual glands. This hypothesis has been put forward by Oudemans, in order to explain why the various species differ from one another in the degree to which the formation of the sex characters depends on the sexual glands. But Herbst has pointed out, for good reasons, that in this conception one is making the old mistake into which investigators who are insufficiently influenced by evolutionist ideas so often fall. For if the formation of the somatic and psychical sex characters in the butterflies does not depend on the sexual glands, it follows that we must look for other regulating factors. Therefore, from the standpoint of the physiology of evolution, nothing is explained by supposing a fixation by heredity.

There are two groups of new facts which show how justifiable Herbst's argument was. We know that in mammals the sexual gland is by no means a homogeneous formation, and we shall see later that the formative influence which the sexual glands exert on other parts of the body is possibly not a direct function of the generative part of the glands. And it may be that the two parts, although endowed with such different functions, are welded together in the mammalian sexual gland into one organ, but are separated in some groups, such as the Arthropoda. In the latter case a removal of the testicles or of the ovaries, containing only the generative cells, will naturally be without any influence upon the sexual characters. *Caullery* (1913, pp. 128, 129), *Harms* (1914, p. 147), and lately *Courrier* (1921) have also considered this possibility. Secondly, the facts discovered by *Goldschmidt* (1917, 1920 a, 1920 b) in moths are of great importance in this connection. In crossing different species of the gipsy moth Goldschmidt obtained different degrees of "intersexuality." The intersexuality concerned all external and internal sexual characters, and even the sexual gland. Further, Goldschmidt stated that all the individuals which became intersexual turn from maleness or femaleness into the other sex at a time which is constant for a given combination of races. It follows from his experiments that the sexual characters of insects are of great lability. Evidently there are in insects other factors besides the sexual glands which control the sexual characters, and even the gonads themselves. We do not know where these factors are localised in the gipsy moth; Goldschmidt is of the opinion that the male and female factors are present in every cell of the body in given quantities. According to *Goldschmidt* (1920 a, p. 18) all the characters by which one sex differs from the other are derived from an identical *anlage*, influenced by a given quantity of the male or female factor. We see that Goldschmidt finds himself forced to make an assumption similar to that which was previously postulated for mammals and birds, i.e., that a neutral soma (asexual or bisexual) becomes monosexual under the influence of a certain internal factor or combination of internal factors at a given time for each species. We shall deal with this most important work of Goldschmidt again in a later chapter (Chapter IX.). In the following section it is shown that in crabs as well as in some insects there are certain external factors which may produce an inversion of the sexual characters from one sex to the other.

2. The Parasitic Castration of Crabs.

It has been known for more than thirty years that in certain species of crabs the sexual glands may be destroyed by parasites. This phenomenon has been called "parasitic castration." *Giard* (1886, 1887) discovered it, and *Geoffrey Smith* (1906) and *Potts* studied it exhaustively in *Inachus*, and in the hermit crab and other species.

The sexual characters are distinctly pronounced in the *Inachus*. The male (*Figs.* 37 *and* 38) has a longer and a larger claw, and the abdomen, which is relatively small, has only two pairs of appendages, the longer serving for copulation, and the shorter being rudimentary appendages. The claw of the female (*Figs.* 39 *and* 40) is shorter and smaller, and on her broad abdomen there are four pairs of fissipedes. The infection of *Inachus* which results in castration is caused by the Cirrhipedian *Sacculina*.

The parasite causes in the male *Inachus* a reduction of the copulatory appendages which are a very pronounced male sexual character, and the assumption of female characteristics

FIGS. 37-45.—*Transformation of Inachus by Sacculina.*—From Geoffrey Smith.

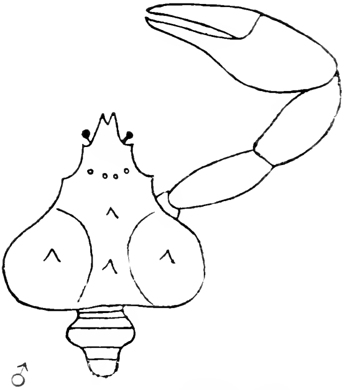


FIG. 37.—*Normal male.*
Dorsal. Nat. size.
Big pincer, small abdomen.

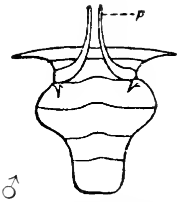


FIG. 38.—*Abdomen of normal male.*
Ventral. x 2 enl.
Big copulatory appendices and reduced extremities.

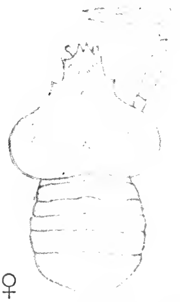


FIG. 39.—*Normal female.*
Dorsal. Nat. size.
Small pincer, big abdomen.

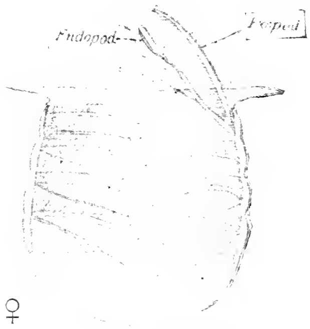


FIG. 40.—*Abdomen of normal female.*
Ventral. x 2 enl.
Four pairs of extremities.

Fig. 41.—*Infected male.*
Dorsal. Nat. size.
Reduced pincer and enlarged abdomen. Compare with Fig. 39; similarity between infected male and normal female.

Fig. 42.—*Abdomen of infected male.*
Ventral. x 2 enl.
Reduced copulatory appendices and development of extremities. Compare with Fig. 40.

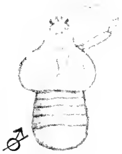


Fig. 43.—*Infected male.*
Dorsal. Nat. size.
Reduced pincer and enlarged abdomen.

Fig. 44.—*Abdomen of infected male.*
Ventral. x 2 enl. Reduced copulatory appendices and four pairs of well developed extremities.

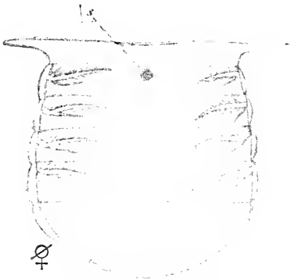


Fig. 45.—*Abdomen of infected female.*
Ventral. 2x enl.
Reduced extremities. At *s* scar from Sacculina.

like the fissipedes. The claw of the male becomes smaller, the abdomen broader. In this way the infected males become more or less female in their external appearance (*Figs.* 41 *and* 42). They sometimes resemble normal females so closely (*Figs.* 43 *and* 44) that they can be recognised as modified males only by the reduced copulatory organ and the slightly smaller abdomen. On the contrary, the infected females are only slightly altered (*Fig.* 45). They differ from normal females only by the shorter fissipedes, and they never assume male characters.

In 70 % of the male and female *Inachus* in which changes in the external sex characters were present, Smith found also changes in the sexual glands. In the female-like males Smith found the sexual glands destroyed to such a degree that even by serial sections no remains of a sexual gland could be found.

A further instance of parasitic castration in crabs is afforded by *Pachygrapsus marmoratus* likewise investigated by Smith in Naples. Here also the castrated male approaches the female in its appearance. The results of castration, however, are not all equally marked in the different species of crabs, the change towards the opposite sex being much more pronounced in some than in others. In some the male sexual characters remain unaltered notwithstanding castration.

The results of the observations made on *Inachus* could be conceived at first sight as similar to those with birds, which after castration change more or less to the male type. But in *Inachus* the change takes place from male to female, and not from female to male as in birds. Like the castrated cock, the castrated female *Inachus* shows only slight changes in the external sexual characters. We have interpreted the assumption of male sexual characters by the castrated hen as of the nature of an approach to an "asexual" or neutral form common to both sexes, and not as an inversion to the other sex. We may in the same way interpret what we observe in *Inachus*, supposing that the common neutral form in this animal resembles the female rather than the male. The absence of fissipedes in the normal male of *Inachus* and their appearance after castration might be explained in the following manner: there is normally an inhibition exerted by the male sexual gland upon other parts of the body, and this inhibition is removed by castration. A similar explanation may be adopted, as we have seen, for birds. From the experiments of Steinach on rats, and those of Pézard and Goodale on cocks, it seems probable that such an inhibitory action on the part of the sexual glands exists. We shall discuss these experiments more fully in Chapter VI.

Smith explains his observations in a wholly different manner. He begins by pointing out that in the female, as in the male, there is sometimes an hermaphrodite sexual gland with almost fully developed ova and spermatozoa. Smith thinks that these were males which were first castrated by parasites, and that afterwards an hermaphrodite gland developed. We have seen that female sexual characters may be present in the castrated male also when no hermaphrodite gland is present; it follows from this that the female somatic characters in the modified male are not caused by the newly formed ovary. Smith suggested that there is another factor, a sexual formative substance which causes the development both of the somatic sexual characters and the sexual glands. According to him this formative substance may be thought of as a product of the general metabolism; under the influence of the parasite the formative substance is changed, and in this way an atrophy of the sexual glands and a change in the sexual characters are caused. Further, Smith assumes that there is in every male a potential formative substance in relation to both sexes, the female one being latent; in the female sex the female substance only would be present. Now he assumes that in the male castrated by the parasite the male substance only is destroyed, and so the female substance inverts the animal to the female sex.

I do not think that Smith's hypothesis is justified in all its *details*, and I do not think that it is sufficiently supported by what Smith observed. But it is interesting to note that in this hypothesis we have a clear foreshadowing as long ago as 1906 of a later and somewhat similar theory based on a remarkable body of evidence, and already tentatively accepted by many. For the experiments of Goldschmidt on moths make it probable that there is indeed a sex specific formative substance controlling both somatic sexual characters and generative cells, and that in the same individual the male and female sex-specific substance may be present, one of them being latent, and that a turning over to the other sex may be caused by changes in the quantitative relations between the two substances.

A third explanation of the sexual inversion of the male *Inachus* was attempted by *Biedl* (1913, p. 225). According to him the Sacculina parasitic on the crab is always female, and he thinks that there is in reality an influence exerted by the female sexual gland of the parasite on its host. There is, according to Biedl, not only parasitic castration, but also a kind of transplantation of a heterosexual gland, a feminization in the sense of Steinach. But Biedl's suggestion is not justified since Sacculina is hermaphrodite (*Smith*, 1906, pp. 19-33).

In the first edition of this book I intimated that parasitic castration in crabs involved something wholly different from what has been observed in experimental castration in Arthropoda. I thought that the persistence of the sexual characters in the moth after castration was an exception even in the group of Arthropoda, and that no general conclusions could be drawn from these experiments in regard to the relation between the sexual characters and the gonads. But I see now that this conclusion is not justified, and I am inclined to accept in principle the explanation of Smith. We have already mentioned that only in 70 per cent. of the male and female *Inachus* in which the external sexual characters changed, were the sexual glands affected. Evidently the destruction of the sexual gland is not a *conditio sine quâ non* for the changes in the sexual characters. Similar observations have been made by Potts on male shore crabs infected by Sacculina; here certain female characters appeared even when the castration was not a complete one. The question has been recently studied also by *Courrier* (1921). He examined 66 male *Carcinus maenas* infected by Sacculina. In 46 cases the abdomen was female in appearance, but only in four were the testicles absent. In most of the animals the testicles were in full activity, athough they were a little smaller than in normal crabs. It would be a mistake to think that the changes in the sexual characters could be changed by the testicular mass being diminished; we know that minute particles of a sexual gland can quantitatively replace the normal testicular mass.

On the other hand one might object to Smith's explanation on the ground that female characters, as already mentioned, often appear in the infected male without an ovary or an hermaphrodite gland being found. But it may be that this is caused by the different organs reacting in a different manner under the conditions created by the parasite in the general metabolism of the host. Discussing in the first edition of this book the results of castration and heterosexual transplantation in mammals (see especially Chapters IX. and XI.) I pointed out that the differences one observes in these experimental conditions in regard to the behaviour of the different parts of the body can only be understood if we take into consideration their different *growth intensity*, which seems to be a function of time. In his remarkable investigation on the gipsy moth *Goldschmidt* (1917, 1920) has shown that the different organs change over to the opposite sex in different degrees; he showed further that those organs or parts of organs which normally become differentiated very late turn to the opposite sex also in slight degrees of intersexuality, as for instance the colouring of the wings. On the contrary, organs which are normally differentiated very early, change to the opposite sex only in crossings with a very pronounced degree of intersexuality; this is especially true for the sexual glands which differentiate embryologically very early, and which are found in different stages of intersexuality only when all the somatic organs are inverted. According to Goldschmidt time is a factor in the degree of intersexuality, the latter being the more pronounced the sooner the inversion to the opposite sex begins. We find here in the crossing experiments of Goldschmidt an explanation of the facts observed by Smith, Potts, and Courrier in parasitic castration of crabs where many male somatic organs become female without the testicle being destroyed or transformed into an ovary or an hermaphrodite gland.

Here again, as in the case of the moth, the possibility must be taken into consideration that there is in the body of the crab a special organ which controls the sexual characters besides the sexual glands. No knowledge exists on this point, but such a conception would not be in any way opposed to Smith's hypothesis.

It may also be mentioned that there are many other examples of Crustacea in which one or more of the sexual characters are sexually inverted to a greater or less extent without interference by a parasite. For details *Morgan's* paper (1920 b) may be referred to

3. The Parasitic Castration of Insects.

Giard (1889 a, 1889 b) about 35 years ago described very profound alterations in insects caused by parasitic castration consequent upon an infection taking place very early in the life history of the insect, possibly in the larval stage. Signs of castration are more pronounced in some species than in others. It must be taken into consideration that the dimorphism of the two sexes is developed to a different degree even in related species. When there is a pronounced dimorphism, destruction of the sexual glands was found to cause an alteration of the sex characters. The penis of the male *Typhlocyba hippocastani* is visibly changed by parasitic castration. "Le caractère spécifique est ainsi profondement atteint," as Giard said. But on the other hand Kopeć's objection that all these phenomena observed in insects could also be explained by the unfavourable conditions amid which the animals are placed in regard to nutrition when infected by a parasite, may be valid.

Further observations on the parasitic castration of insects were made by *Pérez* (1886) on the earth-bee *Andrena*, infected by another little insect, *Stylops*. The sexual dimorphism is very pronounced in *Andrena*, and the sexual characters are altered by the parasitic castration. The brighter design on the head of the normal male tends to become subdued, whereas the design of the infected female becomes brighter. Also the hind legs of the male and female are altered, and the female loses the apparatus necessary for the collection of pollen, normally attached to the hind legs.

Recently *Kornhauser* (1919, quoted from *Morgan*, 1920 b) has made observations on the parasitic castration of the tree hopper, *Thelia bimaculata*, infected by another insect, *Amphelopus*. The infected male exhibits many of the characteristics of the female; the degree of the change is mainly dependent on the stage at which the infection has taken place. On the contrary, infected females do not assume any of the characteristics of the male. The sexual glands in both sexes are usually degenerate. But Kornhauser observed also that an infected male, which showed considerable sexual change in the direction of the female, contained nevertheless full sized normal testes with many spermatozoa. This observation of Kornhauser's fully bears out those of Courrier on the crab.

It seems after all unjustifiable to explain the changes caused by the parasite by destruction of the sexual glands. The inversion of the male towards the female type in the infected Arthropoda must be caused directly by the parasite, and does not necessarily bear any relation to the influence which the parasite has on the sexual gland.

This is further evidence of the fact that the sexual characters are independent of the sexual glands in the Arthropoda.

F. THE RESULTS OF CASTRATION IN OTHER INVERTEBRATA.

We may begin by referring to the parasitic castration of the earthworm. This animal has normally an hermaphrodite gonad and somatic sexual characters of both sexes. Now *Sollas* (1911) observed in *Lumbricus herculeus* a destruction of the male part of the gonad caused by bacterial parasites; the pouches in which the testicles are normally to be found are empty in many infected animals, whereas the ovaries remain normal. The clitellum disappears in such infected animals. The clitellum is an organ consisting of thickened skin near the sexual pores with glands secreting a sticky substance facilitating adherence during copulation; the clitellum increases in size during the breeding season and decreases afterwards. In animals in which the male part of the gonad was destroyed the vesiculae seminales were sometimes found to be smaller. In those animals in which the degeneration of the vesiculae was most pronounced, alterations of the vas deferens and of the genital bristles were also present. In some places where infected worms were found, about half of the individuals were without a clitellum.

We see that in the earthworm many of the male sexual characters are controlled by the male gonad. But the question arises whether we have here a dependence of seasonal changes only upon the gonad as in amphibians or also a dependence of the sexual characters in general as in mammals and birds. This question cannot yet be answered.

Another peculiarity is of the greatest interest. The observations of Sollas show that the ovary which remains intact in the infected earthworm cannot replace the testicle or control the male sexual characters. The influence which the ovary and the testicle in the earthworm exert on its somatic characters are different from one another; the action of the gonads on the body is evidently a *sex specific* one. We shall discuss the question of sex specifity more fully later on.

The observations of Sollas have been extended experimentally by *Harms* (1914). Experimental castration can be performed in Lumbricidae without great difficulty, the male and female gonads being localised in different segments; male or female castration can be performed by cutting away male or female segments and sewing together the remaining segments. Harms showed that the clitellum disappears after male castration, but remains intact after female castration. Some of the animals operated on by Harms lived for nine months after the operation.

In opposition to the observations related above is a statement recently made by *Dragoiu and Fauré-Fremiet* (1920) about a female of *Ascaris megalocephala*.[1] They found an individual in which no generative cells were present in the ovary, the wall only being visible. Nevertheless, the oviducts and the uterus were normal.

Observations on Planaria have been made by *Vandel* (1920). In certain species of Planaria the gonads are situated principally in the front or in the prepharyngeal part of the body, whereas the copulatory organs are to be found in the posterior or postpharyngeal region. Vandel cut off an anterior fragment of the body in order to make observations on regeneration phenomena. He found that an anterior fragment could undergo regeneration and develop very rapidly in about 15 to 25 days a new posterior part with copulatory organs. Now, in one case regeneration took place, but no trace of copulatory organs could be found in the newly-formed posterior part even five weeks after the operation. This was confirmed by histological examination, which revealed only the presence of intestinal branches. But the most interesting result of the histological examination was that the germinative cells in the gonads of the anterior part were degenerated and destroyed, evidently by parasites, as Vandel thinks. He concludes from this observation that the castration did not prevent the process of regeneration or the formation of a new posterior

---

[1] A Nematode or thread-worm parasitic in the horse.

part, but that castration hindered the development of the copulatory organs. Vandel considers this as a proof that the gonads play an important part in the regeneration and development of the copulatory apparatus in Planaria.

Another experiment of *Vandel* (1922) is also of great interest. As a rule the regenerating *posterior* fragment, containing in the beginning the copulatory apparatus but no gonad, loses the former by some process of remodelling. In one case the posterior fragment kept the copulatory apparatus and regenerated to a perfect sexual individual. The histological examination showed that a part of the testicle was left with the posterior fragment. In some experiments Vandel destroyed the gonads in the anterior fragments by exposing the latter to a temperature of about 20° to 21°C. Under these circumstances regeneration takes place, but no copulatory apparatus, or an underdeveloped one, is to be found in the regenerated animal. The objection might be made that both gonads and the regenerating copulatory organs were simultaneously inhibited by the action of the temperature.

As the Planaria are hermaphrodite, the question arises as to whether regeneration or persistence of the copulatory apparatus is controlled by the testicle or by the ovary. To decide the question, Vandel performed the following experiment. He sectioned the animals in such a manner that from the anterior fragment which contains the ovaries and the testicle, the cephalic region with both ovaries was cut away. The fragment regenerated in both directions; in the posterior part the copulatory apparatus regenerated, as likewise happened in the above-mentioned anterior fragments. Evidently the ovaries are not necessary for the regeneration of the copulatory apparatus.

There seems to be some evidence as to the control of the sexual apparatus by the gonad also in Mollusca. According to *Gould* (1917; quoted from *Vandel,* 1922), there is in *Crepidula plana* a very pronounced hermaphroditism. First the testes and the male copulatory apparatus develop; afterwards the testes and simultaneously the male copulatory apparatus degenerate; and the ovaries and the female copulatory apparatus develop. Vandel thinks that there is evidence that the development of the copulatory organs depends upon the sexual glands. This is not true of all the organs, since the uterus develops independently of the gonad. I do not think that Vandel's suggestion is justified; the development of the gonad and that of the copulatory apparatus of the respective sex may both be contolled by some other factor.

Contradictory as they are, the observations made on different Invertebrata show that here also somatic sexual characters depend in some cases upon the sexual glands; this dependence concerns, as we have seen, those parts which are intimately involved in the sexual function.

G. SUMMARY.

The facts recorded permit us to answer the questions put in the first chapter:

1. It is shown with absolute certainty that the formation and the persistence of sexual characters in mammals, birds, amphibians, and some invertebrates depend upon the sexual glands. These sexual characters may be designated as "*secondary*," in a *genetic* sense of the word, in relation to the sexual glands.

2. The formative and conservative influence of the sexual glands does not relate to all the sexual characters. Only some of the sexual characters therefore can be designated as genetically secondary in relation to the sexual glands.

3. The formative and conservative influence of the sexual glands concerns not only those sexual characters which are involved in the sexual function, such as the genital organs, the characteristics of heat and the psycho-sexual behaviour, but it concerns also sexual characters which seem to be in no special relation to the sexual function, such as the plumage, body proportions, and so on. This formative and conservative influence may even relate to other characters which are not necessarily different in the two sexes, e.g., some of the other organs of internal secretion.

4. (*a*) By castration the sexually differentiated type, i.e., the male or the female, loses more or less its sexual characters, and shows a tendency to become a sexually indifferent form common to both sexes. The later castration is performed the greater the number of the sexual characters which remain in the "castrate."

(*b*) It is probable that the somatic basis of mammals and birds is sexually undifferentiated, i.e., it is asexual or bisexual at the beginning, being changed during embryonic life in the male or female direction by the differentiating sexual gland. In other words, we suggest that those sexual differences which develop under the action of the sexual glands are really caused by this action only. On the contrary, those sexual differences which develop and exist independently of a formative or preserving action on the part of the sexual glands might be explained as the result of the independent development of asexual characters common at the beginning to both sexes. These characters merely become sexual owing to their being changed in *one* of the sexes by the sexual glands, as, for instance, the bright plumage and the spurs in the cock on the one hand, and the dull plumage, and the lack of spurs in the hen on the other. The sexual characters which are independent of the sexual glands must not be mistaken for those which are only apparently independent and which remain after castration, merely because the formative action of the sexual glands has already taken place and because the duration of this action was long enough to *fix* these sexual characters in the asexual embryonic soma.

The first three theses and the first part of the fourth are really statements of ascertained facts on which it is only possible to raise doubt in regard to details, whereas the second part of the fourth thesis is a matter of hypothesis. It will be our purpose in the latter part of this book to present further evidence in support of this hypothesis.

BIBLIOGRAPHY FOR CHAPTER II.

[* *Not seen in the original.*]

AMANTEA. 1919. Sulla secrezione spermatica. VIII. Alcune osservazioni su cani castrati e su cani sottoposti a escissione parziale dei deferenti. *Atti della R. Acad. dei Lincei*, 28, ser. 5a.

ARON. 1921a. Sur le conditionnement des caractères sexuels secondaires chez les Batraciens Urodèles. *C. R. de l'Acad. d. Sc.*, 173, p. 482.

—— 1921b. Sur l'existence et le rôle d'un tissu endocrinien dans le testicule des Urodèles. *C. R. de l'Acad. d. Sc.*, 173, p. 57.

ATHIAS. 1919. Effets de la castration sur les mouvement automatiques de l'utérus chez le cobaye. *Jl. de Phys. et Path. Génér.*, 18.

—— 1920. Action d'extraits et produits dérivés d'organes à sécrétion interne sur l'uterus isolé, particulièrement après la castration totale. *Arch. internat. de Pharmacodynamie et de Thérapie*, 25, p. 423.

BELL (W. Blair). 1920. *The Sex-Complex.* London.

BIEDL. 1913. *Innere Sekretion.* 2 Aufl. Berlin-Wien.

BORMANN. 1922. Über die Folgen der Kastration in ihren zeitlichen Beziehungen. *Skand. Arch. für Physiol.*, 42, p. 270.

BRESCA. 1910. Experim. Untersuch. über die sek. Sexualcharaktere der Tritonen. *Arch. f. Entw.-Mech.*, 29, p. 403.

BREHM. 1911 and 1913. *Tierleben*, VII. and IX., 4 Aufl. Leipzig.

BUCURA. 1913. *Geschlechtsunterschiede beim Menschen.* Wien u. Leipzig.

BUSQUET. 1910. *La fonction sexuelle.* Paris.

CARMICHAEL *and* MARSHALL. 1908. The correlation of the ovarian and uterine functions. *Proc. Roy. Soc.*, 79.

—— 1908. On the occurrence of compensatory hypertrophy in the ovary. *Jl. of Physiol.*, 36.

CAULLERY. 1913. *Les problèmes de la sexualité.* Paris.

COURRIER. 1921. Sur le déterminisme des caractères sexuels secondaires. *C. R. de l'Accad. d. Sc.*, 173, p. 668.

DRAGOIOU *et* FAURÉ-FREMIET. 1920. Sur une anomalie du développement de l'ovaire chez l'ascaris mégalocephala. *C. R. de la Soc. de Biol.*, 83, p. 123.

EXNER. 1903. Physiologie der männlichen Geschlechtsfunktionen. *Handb. d. Urologie von Frisch und Zuckerkandl*, I. Wien.

FISHER. 1923. The influence of the gonad hormones on the seminal vesicles. *Amer. Jl. of Physiol.*, 64, p. 244.

*FITZSIMONS. 1912. A hen ostrich with the plumage of a cock. *Agr. Jl. Univ. South Africa*, 4, quot. Goodale, 1916.

FOGES. 1903. Zur Lehre von den sekundären Geschlechtscharakteren. *Pflügers Archiv*, 93.

—— 1914. Keimdrüsen. In Jauregg und Bayer, *Lehrbuch der Organotherapie.* Leipzig.

—— 1920. *Zentralblatt f. Gynäkol.*

FRANZ. 1909. Zur Entwicklung des knöchernen Beckens nach der Geburt. *Beiträge zu Geburtsh. u. Gynäk.*, 13.

GIARD. 1886. De l'influence de certains parasites rhizocéphales sur les caractères sexuals extérieurs de leur hôte. *C. R. de l'Acad. d. Sc.*, 103, p. 84.

—— 1887. Sur la castration parasitaire chez l'Eupagurus Bernhardus L. et chez la Gebia stellata Mont. *Ibidem*, 104, p. 1113.

GIARD. 1889a. Sur une galle produite chez les Typhlocyba rosae L., par une larve d'Hymenoptère. *C. R. de l'Acad. d. Sc.*, 109, p. 79.

—— 1889b. Sur la castration parasitaire des Typhocyba par une larve d'Hymenoptère et par une larve de Diptère. *C. R. de l'Acad. d. Sc.*, 109, p. 708.

GLEY ET PÉZARD. 1921. Modifications des glandes génitales accessoires du cobaye après la castration. *Arch. internation. de Physiol.*, 16, p. 363.

GOLDSCHMIDT. 1917. Intersexuality and the endocrine aspect of sex. *Endocrinology*, 1, p. 433.

—— 1920a. Die quantitative Grundlage von Vererbung und Artbildung. Vortr. und Aufs..über. *Entw.-Mech. d. Org.*, Heft 24. Berlin. English edition, London, 1923.

—— 1920b. *Mechanismus und Physiologie der Geschlechtsbestimmung.* Berlin.

*GOLTZ. 1869. *Beiträge zur Lehre von den Funktionen der Nervenzentren des Frosches.* Berlin.

GOODALE. 1910. Some results of castration in ducks. *Biol. Bull.*, 20.

—— 1913. Castration in relation to the secondary sexual characters of brown leghorns. *American Naturalist.*

—— 1916. Gonadectomy in relation to the secondary sexual characters of some domestic birds. *Carnegie Institution Publications.* Washington.

*GOULD. 1917. Studies on sex in the hermaphrodite mollusc Crepidula Plana. *Jl. Exper. Zool.*, 23, quot. Vandel, 1922.

*GUTHRIE. 1910. Survival of engrafted tissue. *Jl. Exp. Med.*, 12, quot. Goodale, 1916.

HALBAN. 1903. Die Entstehung der Geschlechtscharaktere. Eine Studie über den formativen Einfluss der Keimdrüse. *Arch. f. Gynäk.*, 70.

HARMS. 1910. Hoden- und Ovarialinjektionen bei Rana fusca-Kastraten. *Pflügers Archiv*, 133.

—— 1914. *Experimentelle Untersuchungen über die innere Secretion der Keimdrüsen und deren Beziehung zum Gesamtorganismus.* Jena.

HERBST. 1901. *Formative Reize in der tierischen Ontogenese.* Leipzig.

HESSE-DOFLEIN. 1910. *Tierbau und Tierleben*, 1. Leipzig.

HIRSCHFELD. 1916. Über Geschlechtsdrüsenausfall. *Neurologisches Zentralblatt.*

—— 1917. *Sexualpathologie*, I. Teil. Bonn.

HOFSTÄTTER. ? Unser Wissen über die sekundären Geschlechtsmerkmale. *Zentralbl. f. d. Grenzgeb. d. Med. u. Chir.*, 16, p. 246–267.

KAMMERER. 1912. Ursprung der Geschlechtsunterschiede. *Fortschr. d. naturwiss. Forsch.*, 5, p. 62–91.

—— 1919. Vererbung erzwungener Formveränderungen. I. Mitt. Die Brunstschwiele des Alytes-Männchen aus Wassereiern. *Arch. f. Entw.-Mech.*, 44.

KOCH (Walter). 1921. *Über die russisch-rumänisch Kastratensekte der Skopzen.* Jena.

*KON. 1908. Hypophysenstudien. *Zieglers Beiträge*, 44.

KOPEĆ. 1912. Untersuchungen über Kastration und Transplantation bei Schmetterlingen. *Arch. f. Entw.-Mech.*, 33, p. 1.

—— 1914. Nochmals üb. d. Abhängigkeit der Ausbildung sek. Geschlechtschar. von den Gonaden bei Lepidopteren (Fühlerregenerationsversuche mit Kastration und Keimdrüsentransplantation kombiniert). *Zoolog. Anz.*, 43.

—— 1918. Contribution to the study of the development of the nuptial colour of fishes. *C. R. de la Soc. d. Sc. de Varsovie*, 9, p. 108.

*KORNHAUSER. 1919. The sexual characteristics of the Membracid Thalia bimaculata (Fabr.). I. External changes induced by Aphelopus theliae (Gahan). *Jl. Morph.*, 32, p. 531.

LACASSAGNE. 1913. Etude histologique et physiologique des effets produits sur l'ovaire par les rayons X. *Thèse méd. de Lyon.*

LICHTENSTERN. 1916a. Untersuchungen über die Funktion der Prostata. *Zeitschr. f. Urologie*, 10.

—— 1916b. Mit Erfolg ausgeführte Hodentransplantation am Menschen. *Münch. mediz. Wochenschr.* No. 19.

LIPSCHÜTZ. 1917. Die Gestaltung der Geschlechtsmerkmale durch die Pubertätsdrüsen. *Anz. d. Akad. d. Wiss.*, Wien, No. 10.

—— 1918a. *Archiv f. Entw.-Mech.*, 44.

—— 1918b. Prinzipielles zur Lehre von der Pubertätsdruese. *Arch. f. Entw.-Mech.*, 44.

—— WAGNER *et* TAMM. 1922. Sur l'hypertrophie des fragments ovariens dans la castration partielle. *C. R. de la Soc. de Biol.*, 86, p. 240.

MARSHALL. 1922. *The physiology of reproduction.* 2nd edition. London. Ch. IX.

MARTIN. 1914. *Lehrbuch der Anthropologie.* Jena.

MEYER (Robert). 1921. Ein Mahnwort zum Kapitel "Interstitielle Drüse." *Zentralbl. f. Gynäk.*, No. 17.

MEISENHEIMER. 1909. *Experimentelle Studien zur Soma- und Geschlechtsdifferenzierung*, I. Jena.

—— 1912. *Experimentelle Studien zur Soma- und Geschlechtsdifferenzierung*, II. Jena.

MOORE. 1919. On the physiolog. properties of the gonads as controllers of somatic and psychical characteristics. II. Growth of gonadectomized male and female rats. *Jl. of Exper. Zool.*, 28, p. 459.

—— 1922. On the physiolog. properties of the gonads as controllers of somatic and psychical characteristics. V. The effects of gonadectomy in the guinea pig, on growth, bone lengths, and weight of organs of internal secretion. *Biological Bulletin*, 43, p. 285.

MORGAN. 1915. *Demonstration of the appearance after castration of cock-feathering in a hen-feathered cockerel. *Proc. Soc. Exp. Biol. and Med.*, 13.

—— 1919. The genetic and the operative evidence relating to secondary sexual characters. *Carn. Inst. Publ.* Washington.

—— 1920a. The effects of castration of hen-feathered Campines. *Biol. Bull.*, 39.

—— 1920b. Variations in the secondary sexual characters of the fiddler crab. *American Naturalist.*

NUSSBAUM. 1909. Hoden und Brunstorgane des braunen Landfrosches (Rana fusca). *Pflügers Arch.*, 126.

—— 1912. Über den Bau und die Tätigkeit der Drüsen, VI. Mittl. *Arch. f. mikr. Anat.*, 80, II. Abt.

OBERHOLZER. 1912. Über die Wirkung der Kastration auf die Libido sexualis. *Sexual-Probleme. Zeitschr. Sexualwiss. und Sozialpolitik*, 8.

OCARANZA. 1921, 1922. Contribucion experim. para el estudio de la fisiol. del testiculo. *Revista Mexic. de Biol.*, 1, No. 6; 2, No. 5.

VAN OORDT. 1921. Ornithological Notes from Spitzbergen and Northern Scandinavia. 1921. "Ardea," *Tijdschr. d. Nederl. Ornitholog. Vereen.*

*PÉREZ. 1886. Des effets du parasitisme des Stylops sur les apiaires du genre Andrena. *Soc. Linn. Bordeaux*, 12, p. 21.

PÉZARD. 1911. Sur la détermination des caractères sexuels secondaires chez les Gallinacés. *C. R. de l'Acad. d. Sc.*, 153, p. 1027.

—— 1912. *C. R. de l'Acad. d. Sc.*, 154, p. 1183.

—— 1914. Développement experimental des ergots et croissance de la crête chez les femelles des Gallinacés. *C. R. d. l'Acad. d. Sc.*, 158, p. 513.

—— 1915. Transformation expérimentale des caractères sexuels secondaire chez les Gallinacés. *C. R. de l'Acad. d. Sc.*, 160, p. 260.

—— 1918. Le conditionnement physiologique des caractères sexuels secondaires chez les oiseaux. *Edition du Bulletin Biologique de la France et de la Belgique.* Paris.

PÉZARD. 1919. Facteur modificateur de la croissance normale et loi de compensation. *C. R. de l'Acad. d. Sc.*, 169, p. 997.

—— 1920. Secondary sexual characteristics and endocrinology. *Endocrinology*, 4, p. 527.

—— 1920. Castration intrapubérale chez les coqs et généralisation de la loi parabolique de régression. *C. R. de l'Acad. d. Sc.*, 171, p. 1081.

—— 1921. Numerical law of regression of certain secondary sex characters. *Jl. of Gener. Physiol.*, 3, p. 271.

POLL. 1909. Zur Lehre von den sekundären Sexualcharakteren. *Sitzungsber. d. Gesellsch. naturforsch. Freunde.* Berlin.

*POTTS. 1906. The modification of the sexual characters of the hermit crab caused by the parasite Peltogaster. *Quart. Jl. Micr. Sc., N. S.*, 50, p. 599.

RICHON *et* JEANDELIZE. 1903. Influence de la castration et de l'ovariotomie totales sur le développement des organes génitaux externes chez le jeune lapin. *C. R. de la Soc. de Biol.*, 55, p. 1684.

ROESSLE. 1914. Das Verhalten der menschlichen Hypophyse nach Kastration. *Virchows Archiv*, 216.

SCHÖNBERG *und* SAKAGUCHI. 1917. Der Einfluss der Kastration auf die Hypophyse des Rindes. *Frankf. Zeitschr. f. Pathol.*, 20.

SELLHEIM. 1908. Zur Lehre von den sekundären Geschlechtscharakteren. *Beitr. z. Geb. u. Gynäk.*, 1.

SHATTOCK *and* SELIGMANN. 1904. Observations upon the acquirement of the sec. sex. characters, indicating the formation of an internal secretion. *Proc. Roy. Soc.*, 73.

SMITH. 1906. *Rhizocephala, Fauna und Flora d. Golfes v. Neapel*, 29 Monographie. Berlin.

SOLLAS. 1911. Note on parasitic castration in the earthworm Lumbricus herculeus. *Ann. and Magaz. of Natur. History*, 7, 8th Ser.

STEINACH. 1894. Untersuchungen z. vergleich. Physiologie der männl. Geschlechtsorgane, insbes. der akzessor. Geschlechtsdrüsen. *Pflügers Archiv*, 56.

—— 1910. Geschlechtstrieb und echt sekundäre Geschlechtsmerkmale als Folge der innersekretorischen Funktion der Keimdrüsen. *Zentralbl. f. Physiol.*, 24.

—— 1912. Willkürliche Umwandlung von Säugetier-Männchen in Tiere mit ausgeprägt weiblichen Geschlechtscharakteren und weiblicher Psyche. Eine Untersuchung uber die Funktion und Bedeutung der Pubertätsdrüsen. *Pflügers Archiv*, 144.

TANDLER *und* GROSS. 1909. Über den Einfluss der Kastration auf den Organismus. I. Beschreibung eines Eunuchenskelets. *Archiv f. Entw.-Mech.*, 27, p. 35.

—— 1910a. II. Die Skopzen. *Arch. f. Entw.-Mech.*, 30, Part 2, p. 236.

—— 1910b. Über den Einfluss der Kastration auf den Organismus. III. Die Eunuchoide. *Arch. f. Entw.-Mech.*, 29, p. 290.

—— *und* KELLER. 1910. IV. Die Körperform der weiblichen. Frühkastraten des Rindes. *Arch. f. Entw.-Mech.*, 31, p. 289.

—— *und* GROSZ. 1913. *Die biologischen Grundlagen der sekundären Geschlechtscharaktere.* Berlin.

VANDEL. 1920. Le développement de l'appareil copulateur des Planaires est sous la dépendance des glandes génitales. *C. R. de l'Acad. d. Sc.*, 170, p. 249.

—— 1922. Recherches experimentales sur les modes de reproduction des Planaires Triclades Paludicoles. *Bull. Biol. de la France et de la Belgique*, 55, p. 343.

WITSCHI. 1921. Der Hermaphroditismus der Frösche und seine Bedeutung für das Geschlechtsproblem und die Lehre von der inneren Sekretion der Keimdrüsen. *Arch. f. Entw.-Mech.*, 49, p. 316.

ZAWADOWSKY, M. M. 1922. *Das Geschlecht und die Entwicklung der Geschlechtsmerkmale.* (Russian. with German summary.) Moscow.

Chapter III.

The Internal Secretions of the Sexual Glands.

THE question now arises as to the nature of the mechanism whereby the sexual glands exert their influence on the sexual characters in different species.

Two possibilities present themselves; an influence may be by the intermediation of the nervous system (as by some kind of a reflex), or directly through internal secretions which pass into the circulation. Experiments with transplantation and injection of sexual glands have been made on mammals, birds and amphibians with the purpose of solving this question. It is to-day generally agreed that the sexual glands act by means of internal secretions.

Before entering into a discussion of the experimental proofs of this contention we shall state in a few words what we mean by "internal secretion."[1] It is really a more or less arbitrary matter to distinguish between the special internally secretory organs and the other parts of the body. All organs and cells in a multicellular organism are connected with and dependent upon each other by the intermediation of products of metabolism secreted into the body fluids. These substances may be specific or otherwise for the respective organs by which they are secreted. We know that the secretions produced by one set of organs influence all the other cells and organs of the body. Take, for instance, carbonic acid, a katabolic product secreted by every cell and thus without any specifity. The action of the respiratory centre in the medulla oblongata depends upon the quantity of carbonic acid present in the blood. Thus every cell in the multicellular organism acts by some kind of "internal secretion" on the respiratory centre. This action of the carbonic acid or of the hydrogen ion is a specific one. The specifity of the action which different secretions have on

---

[1] Besides the literature quoted in the text see *Gley*, (1914); *Caullery* (1913, p. 115); *Lipschütz* (1917).

other organs or on the metabolism in general by the intermediation of the body fluids is often taken as the only characteristic feature of what we call an internal secretion *par excellence*. But I think that such a conception, which seems now to be very widespread, cannot be of much use in physiology. If any kind of specific action by intermediation of a katabolic substance entering into the body fluids is alone sufficient for designating this substance an internal secretion, there is in the multicellular organisms of animals and plants, no organ or no cell which could not be designated an organ of internal secretion. If one takes this standpoint, it is possible to speak of an internal secretion of the lungs, of the skin, or any other organ. But an organ of internal secretion should not be simply characterised by the fact that it is connected with other organs by the intermediation of chemical messengers or hormones (*Bayliss and Starling*, 1906). It must also be an organ which has *no other function* than to secrete chemical messengers or hormones of a special chemical composition and such as are never produced in other organs. Organs such as the thyroid gland, the hypophysis, the adrenals, and so on, are only characterized functionally by these specific substances which have a specific action. So I think that it would be best to restrict the term "endocrine organ" *in the first instance* to glands which, as far as we know, have no other function than the secretion of specific substances which enter into the blood and influence the other organs in a specific manner, i.e., organs secreting chemically specific hormones.

Such a definition of an endocrine organ is not an ideal one. But, unfortunately, as so often happens in physiology, we cannot hope for an ideal definition on account of the numerous transitional conditions which exist. There are organs producing chemically specific hormones, i.e., performing an endocrine function besides their other well-known functions; this is the case with the pancreas, with the mucosa of the duodenum or small intestine, and with the sexual glands; the same may be true also for other organs, as for the skin. We must never forget that knowledge of the secretion of chemically specific hormones is merely additional biochemical knowledge of the mutual relations between the organs in the body; endocrinology in the larger sense would be only another name for biochemistry.

It is of great interest to ascertain whether in those organs, which have an endocrine function besides their other special function, such as the pancreas and the sexual glands, the internal secretion is really produced by the same cellular elements as the external secretion. This question will be discussed in the case of the sexual gland in Chapters IV. and V.

A. TRANSPLANTATION.[1]

The first experiment upon the transplantation of the sexual glands was performed by *John Hunter* in 1762 on fowl. *Berthold* (1849) made a similar experiment on cocks two or three months old. He removed the testicles of several birds; in one of them he replaced the testicles into the abdomen (autotransplantation); in the abdomen of a second castrated bird the testicles of another cock were placed (homoiotransplantation). The engrafted testicles "took" in different places, normal or abnormal, especially on the intestine. The appearance of the birds was like that of normal cocks. Two months later Berthold removed the engrafted testicles in one of these; the bird became a capon. Some other experiments of a similar kind were also performed by Berthold on cocks. He found the engrafted testicle five months after the transplantation adhering to the large intestine and containing spermatozoa. Berthold concluded from his experiments that the characteristic features of sexual maturity are caused by the testicle producing some kind of substance, and through this changing the composition of the blood which reacts on the organism in general, especially on the nervous system. We thus see that the fundamental principles underlying our knowledge of the internal secretions of the sexual glands had been already laid down by Berthold seventy-five years ago. But in those days nobody seems to have taken any interest in this matter and Berthold's experiments were forgotten; they remained too isolated to have any immediate bearing on physiology and

---

[1] Manifold terms are in common use to describe the different forms of transplantation. We shall confine ourselves to the following:

*Auto*transplantation—or transplantation in the body of the same individual.

*Homoio*transplantation—or transplantation into the body of another individual of the same species.

*Hetero*transplantation—or transplantation into the body of an animal of another species.

medicine, they were not brought into relation with other similar phenomena, and so they had no influence on scientific thought, and temporary oblivion was their inevitable fate.

New experiments with transplantation were made about fifty years later by *Foges* (1902) on cocks. He succeeded in completely removing the testicles in two cases and transplanting them into another position in the abdominal cavity. Foges relates that these animals appeared to stand midway between a normal cock and a capon, the head apparel being small and pale, while there was an increase of fat, but the spurs and plumage of the cock were well developed. Foges concluded from this experiment that there is an internal secretion produced by the testicle, but that the sexual characters were only partly developed in his birds because the engrafted testicular mass was smaller than that of the normal testicles. But from what we know today of the results of castration in the cock it is clear that in reality the two birds became capons and that autotransplantation had not succeeded. Homoiotransplantation was also attempted by Foges without success.

New and careful experiments have been made on cocks by *Pézard* (1911, 1918, pp. 91–98). After having completely removed the testicles of birds five months of age, the organs were cut into small pieces and replaced in the abdomen. At first there were signs of castration; a regression of the comb began, sexual instincts and crowing did not develop, though already manifested in the control animal. But about a month after the operation the experimental birds were normal in regard to head apparel and sexual behaviour. Pézard continued his observations for two months longer without observing any abnormality in his animals.

Whereas it is very difficult to remove completely the testicle in the cock, castration in mammals can be done without any difficulty. But on the other hand it seems that in the mammal the testicle does not "take" so well as in the cock. Many experiments have been made by different investigators on the dog, rabbit and rat (*Biedl*, pp. 282–284). These experiments were not always successful, even when an autotransplantation was made. Positive experiments, however, with autotransplantation have been described by *Steinach* (1910). He operated on 40 rats from three to six weeks old; in 36 cases the graft took and remained and was observed functioning for more than nine months. The operation was made by *Steinach* (1916, p. 312) in such a way as to guarantee a good vascularization of the graft. Both testicles were fixed on to the peritoneum or the abdominal muscles, the funiculus spermaticus remaining intact; a few days later the connection with the funiculus was cut. Similar grafts may remain even for the whole life of the animal. Auto- and homoiotransplantations on guinea pigs and rats were made by *Sand* (1918), who succeeded especially when puncturing the graft with a needle; evidently this method assures a better vascularization.

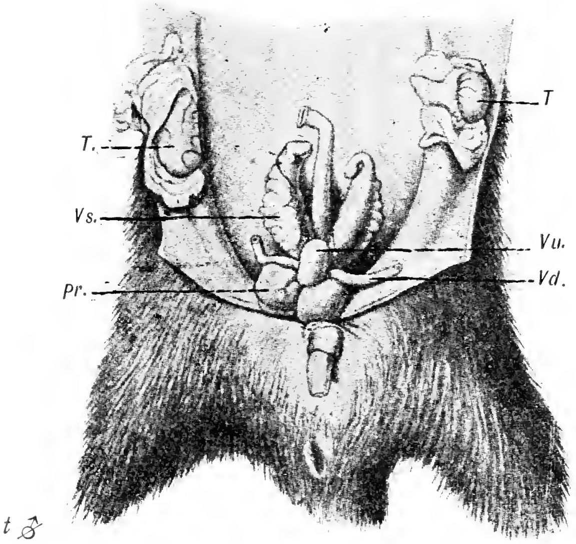


FIG. 46.—*Male rat, 8 months old, with testicular autotransplantation at an age of 1 month.* Compare with Figs. 7 to 9. Prostate, seminal vesicles and penis developed as in normal animal of same age. Explan. signs as in Fig. 7.—From Steinach.

In view of the experiments performed there can be no doubt that an animal in which the testicles were removed at an early age and to which simultaneously its own testicles or those from another animal were engrafted and took in the new place, can develop in a normal way in regard to somatic and functional sexual characters. The prostatic gland, the vesiculae seminales and the penis in such animals are found to be as large as in normal ones (*Fig.* 46).

Steinach relates having observed in some of his experiments an underdevelopment of the sexual characters; in these cases the testicular grafts were small. He concluded from these observations that there is a correspondence between the degree of maleness and the quantity of testicular mass in the animal. But I think that this conclusion is not justified, since complete maleness is possible even when the testicular fragment is extremely small, as in partial castration (*Pézard*, 1918; *Lipschütz* and co-workers, 1920 and 1921). I am inclined to believe rather that the underdevelopment of the sex characters in some of these experiments was caused by the underdevelopment of the testicles. In Chapter IV. we shall discuss more fully our own experiments, in which we were able to show that, by manipulating the testicle of a young animal, development of the organ and of the sex characters can be retarded, although finally normal maleness may be attained.

As to the psycho-sexual behaviour Steinach relates that some animals with a transplanted testicle showed an abnormally intense libido. But I am rather sceptical as to detailed data concerning the intensity of the psycho-sexual behaviour in small experimental animals.

If the graft does not take the animal will show all the usual signs of castration.

In general one is inclined to consider such experiments as sufficient proof for the contention that the influence the testicle has on the sex characters is produced not by intermediation of some kind of nervous reflex beginning in the sexual gland, but by the action of internal secretions. We shall see later on that these experiments taken by themselves are open to criticism, that is to say, they do not afford sufficient proof for the assumption that the testicle acts really by an internal secretion.

The medical practitioner must know that successful transplantation of testicles is practicable also in man (for literature see especially *Mauclaire*, 1923). As far as I am aware, the American surgeon Lespinasse was the first to perform a successful testicular transplantation in man. Pieces of testicle were implanted on the musculi recti of a man who lost both testicles in an accident. Sexual capacity was regained and persisted for many months when the patient was under medical observation.

The question of testicular transplantation in man has been advanced by the experiments of Steinach, and since 1916 testicular transplantation has been accomplished a number of times. It is impossible here to give a full account of this matter which is more especially of a surgical interest. Some of the successful cases which have so far been recorded may be taken as examples. *Lichtenstern* (1916) operated on the man mentioned already in Chapter II. (p. 12), where examples were given of the results of castration in man. The individual in question lost both testicles when 29 years old, owing to being wounded in the war. When he came under medical observation, pronounced signs of castration were already present; these were the accumulation of fat, the hairless face, and the configuration of the hair in the regio pubis characteristic of the eunuch. Sexual libido and sexual ability were absent for the whole of the six weeks the man spent in the hospital before transplantation was attempted. Then a testicle was taken from a man of 40 who suffered from a congenital hernia which caused a painful pressure on the retained testicle. A thorough clinical examination and an examination of the blood of the man from whom the testicle was to be taken were made previously. The extirpated testicle was cleared from the epididymis, cut in two, and inserted in the obliquus externus muscle, at a spot previously scarified with the cut surface underneath. Thin catgut stitches were made to fix the albuginea to the muscle; one stitch going through the muscle from both sides and through the top of the graft was tied above the top to make the contact between the cut surface of the graft and scarified muscle closer. The fascia of the muscle previously split was not tied so as to avoid any pressure on the graft. The first day after the operation hot cloths were put over the bandage to promote hyperæmia and favour vascularization. Lichtenstern relates that about the second week after the operation signs of regained sexual desire and capacity (erotic dreams and erections) were experienced. The first normal sexual act was performed about six weeks after the operation. The accumulation of fat decreased and the beard began to grow. When examined nine months after the operation all the somatic and physical signs of castration were absent, the sexual life of the man was normal and he intended to marry; fifteen months after the operation he did marry; according to a communication made by the patient two and a half years after transplantation the marriage is a happy one. The last statement of Lichtenstern concerning this patient which I have read, was made four years after the operation; at this time the man was still sexually normal.

Lichtenstern (1918) describes also a transplantation performed on a man castrated ten years ago on account of tuberculosis. All the signs of castration were present. Testicular transplantation was successful likewise in this case; signs of sexual ability appeared within three weeks. In a series of subsequent communications Lichtenstern has described several other cases in which successful testicular transplantations were made on castrated and eunuchoid men.

Also autotransplantations were made with men which are of a still greater practical interest. All these cases relate to tuberculosis of the testes. The Swiss practitioner *Stocker* (1916) of Lucerne seems to be the first to have adopted the method of engrafting healthy parts of the removed tuberculous testes into the scrotum. A year after the operation, when Stocker made his communication, the man was still sexually normal. Successful autotransplantations in cases of tuberculosis of the testes were made also by *Els* (1920) in the same manner as Stocker. He stated that two years after the operation the engrafted testicular fragment was of the same size as in the beginning. Els engrafted healthy fragments of the testes also in those cases where only a unilateral tuberculosis was present. In five out of seven cases Els engrafted into the scrotum, whereas in two cases, on account of a scrotal fistula, transplantation was made on to the abdominal wall. Out of these seven cases five were successful and Els is of the opinion that in all cases of tuberculosis where a resectio epididymidis is no longer advisable, castration with transplantation of healthy fragments should be performed.

It is not our purpose to give a full description of all the testicular transplantations made in man with a view to counteracting the symptoms or effects of castration or eunochoidism or homosexuality. But papers by *Wildbolz* (1917), *Lichtenstern* (1916–20), *Mühsam* (1920–21), *Forster* (1920), and *Mauclaire* (1923) may be mentioned in this connection. Abstracts of the English papers concerning testicular transplantation will be found in the American Journal, *Endocrinology*. A paper by

Stanley and Kelker (1920) may be referred to. These surgeons transplanted on to men suffering from testicular atrophy or abnormal sexuality testicles taken from executed individuals. The graft was simply placed in the scrotum or sewn together with the freshly cut atrophying testicle. The last method (already used in 1902 by Mauclaire for testicular autotransplantation) gave better results. The effect on the sexual behaviour was extraordinarily striking; a man of 72, having received a double testicular graft from an Indian of 19, had an erection on the third night after operation, although he had experienced none for many years. Changes of voice and vision (in a man of 54) were also observed. Moreover, the authors record a general improvement in condition, the operated men being livelier, moving more rapidly and feeling in better condition generally.

Many of the testicular transplantations performed during recent years have been successful, whereas others have had no effect, the graft degenerating and disappearing sooner or later. Probably the number of unsuccessful transplantations is much greater than those which were successful, since surgeons are naturally more inclined to make public a therapeutical success than a result which is negative or unsuccessful. But in discussing the practical side of the question it is obvious that the unsuccessful cases must be taken into consideration. The technical side of the transplantation operation is undoubtedly of great importance. And failure when it occurs should not be allowed to cause discouragement in the use of the method. It is also of practical interest that even very minute testicular fragments may suffice for the full development of the sexual characters (*Pézard*, 1918; *Lipschütz, Ottow and Wagner*, 1920, 1921).

That failure should often be met with ought to be only an incentive to discover better methods for increasing the chance of survival of the autoplastic or homoioplastic graft. This is the only practical conclusion to be drawn from what we actually know about testicular transplantation. It is of importance also to obtain more certain knowledge as to the cases in which testicular transplantation is indicated. There are indeed many conditions of eunuchoidism in which testicular transplantation must necessarily be unsuccessful; in eunuchoidism testicular transplantation is indicated only when it is caused primarily by testicular dystrophia and not by a disturbance of some other endocrine gland. From what *Stabel* communicated at the meeting of the Society for Sexual Reform held in Berlin in 1921 it seems clear that in homosexuality good results are very rare. We shall discuss this side of the question in another chapter.

Heterotransplantations have also been attempted several times in man. *Stanley and Kelker* (1920, 1921) have reported on an experiment with implantation of rams' testicles; the glands were laid in the pampiniform plexus or imbedded in the fascia overlying the rectus muscle of the abdomen. But the grafts always became necrotic and were gradually absorbed. *Falcone* (1920) transplanted rams' testicles in the abdominal wall of three men, 53 to 74 years of age, all of them sexually impotent. All the patients showed remarkable improvement in regard to sexual behaviour and general health; in two cases an increased sexual excitability was observed. The men did not know what effect was to be expected from the graft, so suggestion was excluded. Their own testicles increased in size.

I observed during several months a patient into whom the testicle of a goat had been engrafted by Krause in our Institute; the graft was made on the scarified surface of the m. rect. abdom. There was a definite erotising influence, which began a few days after the operation, and lasted for several months. The graft disappeared some weeks after the operation.

A great number of very successful testicular grafts were made from ape to man by *Voronoff* (1923, 1924) and by *Thorek* (1923). The observations of these authors leave no doubt that a testicular graft from certain anthropoids can survive in the human body for several months, and possibly even for years, exhibiting a normal hormonic activity.

A great number of ovarian transplantations have been made during the last twenty-five years in the lower mammals as well as in women. There is no need to give a detailed account of the question as it has already been discussed by various authors [see especially *Biedl*, pp. 280–2; *Stocker* (1916); *Unterberger* (1918)]. It may be mentioned that the atrophy of the uterus and of the tubes does not take place when an auto- or homoiotransplantation of the ovary is made (*Figs.* 47-49). *Athias* (1919) has stated that the functional alterations undergone by the uterus of the guinea pig after castration, are prevented by subcutaneous transplantation of ovaries. It seems very likely that the ovarian graft has a better chance of survival than the testicular one; even successful ovarian heterotransplantation has been described by *Bucura,* who engrafted the ovaries of rabbits and guinea pigs into female hares. He relates that these animals behaved like normal females, and admitted

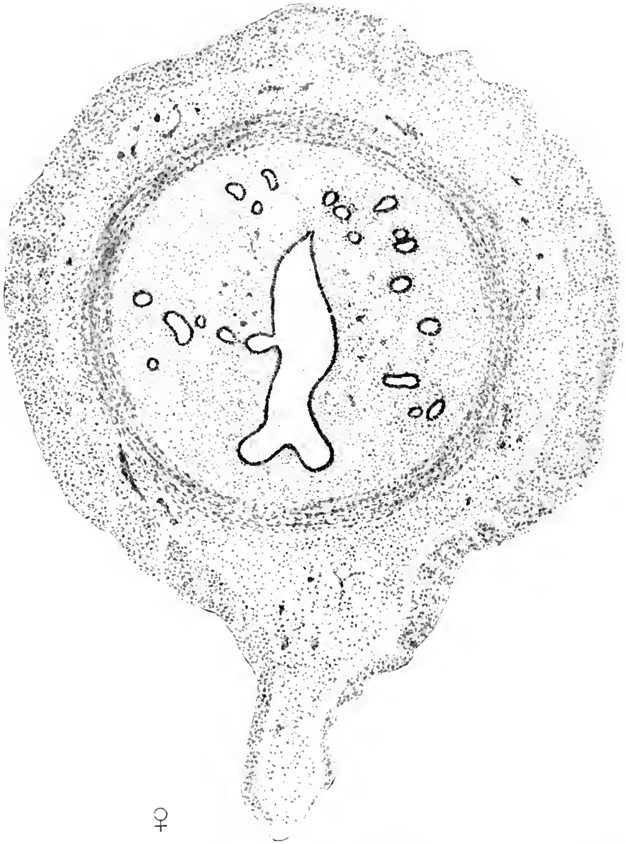


FIG. 47.—*Section through uterus of a normal rat.* To be compared with Fig. 48.—From Marshall and Jolly.

the males, a process which never occurs with castrated females; but I am doubtful whether a castrated female is really so easily distinguishable in her behaviour from a normal one. As regards ovarian transplantation in women there can be no doubt that the atrophy of the uterus can be prevented by transplantation; menstruation occurs and even returns when it had formerly disappeared in consequence of the removal of both ovaries. For a discussion of the practical side of the question the reader may be referred to *Blair Bell's* book (1920, pp. 180-1) where some of the clinical literature is quoted, and to the paper by Unterberger mentioned above, and to the paper by *Sippel* (1923) from the clinic of Bumm. It would seem that, wherever possible, any healthy portion of a removed ovary should be engrafted.

The question may also be discussed as to whether an ovarian graft can "take" when the normal healthy ovaries are present in the body. Bell relates that in his experiments on rabbits the graft grew as well when one ovary was left in situ as when both were removed. I made homoiotransplantations on rabbits with both ovaries in situ; 15 ovaries of animals of the same litters were implanted into five rabbits one to about three months of age. The ovaries were placed on one of the abdominal muscles. Two months later grafts could be felt in two or three animals; in one of these animals the graft seemed to be in a state of cystic degeneration. When killed five to six months after the operation no remains of the grafts could be found. Similar experiments were recently made with success by *Haberlandt* (1921) on adult rabbits; we shall return to these experiments in Chapter V.

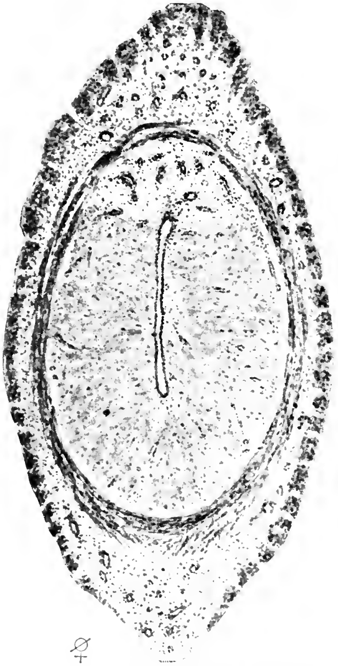


FIG. 48.—*Section through the uterus of a castrated rat.* Much reduced muscle layers. Uterine glands absent.—From Marshall and Jolly.

There can be no doubt that a testicular or ovarian graft not only can "take" in mammals and man, but that the ovary, as we shall see in Chapter V., can undergo after transplantation the cyclical changes of the organ in situ.

Testicular transplantations in the frog were made by *Nussbaum* (1909, p. 546) who went carefully into the whole question. He points out that one can improve the chances of the graft "taking" easily in the abdominal cavity by inducing an hyperæmia of the organs before transplantation through exposure to the air; a good vascularization seems to be assured by this method. The atrophy of the callosities on the forearm and

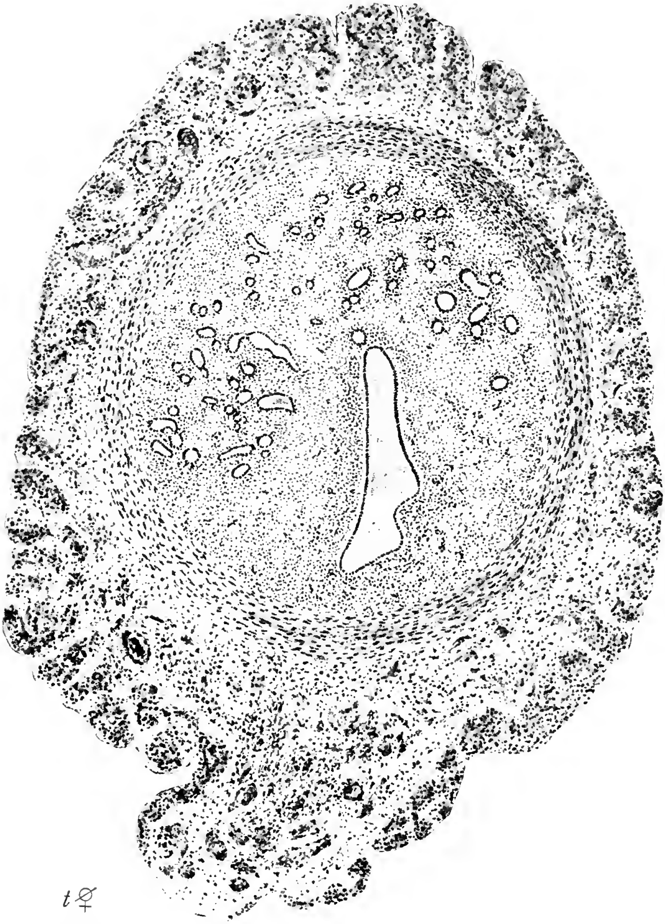


FIG. 49.—*Section through the uterus of a rat with ovarian autotransplantation.* Compare with Figs. 47 and 48. Normal development of the uterus.—From Marshall and Jolly.

that of the vesiculae seminales can be prevented to a certain degree if the graft survives. If this is not the case, all the usual signs of castration manifest themselves. A great many successful transplantations in toads (*Bufo vulgaris*) have recently been made by *Guyénot* and his co-workers, *Ponse* (1922) and *Welti* (1923).

But do all these experiments really afford sufficient proof that the sexual glands act on the sexual characters by internal secretions? I mentioned above that we are confronted with an objection here. We cannot exclude the possibility that centripetal nervous fibres have grown into the graft and that a nervous path was re-established between the sexual gland and the central nervous system. Nussbaum seems to have been the first to have called attention to this. He pointed out that by testicular or ovarian transplantation a new logical position is not thereby created, and that there is nothing to decide the question whether the graft is acting on the sexual characters by the intermediation of a nervous path or by some chemical substances. As far as I know the question whether nerves also enter into the graft along with blood vessels has not yet been studied anatomically. But observations certainly show that a nervous connection between the engrafted sexual gland and the central nervous system is established. A man on whom a testicular transplantation was made by *Lichtenstern* (1916) said, about five weeks after the operation, that bending low (and pressing on the graft placed on the obliquus externus) gave him the same pain as formerly when his own testicles were pressed upon. The same thing was told me by another patient also operated on by Lichtenstern. *Els* (1920) also describes a case where the sensitiveness of the testicular graft was like that of a normal testicle. In view of these observations it seems certain that the graft really becomes connected by nerves to the central nervous system and that transplantation experiments cannot absolutely decide the question whether the sexual glands act by nervous reflexes or by internal secretions discharged into the circulating blood.

B. FEEDING WITH SEXUAL GLAND.

Unlike the experiments with transplantation, those upon feeding with testes or ovary should supply satisfactory proof of an endocrine action on the part of the sexual glands if proved to be successful in preventing the symptoms of castration. The important part played by feeding experiments with thyroid gland or its extracts in contributing to our knowledge of internal secretion in general may be mentioned here

But what is stated about the results of feeding with sexual glands is very contradictory, especially in therapeutical experiments where different pharmaceutical preparations were administered. We shall restrict ourselves here to giving an example of one successful and one unsuccessful experiment. The first was made by *A. Loewy* (1903, pp. 138–40) on capons which were fed with testes. Loewy relates that the head apparel developed better than in control capons. He mentions also an effect on the skeleton in which all the changes characteristic of the "castrate" were prevented when young capons were fed with testes. *Steinach* (1910) fed rats castrated at an age of four weeks with fresh testes of adult rats, guinea pigs and rabbits. Although the feeding experiment lasted more than three months the animals remained typical "castrates," and not the smallest effect could be observed.

The negative result does not however imply that feeding with testis or with ovary must necessarily always be negative in its results with mammals. On the other hand there can scarcely be any doubt that the metabolism of mammals may be changed in one or other direction by feeding with ovary or its preparations. This is in accordance with Loewy's experiment mentioned above and with numerous experiments performed lately by many investigators on tadpoles for different purposes. In my Institute *Wagner* (1922) found that the metamorphosis of tadpoles, retarded by late artificial fecundation, can be accelerated by feeding with ovary. But no specific influence through feeding with testis or ovary has ever been observed, i.e., the formative influence which the testicle or the ovary exerts on the sex characters in the body could not be replaced by feeding upon these organs.

C. INJECTION.

As with the feeding experiments injection experiments with testis or ovary on mammals have given very contradictory results. It suffices to mention the experiments of *Brown-Séquard* (1889) and others upon man. New experiments of this kind have been recently performed by *Stanley* (1921), who made numerous injections in over 300 cases. He used aseptically prepared material from ram, goat or boar a year to eighteen months old, i.e., from animals which had reached sexual maturity. The injections were made subcutaneously on the abdomen. Sometimes material kept frozen at −18°F. for as long as 30 days after the death of the animal was used without the potency seeming to be affected. The cases treated were of a very different order, and included neurasthenia, senility, asthma, different chronic nervous diseases, testicular atrophy, rheumatism and diabetes. Some of the treated men stated that their eyesight was improved, that they experienced a renewed joy in living and an increased energy, besides other beneficial effects. Stanley concluded from his experiments that animal testicular substance injected into the human body really produces definite effects.

One can scarcely say that these experiments on men provide proof of a specific testicular internal secretion. But positive results in replacing the specific influence of the sexual glands on the sex characters by means of injection were obtained by Bouin and Ancel in experiments on guinea pigs and in the experiments of Pézard on cocks. *Bouin and Ancel* (1906) gave to three guinea pigs castrated when two to four weeks old, subcutaneous injections of an extract from retained testicles of mammals. The extract was prepared with glycerine and water, and injections were made every two days. The experiment lasted nine months. It was found that the penis and the vesiculae seminales were much more developed than in ordinary "castrates." The striking way in which the penis and the vesiculae seminales of the guinea pig react to castration may be recalled, as well as the marked difference between, for instance, the length of the vesiculae seminales of a normal and a prepuberally castrated adult guinea pig (*Figs.* 12 *and* 13). Now Bouin and Ancel found that the length of the vesiculae seminales of the injected animals was not only greater than in "castrates," but that in one case the length shown by a control normal animal was nearly attained. Moreover, they measured various bones, and claim to have found differences between normal and castrated animals, whereas the proportions in the injected animals were like those in the normal; but in my judgment the differences are very small. It is the same with another experiment performed by Bouin and Ancel with the purpose of studying the body weight of injected guinea pigs. (1906 b). They found that the injected animals had about the same weight as normal ones, whereas the "castrates" weighed less. But the question as to the body weight after castration is a very complicated one, since it is influenced by many factors such as the skeleton, muscles, internal organs and fat deposit. In male rabbits I found no difference between the weight of normal and castrated animals in the first six months after birth, or about four months after castration, whereas later on I found a striking difference, the "castrate" attaining a greater weight. This seems to be due especially, as already said, to the accumulation of fat.

Pézard's experiment (1911) was performed on a cockerel castrated two months before and showing signs of castration. Intraperitoneal injections of an extract of retained pig testicle were made twice a week for about five months. The comb of the injected bird got longer than in the control which was an ordinary "castrate." The entire head apparel underwent development, became rich in blood, and capable of erection. When the injections were stopped the comb decreased in length, and about 2½ months later was of the same length as in the uninjected control "castrate." The whole of the head apparel also became pale. Pézard relates also that sexual instincts were shown by the injected bird which crowed and fought with other birds. The sexual instincts disappeared and the crowing ceased when the injections were stopped. The body weight of the castrated bird was not changed by the injections.

Experiments have been made on the frog by several investigators. *Nussbaum* (1909, p. 554) inserted the testicles into the lymphatic sacs in a number of castrated frogs; the pads and the vesiculae seminales grew, although the testicles gradually degenerated. In order to bring about a successful result it is necessary to place a new portion of testicle into the lymphatic sac before the previous portion has entirely degenerated. Castration effects can be prevented also by repeated injections into the lymphatic sac with a pulp made of testicle. A great number of similar experiments were made by *Steinach* (1910), who studied the dependence of the clasp reflex upon the testicle. Having castrated the frogs and found by repeated testings that the reflex could no longer be evoked, he injected into the dorsal lymph sac a pulp of testicular substance taken from frogs "in heat." About 12 to 24 hours later the clasp reflex appeared; in some cases it began gradually. In about two days the maximum was reached and the reflex disappeared gradually in from three to four days. The reflex could be evoked again when new injections were made. Such striking results were not, indeed, obtained in all the experiments performed, but in the greater number the reflex could be evoked after injection. The disappearance of the clasp reflex evoked by injections could be accelerated by washing out the dorsal lymph sac with isotonic salt solution. According to Steinach, among frogs caught at the time of heat some are found in which the clasp reflex is naturally absent; in these animals also, however, the reflex could be evoked after injection. Control experiments were made with pulp of muscle and liver of frogs in heat, but no effect could be obtained. Simultaneously with Steinach's work a paper was published by *Harms* (1910) containing an account of similar observations on the clasp reflex. The above-mentioned observations of Nussbaum on the influence produced by testicular injections on the thumb pads were confirmed by Steinach, Harms, *Meisenheimer* (1912), and *Takahashi* (1919).

All these experiments performed on mammals, birds and amphibians show that the formative and preserving effects possessed by the sexual glands in relation to the sex characters are caused not by nervous impulses from these glands, but by chemical substances secreted by the latter into the circulation. We know practically nothing about the chemical nature of these substances. But they are in any case specific, as the same effect cannot be evoked by the injection of any other gland or tissue. The active substances present in the sexual gland are therefore specific hormones. The question as to the chemical nature of these hormones will be discussed more fully in Chapter VII.

According to Steinach the clasp reflex can be evoked only by testicular injection from a frog in heat. When heat is over, the testicle has no effect when injected into a "castrate." From this one would conclude that the specific hormone evoking the clasp reflex is produced only at the time of heat.

D. INTERNAL SECRETION OF THE SEX GLANDS AND NERVOUS SYSTEM.

1. IS THERE AN ACCUMULATION OF THE INTERNAL SECRETION IN THE CENTRAL NERVOUS SYSTEM?

We have seen that the nervous system is erotized by an internal secretion of the sexual glands in such a manner that the psycho-sexual reflexes are rendered possible, and further that this erotizing action is caused by hormones The question next arises as to whether this action is an elective one similar to that of certain well known chemical poisons. Such an elective action could be proved, if one could demonstrate that erotizing substances secreted by the sex gland are accumulated in the central nervous system. Steinach relates having observed such an accumulation. He injected into a series of castrated frogs extract of brain and spinal cord from frogs on heat, and into a second series of castrated frogs brain and spinal cord of "castrates" were injected. In the first series a good clasp reflex appeared, in the second series no changes were visible. On the other hand Steinach claims to have shown, as already mentioned, that injections of other organs of frogs in heat are unable to evoke the clasp reflex in a "castrate." These experiments seem to show that there is an elective action of substances secreted by the testicle upon the central nervous system, due to an accumulation like that of strychnine; but the subject requires a more detailed experimental investigation.

It has also been claimed that the central nervous system acts as a mediator between the sex glands and the organs influenced by the internal secretion during heat. This question was investigated by *Nussbaum* (quoted from *Pflüger*, 1907) experimentally. He severed the nerve of the forearm of the frog on one side just at the time when the pads begin to hypertrophy. The development of the pad did not take place on the operated side. Nussbaum concluded from this observation that the internal secretion of the testicle acts in a specific manner only on certain nervous centres from which impulses are sent to certain organs, and the metabolism of the latter is changed in a given direction. A similar view was held by Steinach, who pointed out that the primary action of the internal secretion would be that on the central nervous system, by which, possibly through local changes of blood supply, the development of certain sex characters during the state of heat would be promoted. But *Pflüger* (1907) raised the objection that by sectioning the nerve of the forearm disturbances may be caused which are sufficient to explain the underdevelopment or degeneration of the pad.

The question as to the rôle played by the nervous system in regard to the effect of the sex glands on the somatic sexual characters is a very important one. It would be useful to investigate this question more fully than has so far been done experimentally.

2. Physiology of the Clasp Reflex.

The clasp reflex is a relatively simple and very pronounced physiological phenomenon characteristic of heat, and it may be conveniently considered here in preference to the more complicated psycho-sexual reactions observable in mammals. There are no special difficulties in experimenting on the physiology of the clasp reflex, whereas enormous difficulties arise when the psycho-sexual reflexes of mammals and man are studied. On the other hand the slight results obtained by experimental investigation of the clasp reflex of the frog may show us that we must not expect too much from research work on the psycho-sexual reactions in mammals and man. We see that the question as to the physiology of the clasp reflex, and the rôle played by the internal secretion of the sex gland in connection with it, is of a greater importance than one might at first think.

The clasp reflex has been studied by many investigators and over a long period. *Spallanzani* (1786, pp. 93 and 319) showed experimentally that for the reflex to occur, only the spinal cord and no higher parts are necessary. He decapitated male frogs when clasping the females, and they continued to clasp. We shall see below that by decapitation the clasp reflex can be evoked even outside of the time of heat. Further detailed experiments on the clasp reflex were made by *Goltz* (1869, quoted from *Tarchanoff,* 1887), who stated that the clasp reflex can be evoked when the skin of the breast or the ventral side of the arm is stimulated. After excising these parts of the skin or cutting through the corresponding posterior roots of the spinal cord the clasp reflex can no longer be evoked. According to Goltz there are influences emanating from the female by which the male is attracted, and the clasp reflex is kept up by the continuous stimulation of the above-mentioned parts of the skin. According to Goltz there is also a reflex dilatation of the seminal ducts and a reflex ejaculation. Goltz supposed that the spinal cord and the sensory organs in the skin are, during heat, in a state of increased irritability.

Since Goltz' time many experiments have been performed to determine the rôle played by different parts of the central nervous system on the clasp reflex. All these experiments have shown that the mechanism of this reflex is a much more complicated one than Spallanzani and Goltz supposed.

Albertoni (1887, 1889) and *Tarchanoff* (1887) showed that the clasp reflex in toads and frogs can be inhibited by stimulation of the corpora bigemina (*Fig.* 50). *Schrader* (1887) concluded from experiments on the frog that centres inhibiting the clasp reflex are to be found also in lower parts of the brain, such as the cerebellum and the upper portion of the medulla oblongata. The later experiments of *Busquet* (1910), *Steinach* (1910), and *Baglioni* (1912) afforded a more detailed knowledge of this question. Busquet separated the spinal cord from the brain in the frog by an incision just below the medulla oblongata, outside the time of heat. By touching the skin of the breast, or by laying the operated animal on another frog, the clasp reflex may be evoked, and may persist for several hours. This experiment may be successful at any time of the year. Busquet performed 200 of these experiments with success. The reflex can be evoked for about a week after the operation, i.e., as long as the animal survives. Similar results may be obtained after decapitation or a strong blow on the head. Evidently outside the time of heat certain impulses from above the spinal cord inhibit the clasp reflex, and we must suppose that the hormones produced by the sex gland during heat lower the irritability of these inhibiting centres. According to Busquet, this nervous mechanism is present only in the adult male; in 200 females Busquet never could evoke the clasp reflex after the operation mentioned above. Further, Busquet tried to show that this nervous mechanism develops

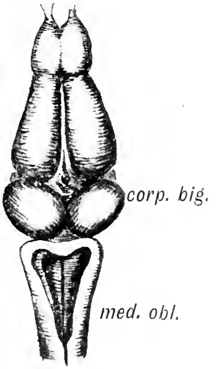


FIG. 50.—*Brain of frog.*

gradually in the male; in young males of about 15 to 25 gr. the experiment was unsuccessful, as in females, whereas in males of 35 to 40 gr. the clasp reflex, although evoked, was weaker than in males of 50 to 60 gr.

Similar experiments were performed by Steinach and Langhans (*Steinach*, 1910). They made incisions just below the medulla oblongata or between the cerebellum and the medulla oblongata, and evoked the clasp reflex in some cases for as long as two days. Like Schrader, they take the view that inhibitory centres are to be found, not only in the corpora bigemina, but also in the cerebellum and in the medulla oblongata. Busquet, on the contrary, holds that inhibitory centres are localised in the cerebellum only; the clasp reflex cannot be evoked after removal of the lobi olfactorii or of the corpora bigemina. When he destroyed the cerebellum only, which consists in the frog of a small transverse border above the medulla oblongata, the reflex could be evoked. The same result was obtained when the middle part of the cerebellum was destroyed with the point of a pin.

Besides the inhibitory centres there must be a centre for the clasp reflex in the spinal cord; it is the cervical part by which the muscles of the fore legs are innervated. By destroying the spinal cord 2 to 3 mm. below the medulla oblongata, Busquet caused the reflex to disappear. But the reflex persists when incisions are made just below the medulla oblongata and between the third and fourth cervical vertebrae. It is possible that the clasp reflex is caused not only by the weakening or absence of the inhibition from the upper parts, but also by an increased irritability of the spinal cord during heat; the question is worth further investigation as to whether the irritability of the spinal cord may be altered by the internal secretion of the testicle.

The results obtained in experiments on toads and frogs by Baglioni are contrary to those of the earlier investigators. He confirmed the statement of Albertoni and Tarchanoff, however, that the clasp reflex in the frog can be inhibited by mechanical stimulation of the corpora bigemina. But, on the other hand, Baglioni stated that the clasp reflex is not inhibited when the corpora bigemina are stimulated electrically, since under these conditions the reflex became even stronger. Another observation of Baglioni corroborates this; by placing a cotton wool pad soaked with stovaine on the corpora bigemina the clasp reflex could be inhibited. Contrary to the former authors, Baglioni concludes that in the corpora bigemina there are no inhibiting centres; Baglioni suggests that centres evoking the clasp reflex are to be found in the corpora bigemina.

The contradictory results obtained by Baglioni are possibly to be explained by the assumption that the electric stimulation or the influence of the poison affected in reality not only the corpora bigemina, but also the spinal cord. Baglioni confirmed the statement that by sectioning the spinal cord just below the medulla oblongata the clasp reflex can be evoked also outside the time of heat. In toads Baglioni obtained the clasp reflex by this operation, even in females. But as Baglioni points out, the reflex obtained in male and female in such a way is in reality not the true clasp reflex, but a climb reflex. Some further observations of Baglioni show also that certain inhibitory effects, due normally to the cerebral centres, are not displayed during heat. He found that the clasping male frog makes a prolonged extensory movement with the hind legs when touched on the soles of the feet. Outside the time of heat the same tonic movement can be observed only in frogs in which a section had been made between the medulla and the spinal cord.

As regards the sensitive parts in the skin from which the clasp reflex can be evoked, Steinach and Langhans made observations showing that probably the pads are a special sensitive organ. According to them the clasp reflex can be inhibited by painting the pads with a 5 per cent. solution of cocaine. Steinach thinks that the clasp reflex can be evoked by stimulation of the skin itself, owing to the fact that by stimulation of the skin the pads are in reality simultaneously mechanically stimulated. According to Schrader the clasp reflex lasts very long only in cases where it is evoked by the female itself, although, as we know, anything touching the skin of the breast can evoke the reflex. Evidently there are certain special influences coming from the female and acting on the male which cause the prolonged reflex.

In view of these considerations one sees that the clasp reflex of the frog in heat, which at first sight seems to be so simple, is in reality a very complicated nervous mechanism, in which both stimulating and inhibitory impulses play a part. The irritability of the nervous centres involved in this mechanism seems to be regulated by the hormones of the testicle.

How much more complicated must be the physiological mechanism underlying the psycho-sexual behaviour of the mammal or man! One realises how manifold must be the variations in psycho-sexual behaviour which have arisen on so complex a physiological basis, especially when one takes into consideration that the inter-play of irritation and inhibition may be changed by variation in the activity of the hormone-producing sexual gland.

3. THE PSYCHO-SEXUAL BEHAVIOUR OF MAN.

The observations which have been made on castrated men leave no doubt that the internal secretion of the sex gland is one of the physiological conditions of the characteristic psycho-sexual behaviour in the human species. After seeing how complicated the mechanism of the clasp reflex is, we come to understand how hopeless it is at present to attempt to build up a comprehensive account of human sexual behaviour on purely physiological lines. What we know about these physiological conditions is very little, and theories in this field are usually elaborated rather on analogies than on real knowledge of facts.

It must not be forgotten also that the influence of *external* factors on the sexual behaviour attains in man the highest degree observed in the animal kingdom. There is in the psycho-sexual behaviour of man almost unlimited variation. Every epoch, every social class, every profession, and even every individual has a characteristic sexuality very different from that of others. The conditions determining the psycho-sexual behaviour of man relate not only to a certain type of structure of the nervous system and to the hormones of the sex gland, but at the same time to the whole complex designated under the terms "culture" or "civilisation." We must admit that the psycho-sexual behaviour may be very different even when the physiological basis is the same (*Lipschütz,* 1922). It is absolutely necessary to emphasize this, because it would be dangerous for human society to overlook the external conditions on which sexuality in man depends. This is true not only within the limits of normal sexuality, but also for all the numerous pathological deviations which the medical man and the educationalist have to cope with.

It is merely an abstraction that we are dealing with when we consider the relations existing between the internal secretion of the sex gland and the psycho-sexual behaviour of man. But even within the limits of this problem our knowledge relates only to some general points. We shall see in the following chapters how little we know about the pathological changes in the sex glands or in the other glands of internal secretion in cases of quantitative and qualitative variation in human psycho-sexual behaviour. But, on the other hand, anyone who has learnt something about the physiology and pathology of the organs of internal secretion, and especially of the hormone-producing sex gland, will agree that in a scientific analysis of the psycho-sexual behaviour of man the endocrinological aspects cannot be left unconsidered.

* * *

Another question may be shortly discussed here. Many authors in recent years have adopted the view that the sex characters depend in reality not only upon the sex glands, but upon the whole internal secretory system. We have already touched on this question in Chapters I. and II. There can surely be no development of sex characters without all the other organs of internal secretion participating; all of these glands are influenced by the internal secretion of the sexual glands, and the latter are influenced by the former, and no doubt these interrelations between the endocrine glands are of the greatest importance in relation to the development of the sex characters. But this does not mean that the determination of somatic and psychical sex characters is in no special relation with the sexual glands, or that there is no special link between the sex gland and somatic and psychical sexuality.

I think that in belittling the influence of the gonads one is making two great mistakes. The first mistake is a logical one, whereas the second is due to not taking into consideration the facts concerned. Let us discuss these two points.

When we speak in science of the "cause" of a thing we mean by this a factor which is able to change a certain thing into the given thing. We always leave on one side the whole complex of other factors involved in this given thing; scientific research, and even practical understanding, would be wholly impossible if such a proceeding were not adopted. What we mean when we state that an internal secretion of the sex glands causes male or female characters, is, in the first instance, merely that male or female sex characters can develop only when *in an otherwise healthy organism* and *ceteris paribus* the internal secretion of the testicle or the ovary is produced. It is the same with all the other functions attributed to the different structures or organs. Take, for instance, the cortex of the cerebral hemispheres considered as an organ of intelligence. Nobody presumably will doubt that the cortex really has this function. But the accomplishment of this function depends upon manifold factors: upon the heart, the blood vessels, and the stimuli acting on the organs of sense. Nevertheless, everyone will agree that great confusion would arise in physiology if a man of science put forward the view that the cerebral cortex was not responsible for the intelligence merely because the other living organs and tissues were involved in giving effect to intelligent action. And similarly with the sexual gland.

Complete maleness or femaleness does not occur without the hypophysis, the adrenals, the thyroid, and so on. In such an objection the second error manifests itself. Extirpation or destruction by disease of any one of these endocrine glands will cause a pathological condition which is incurable except by the transplantation of the gland or by feeding or injecting its extract. The position after castration (or in cases of true genital eunuchoidism) is different; no pathological condition arises. It is true that the organism becomes altered functionally and structurally, but there are no disturbances of a pathological order if the other endocrine glands or organs were in a healthy state before. The ovary and the testicle have a specific *sexual* effect; *ceteris paribus* femaleness depends upon the ovary, maleness upon the testicle. This *sex specific* action of the gonads through their internal secretions is a characteristic feature of these glands. It will be dealt with later in this book.

BIBLIOGRAPHY FOR CHAPTER III.

[* *Not seen in the original.*]

ALBERTONI. 1887. Sui centri d'arresto nel rospo. *Arch. ital. de Biol.*, 9. (Reprinted in Ricerche sperimentali eseguite nel laboratorio diretto dal Albertoni. Bologna, 1889, p. 14.)

BAGLIONI. 1912. Zur Kenntnis der Zentrentätigkeit bei der sexuellen Umklammerung der Amphibien. *Zentrlbl. f. Physiol.*, 25.

—— 1913. Physiologie des Nervensystems. *Handb. d. vergleiel. Physiologie von Winterstein*, 4. Jena. (See the section: "Die die sexuelle Umklammerung vermittelnden Nervenvorgänge," p. 401.)

BAYLISS *und* STARLING. 1906. Die chemische Koordination der Funktionen des Körpers. *Erg. d. Physiol.*, 5.

BELL (W. Blair). 1920. *The Sex-Complex.* London.

BERTHOLD. 1849. Transplantation der Hoden. *Arch. f. Anat. u. Physiol., Physiol. Abt.*, p. 42.

BIEDL. 1913. *Innere Sekretion*, 2 Aufl. Berlin-Wien.

BOUIN *et* ANCEL. 1906a. Action de l'extrait de glande interstitielle du testicule sur le développement du squelette et des organes génitaux. *C. R. de l'Acad. d. Sc.*, 142, p. 232.

—— 1906b. Sur l'effet des injections d'extrait de glande interstitielle du testicule sur la croissance. *C. R. de l'Acad. d. Sc.*, 142, p. 298.

*BROWN–SÉQUARD. 1889. Expériences démonstrant la puissance dynamogénique chez l'homme d'un liquide extrait de testicules d'animaux. *Arch. de Physiol.*, 1, p. 651.

*—— 1889b. Du rôle physiologique et térapeutique d'un suc extrait de testicules d'animaux d'après nombre de faits observés chez l'homme. *Ibidem*, 1, p. 738.

*—— 1890. Nouveaux faits relatifs à l'injection souscoutanée chez l'homme d'un liquide extrait de testicules mammifères. *Ibidem*, 2, p. 204.

BUCURA. 1913. *Geschlechtsunterschiede beim Menschen.* Wien u. Leipzig.

BUSQUET. 1910. *La fonction sexuelle.* Paris.

—— 1910a. Existence chez la grenouille mâle d'un centre médullaire permanent présidant à la copulation. *C. R. de la Soc. de Biol.*, 68, p. 880.

—— 1910b. Action inhibitrice du cervelet sur le centre de la copulation chez la grenouille. Indépendance fonctionnelle du centre vis-à-vis du testicule. *C. R. de la Soc. de Biol.*, 68, p. 911.

CAULLERY. 1913. *Les problèmes de la sexualité.* Paris.

ELS. 1920. Neuere Gesichtspunkte bei der Behandlung der Hodentuberkulose. *Dtsche med. Wochenschr.*, No. 17.

*FALCONE. 1920. Sugli innesti della ghiandola interstiziale. *Riforma med.*, 36, p. 1177.

FOERSTER (W.) 1921. Ein Fall von Hodentransplantation mit Kontrolle nach einem Vierteljahr. *Dtsche med. Wochenschr.*

FOGES. 1902. Zur Lehre von den sekundären Geschlechtscharakteren. *Pflügers Archiv*, 93.

—— 1914. Keimdrüsen. In Jauregg und Bayer, *Lehrbuch der Organotherapie.* Leipzig.

GLEY. 1914. *Les sécrétions internes.* Paris.

—— 1921. *Quatre leçons sur les sécrétions internes*, 2 éd. Paris.

*GOLTZ. 1869. *Beiträge zur Lehre von den Funktionen der Nervenzentren des Frosches.* Berlin.

HABERLANDT. 1921. Über hormonale Sterilisirung des weiblichen Tierkörpers. (Vorl. Mitt.) *Münch. med. Wochenschr.*, No. 49, p. 1577.

HARMS. 1910. Hoden- und Ovarialinjektionen bei Rana fusca Kastraten. *Pflügers Archiv*, 133.

LICHTENSTERN. 1916a. Untersuchungen über die Funktion der Prostata. *Zeitschr. f. Urologie*, 10.

—— 1916b. Mit Erfolg ausgeführte Hodentransplantation am Menschen. *Münch. mediz. Wochenschr.*, No. 19.

—— 1918. Offiz. Protokoll d. Gesellsch. d. Aerzte in Wien. *Wiener klin. Wochenschr.*, No. 45, p. 1217.

*—— 1920. Bisherige Erfolge der Hodentransplantation beim Menschen. *Jahresk. f. ärztl. Fortbild.*, 11, p. 8.

LIPSCHÜTZ. 1917. Zur allgemeinen Physiologie des Wachstums. *Zeitschr. f. allgem. Physiol.*, 17. (See espec. Part VIII.)

—— *et* OTTOW. 1920. Sur les conséquences de la castration partielle. *C. R. de la Soc. de Biol.*, 83, p. 1340.

——, OTTOW *et* WAGNER. 1921. Nouvelles observations sur la castration partielle. *Ibidem*, 85, p. 42.

—— 1921. Quantitative Untersuch. über die innersekretorische Funktion der Testikel. *Dtsche med. Wochenschr.*, No. 13.

—— 1922. Die innere Sekretion der Geschlechtsdrüsen und ihre Bedeutung für die Sexualität des Menschen. Referat I., Internat. Tagung f. Sexualreform in Berlin. *Sexualreform und Sexualwissenschaft.* Stuttgart.

LOEWY (A.) 1903. Neuere Untersuchungen zur Physiologie der Geschlechtsorgane. *Ergebn. d. Physiol.*, 2, 1 Abt.

MAUCLAIRE (P.) 1923. Les greffes testiculaires chez les animaux et chez l'homme. *Arch. des maladies des reins et des organes genito-urin.*, 1, p. 513.

MEISENHEIMER. 1912. *Experimentelle Studien zur Soma- und Geschlechtsdifferenzierung*, II. Jena.

MÜHSAM. 1920. Über die Beeinflussung des Geschlechtslebens durch freie Hodenüberpflanzung. *Dtsche med. Wochenschr.*, No. 30.

—— 1921a. Der Einfluss der Kastration auf Sexualneurotiker. *Ibidem*, No. 6.

—— 1921b. Weitere Mitteilungen über Hodenüberpflanzung. *Ibidem*, No. 13.

—— 1921c. Influencia de la transplantación del testiculo y de la castración sobre el sentido sexual. *Revista médica de Hamburgo*, 2, No. 7.

*NUSSBAUM. 1906. Innere Sekretion und Nerveneinfluss. *Anat. Anz.*, 29, p. 431.

*—— 1906. Innere Sekretion und Nerveneinfluss. *Erg. Anat. u. Entw.-Gesch.*, 15, p. 39 (both quoted Pflüger, 1907).

—— 1909. Hoden und Brunstorgane des braunen Landfrosches (Rana fusca). *Pflügers Arch.*, 126.

—— 1912. Über den Bau und die Tätigkeit der Drüsen, VI. Mittl. *Arch. f. mikr. Anat.*, 80, II. Abt.

PÉZARD. 1911. Sur la détermination des caractères sexuels secondaires chez les Gallinacés. *C. R. de l'Acad. d. Sc.*, 154, p. 1183.

—— 1918. Le conditionnement physiologique des caractères sexuels secondaires chez les oiseaux. *Edition du Bulletin Biologique de la France et de la Belgique.* Paris.

PFLÜGER. 1907. Ob die Entwicklung der sekundären Geschlechtscharaktere vom Nervensysteme abhängt? *Pflügers Archiv* 116.

PONSE. 1922. Disparition et récupération des caractères sexuels secondaires mâles par castration et greffe chez Bufo vulgaris. *C. R. de la Soc. de phys. et d'hist. nat. de Genève*, 39, p. 144.

SAND. 1918. *Experimentelle Studier over Kønskarakterer hos Pattedyr.* Copenhagen.

SCHRADER. 1887. Zur Physiologie des Froschgehirns. (Vorl. Mitt.) *Pflügers Arch.*, 41, p. 75.

SIPPEL. 1923. Die Ovarientransplantation bei herabgesetzter und fehlender Genitalfunktion. *Arch. f. Gynäkol*, 118, p. 445.

SPALLANZANI. 1786. *Versuche über die Erzeugung der Tiere und Pflanzen.* Deutsche Übersetzung. Leipzig.

*STANLEY. 1920. Experiences in testicle transplantation. *Calif. State J. M.*, 18, p. 251; quoted *Ber. ges. Physiol.*, 3, 1921, p. 514.

*—— *and* KELKER. 1920b. Testicle transplantation. *Jl. Am. M. Ass.*, 75, p. 1501; quoted *Ber. ges. Physiol.*, 2, 1920, p. 575.

—— 1921. Testicular substance implantation. *Endocrinology*, 5, p. 708.

STOCKER. 1916. Über die Reimplantation der Keimdrüsen beim Menschen. *Korresp.-Blatt f. Schweizer Aerzte*, No. 7.

STEINACH. 1910. Geschlechtstrieb und echt sekundäre Geschlechtsmerkmale als Folge der innersekretorischen Funktion der Keimdrüsen. *Zentralbl. f. Physiol.*, 24.

—— 1916. Pubertätsdrüsen und Zwitterbildung. *Arch. f. Entw.-Mech.*, 42, p. 307.

*TAKAHASHI. 1919. Über die Geschlechtsdrüsen der Wirbeltiere. *Mitt. Med. Fak. Univ. Tokyo*, 22 (quoted from Witschi, 1923, *Zeitschr. f. ind. Abst. und Vererb.-Lehre*, 31, p. 307).

TARCHANOV. 1887. Zur Physiologie des Geschlechtsapparates des Frosches. *Pflügers Arch.*, 40.

THOREK. 1922. The present position of testicle transplantation in surgical practice; a preliminary report of a new method. *Endocrinology*, 6, p. 771.

—— 1923. Über eine neue Methode der Hodenverpflanzung u. verwandte Probleme. *Wien. Med. Wochenschr.*, No. 50.

UNTERBERGER. 1918a. Hat die Ovarientransplantation praktische Bedeutung? *Dtsche med. Wochenschr.*, No. 33.

—— 1918b. Die Transplantation der Ovarien. *Arch. f. Gynäkol.*, 110, p. 1.

VORONOFF. 1923. *Greffes testiculaires.* Paris.

—— 1924. *Quarante-trois greffes du singe à l'homme.* Paris.

WAGNER. 1922. Experimentelle Untersuchungen über die Umwandlung des Geschlechts beim Frosch. *Arch. f. Entw.-Mech.*, 52, p. 386.

WELTI. 1923a. Le sort des autogreffes chez le Crapaud. *C. R. de la Soc. de phys. et d'hist. nat. de Genève*, 40, p. 152.

—— 1923b. Les homogreffes sont-elles capables de persister chez le Crapaud? *C. R. de la Soc. de phys. et d'hist. nat. de Genève*, 40, p. 156.

WILDBOLZ. 1917. Ein Fall von kongenitaler Anorchie. *Korr.-Bl. f. Schweizer Aerzte*, No. 39.

WITSCHI. 1921. Der Hermaphroditismus der Frösche und seine Bedeutung für das Geschlechtsproblem und die Lehre von der inneren Sekretion der Keimdrüsen. *Arch. f. Entw. Mech.*, 49, p. 316.

Chapter IV.

The Seat of Production of the Internal Secretion of the Testicle.

FROM the facts communicated in Chapter III. it follows that in all vertebrates and in some invertebrates the sexual glands influence by an internal secretion the sexual characters both in forming and also in conserving them. There are different tissues in the sexual glands, and the question now arises which of these tissues represent the organ of internal secretion in the sexual gland. The question is, indeed, as *Gley* (1922) has rightly pointed out, histological rather than physiological. But it is one which can be decided only by the help of experimental physiology.

At first sight one might suppose that the internal secretion of the testicle is produced by the generative part. This suggestion has been contested in recent years by several authors. A long series of investigations has encouraged the belief that the internal secretion ascribed to the sexual glands is elaborated by the so-called cells of Leydig, the "interstitial substance," or "*interstitial cells*," situated in the connective tissue between the seminiferous tubules. It was shown by these investigations that the formation and the preservation of the sexual characters in the organism of mammals occur also when the generative part of the testicle is in a state of degeneration. *Bouin and Ancel* (1903) were the first to identify the cells of Leydig with the organ of internal secretion in the mammalian testicle. They called these cells *Glande interstitielle*, or interstitial gland, whereas *Steinach* (1912) described them later under the name *Puberty gland.*

As regards other vertebrates and invertebrates no sufficient knowledge of the interstitial cells in the testicle yet existed for locating the internally secreting elements. Not until lately has a systematic investigation in this direction been undertaken for amphibians and birds and fishes, but this has now been done by Bouin and his co-workers.

A. MAMMALS.

1. The Interstitial Cells of the Testicle.

In his first account of the interstitial cells, *Leydig* (1850, p. 47) described them as follows:—"One sees in studying the comparative histology of the testicle that besides the seminiferous tubules, blood vessels and nerves, there is present in the testicle of mammals another constant part, a cellular mass which surrounds the blood vessels when present only in small quantity, and in which the seminiferous tubules are

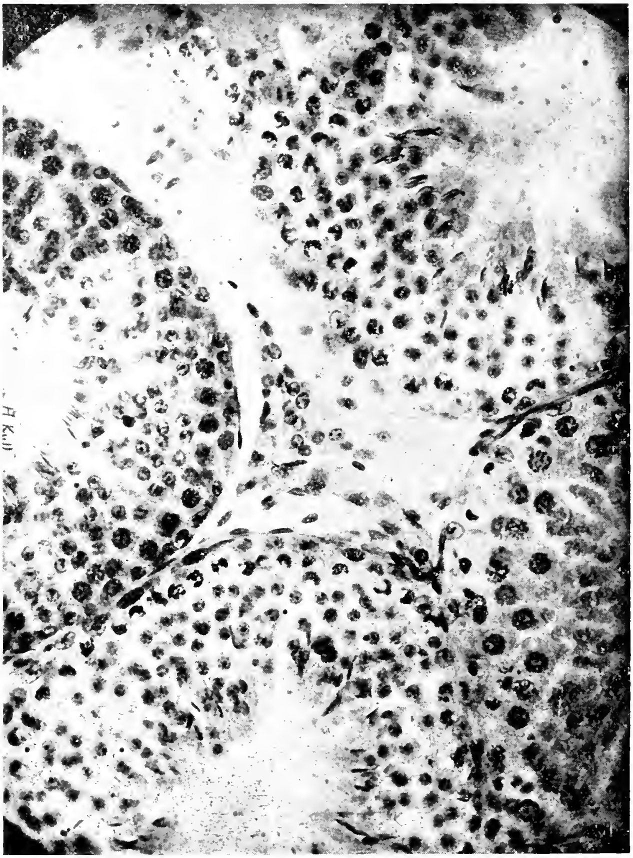


Fig. 51a.—*Section through testicle of normal guinea pig, aged about 4½ months.* (Prot. Nr. 27). x 280. Quadrangle between four tubules. Interstitial cells surrounding a capillary. Granulated interstitial mass.

wholly embedded when the quantity of this cellular mass is greater. The principal part of this mass consists of corpuscles of fatty appearance which do not change in acetic acid and in caustic soda, and which are colourless or yellowish." (See also *Leydig*, 1857, p. 495.) Since Leydig a great number of papers have been published on the histology of the interstitial cells. The most important paper of this kind dealing with the history of this question is that of *Bouin and Ancel* (1903 a). The papers of *Boring and Pearl* (1917), *Waldeyer* (1921), and *Benda* (1921) may also be referred to.

FIG. 51B.—*Section through testicle of normal guinea pig, aged about 4½ months.* (Prot. Nr. 27). × 280. Interstitial cells, capillaries and granulated mass in intertubular space.—Prepar. of Wagner; photo of Kull.

I shall give in this section a description of the interstitial cells, based on observations made by myself and Dr. Wagner on different species, especially on the rabbit, the guinea pig, the mouse and the cat. The interstitial cells in the testicle of mammals can be well recognised under normal circumstances by staining with haematoxylin and eosin; the solution of Bouin for fixation gives very good results; that of Helly (solution of Müller with sublimate and 5 per cent. formalin) is also very useful. In the testicle of an adult rabbit or guinea pig we see between the tubules triangular or quadrangular masses or cords of cells very well stained by eosin (*Figs.* 51, 52). The spherical nucleus is large and light coloured, the quantity of chromatin

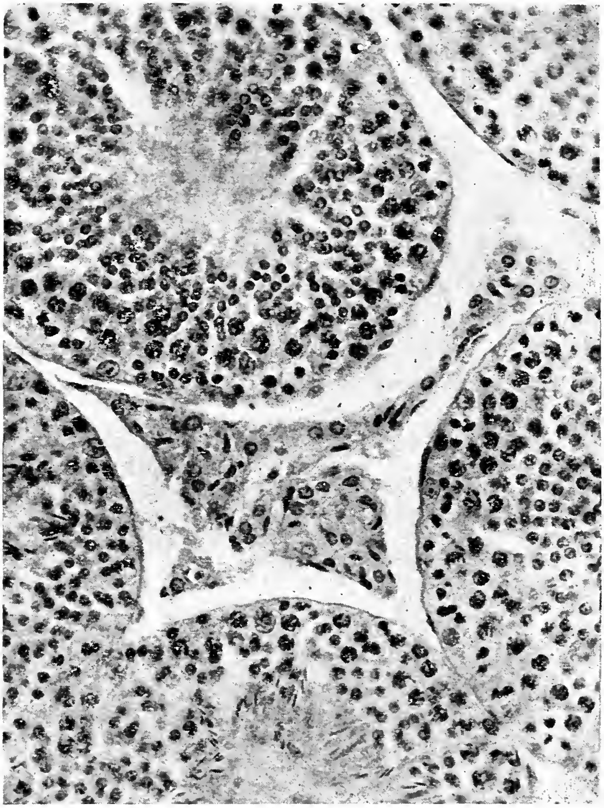


FIG. 52.—*Section through testicle of normal rabbit*, 14 *months old* (Prot. Nr. 82). x 280.—Prepar. of Wagner; photo of Kull.

being small; two or three nucleoli are generally present. The protoplasm surrounding the nucleus is very large. The dimensions of these cells are very variable, but by their characteristic appearance they are as a rule easy to distinguish from common connective tissue cells which are present in the testicle of an adult rabbit or guinea pig only in small quantity. In the testicle of the mouse the number of the interstitial cells is less, whereas, as stated by different authors, it may be enormous in other species as, for instance, in the wild boar. In the cat (*Fig.* 53) the interstitial cells are also very well developed. In man the interstitial cells are embedded in connective tissue consisting of fine filaments (*Fig.* 54). Very often one finds between the tubules and the interstitial cells empty spaces about which there has been much discussion (*Figs.* 51, 52); some authors consider these spaces to be artificial, whereas others regard them as something in the nature of lymphatic spaces. Lately

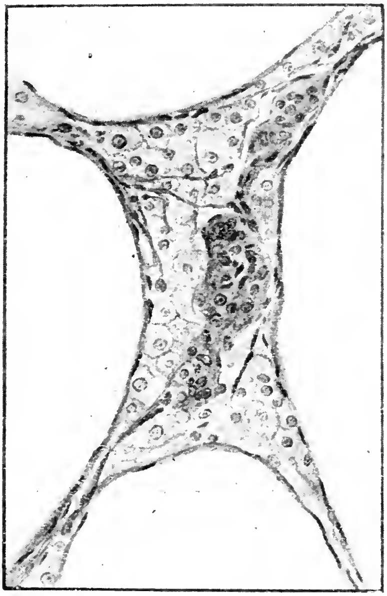


FIG. 53.—*Group of interstitial cells in testicle of adult cat* (Prot. Nr. 277, weight 3·2 kgr.). Weight of testicle, 1·2 gr. The big interstitial cells with spherical nucleus and vacuolated protoplasm can easily be distinguished from connective tissue cells.—Prepar. Wagner; design, Lehbert.

Wagner showed that these spaces are often filled with a homogeneous or granular mass, and as this phenomenon could be observed after fixation likewise in formalin and in the solutions of Flemming, Bouin and Helly, it seems very probable that these spaces are not artificial, but have something to do with the function of certain parts of the testicle.

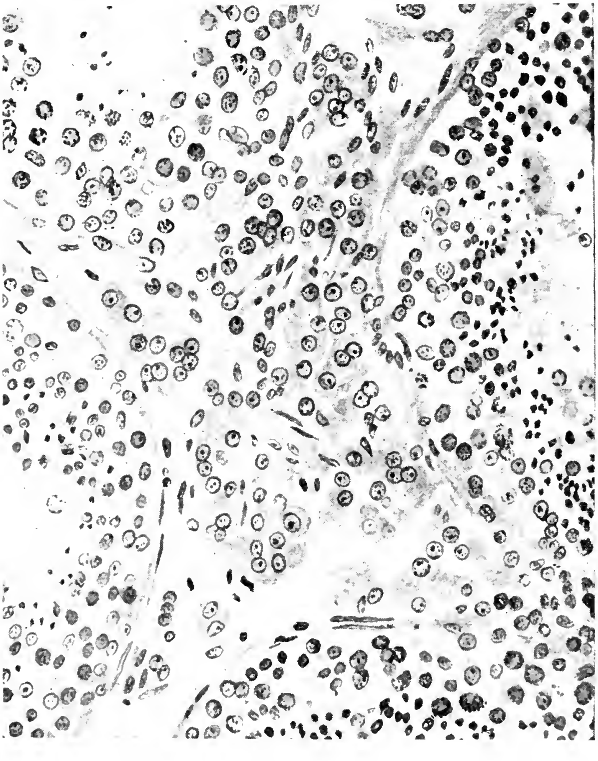


FIG. 54.—*Section through testicle of man 26 years old* (executed). Haematox.-eosin. Complete spermatogenesis; well developed interstitial cells.—From a preparation kindly lent by Aunap; design, Lehbert.

By differential stains inclusions may be observed in the protoplasm of the interstitial cells. There has been much discussion about the fatty granules in these cells; such granules are, indeed, to be found generally in the interstitial cells. Some authors are inclined to consider them as the most characteristic feature. But on staining preparations of an adult rabbit or mouse with "Sudan," one can see that the quantity of fat in the interstitial cells is very inconstant, and that fat may even be absent. On the other hand, the interstitial cells are sometimes completely filled up with fatty inclusions; a "Sudan" preparation from the testicle of an adult cat shows this in a very striking manner (*Fig.* 55). It seems to us improbable that the fatty inclusions are to be considered as the characteristic feature of the interstitial cells, and it is not possible to deduce therefrom conclusions as to the function of these cells. This is clear if we take into consideration the fact that numerous other inclusions are detected in the interstitial cells by other differential stains. I mention only the crystaloids detected by Reinke in the testicle of man, and the

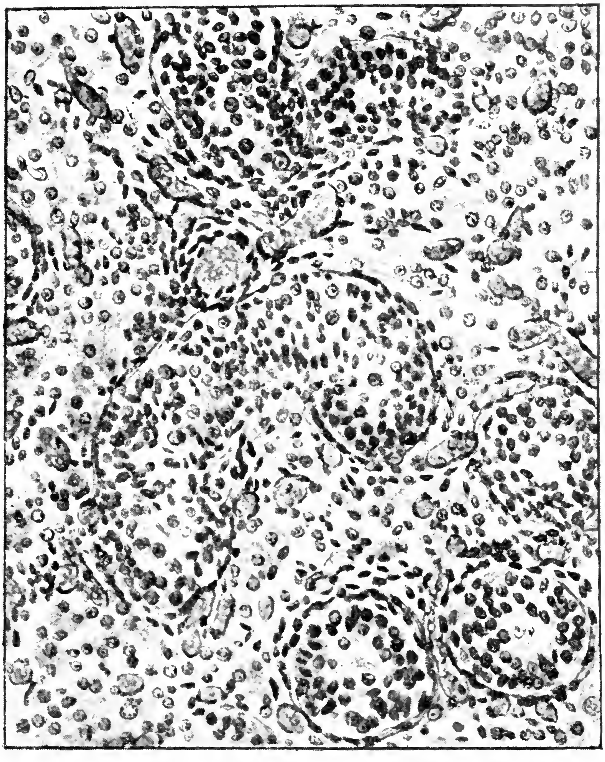


FIG. 54a.—*Section through testicle of human embryo of fifth month.* Same augmentation as 54. The greater part of the testicle consists of interstitial cells. Note the great quantity of capillaries in the interst. tissue.—From a preparation kindly lent by Aunap; design, Lehbert.

different granules of protein nature detected afterwards by other investigators (see *e.g. Whitehead*, 1912 b). The secreting granules characteristic of glandular cells and chondriosoma can be seen in the interstitial cells (*Wagner*, 1923) (*Fig.* 56). Dr. Wagner finds that, when a common connective tissue cell is in process of transformation into an interstitial cell, the protoplasm is characterised by an increase in size of the secreting granules and the chondriosoma which augments the size of the whole cell. Wagner has also made some observations which tend to show that, so far as fat appears in an interstitial cell, this fat is very specially localised (see *Fig.* 56). If it is permissible to draw conclusions as to function from histological appearance, one must presume that the interstitial cells are *glandular*.

FIG. 55.—*Section through testicle of adult cat, stained with Sudan.*—Complete spermatogenesis; great quantity of interstitial cells full of fat.—Prepar. Wagner; design, Lehbert.

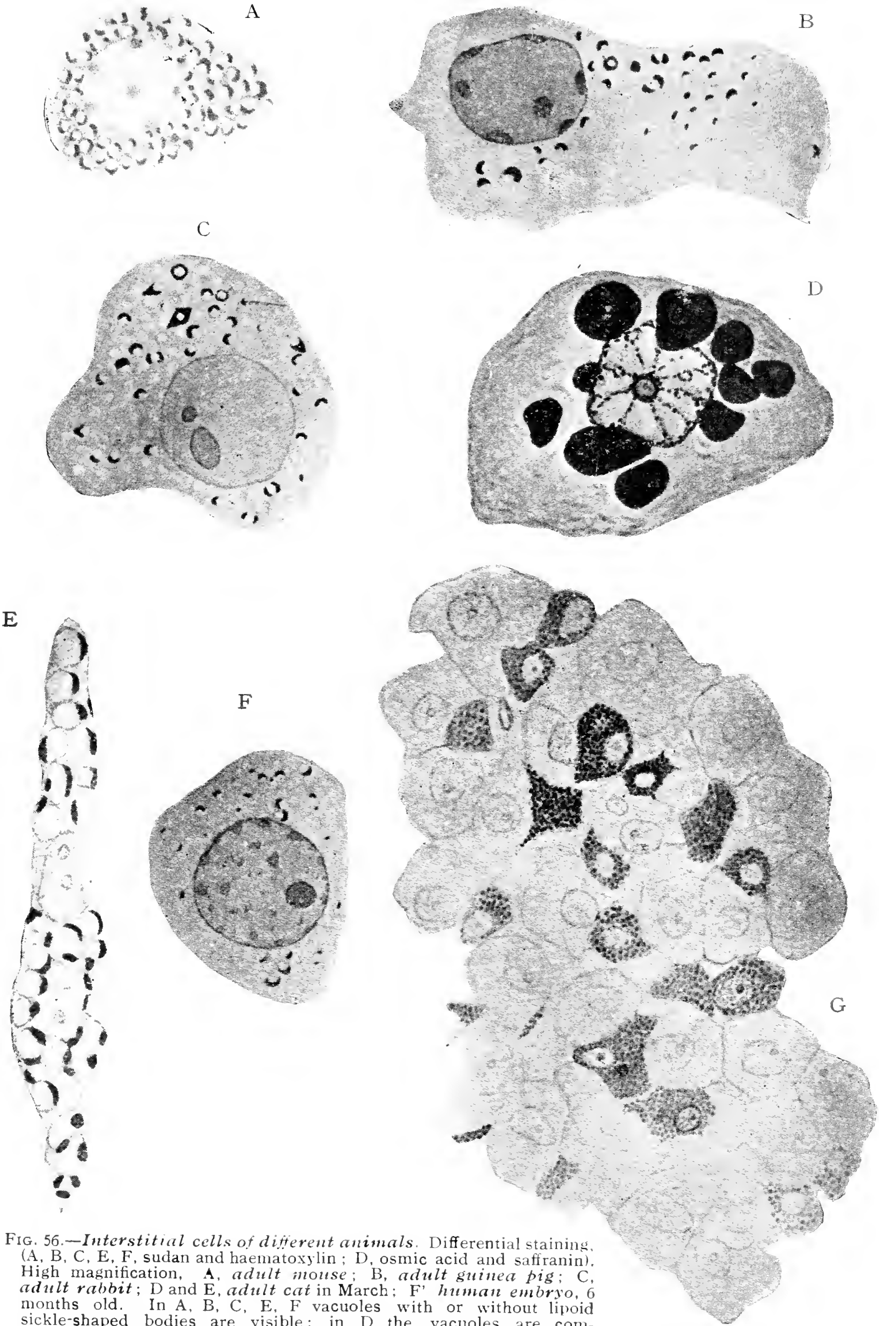


FIG. 56.—*Interstitial cells of different animals*. Differential staining, (A, B, C, E, F, sudan and haematoxylin; D, osmic acid and saffranin). High magnification, A, *adult mouse*; B, *adult guinea pig*; C, *adult rabbit*; D and E, *adult cat* in March; F, *human embryo*, 6 months old. In A, B, C, E, F vacuoles with or without lipoid sickle-shaped bodies are visible; in D the vacuoles are completely covered by fat. G, *adult mouse*, Vital staining of Goldmann; the animal was treated during six weeks with "Pyrrholblau." The smaller, rather spindle-shaped cells became blue, whereas the big epithelioid cells remained uncoloured. Possibly the smaller "pyrrholic" interstitial cells are in a different functional state from the big interstitial cells.—From Wagner.

As to the origin of the interstitial cells there are two different opinions. According to *Bouin and Ancel* (1903 c), who made observations on the embryo of the pig, the interstitial cells belonged to the mesenchyme, but grew into the primitive generative epithelium, separating the latter into solid cords. On the other hand, *Rubaschkin* (1912), who published very detailed observations on the guinea pig, showed that it is probable that the interstitial cells originate from mesodermal epithelium, i.e., from the generative cords; it may be mentioned that from the mesoderm arise also some other glandular cells, for instance, those of the renal tubules.

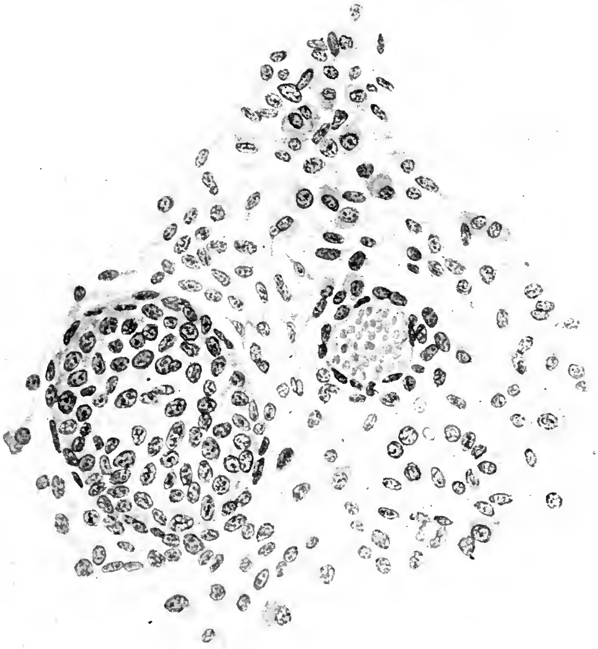


FIG. 57A.—*Development of interstitial tissue in guinea pig.* Abortus, not very far from normal birth (Prot. Nr. 101).

It seems to me that the views are not so contradictory as one might at first think. The observations of a number of workers whom Wagner has confirmed (*Figs.* 57A, B, C, D), for guinea pigs, before and after birth, leave no doubt that real interstitial cells can arise from connective tissue cells. The same conclusion seems to follow from new observations by Guilera and *Kronfeld* (1921). Sometimes all transitions between the spindle-shaped nucleus of the connective tissue cell to the spherical nucleus of the interstitial cell can be observed; but Rubaschkin suggested that the connective tissue cells, from which after birth interstitial cells arise, are also possibly elements originating from the generative cords or the mesoderm. There might be present in the intertubular tissue two different kinds of connective tissue cells: those which primarily were mesenchymatous cells, and those which primarily were epithelial and afterwards became connective or mesenchymatous, but remained able to transform themselves again into epithelioid interstitial cells.

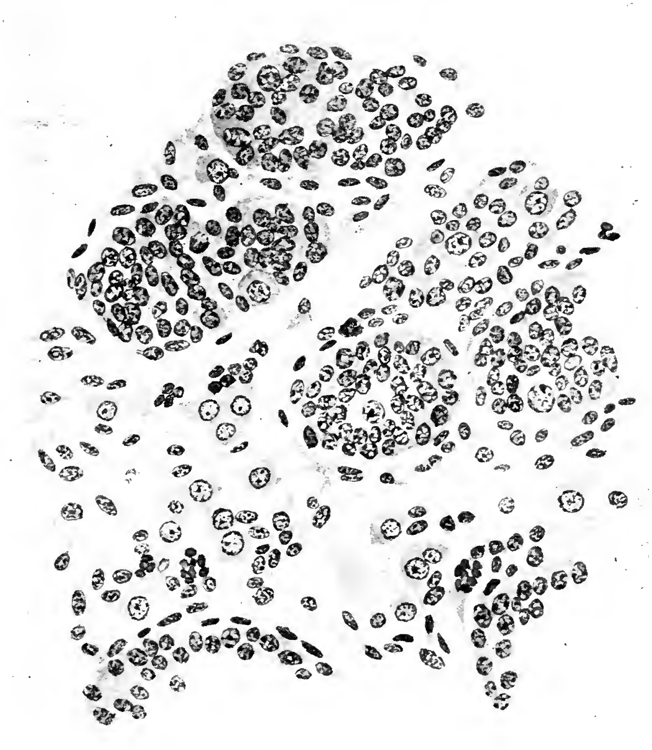


FIG. 57B.—*Development of interstitial tissue in guinea pig.* New-born animal (Prot. Nr. 103).

Alfred Kohn (1914 a) summarises our knowledge in this field in the following terms: "The interstitial cells of the generative glands are certainly not common connective tissue cells. The interstitial tissue is not a connective one like the connective tissue which is to be found everywhere in all organs and which, indeed, is present also in the generative glands. The interstitial cells are elements which are confined to the generative glands, and they are no less peculiar and specific than the epithelial generative cells themselves. How is this to be explained? The most likely explanation seems to lie in the suggestion that they are autochthonic elements formed on the spot and originating from the same primitive tissue as the

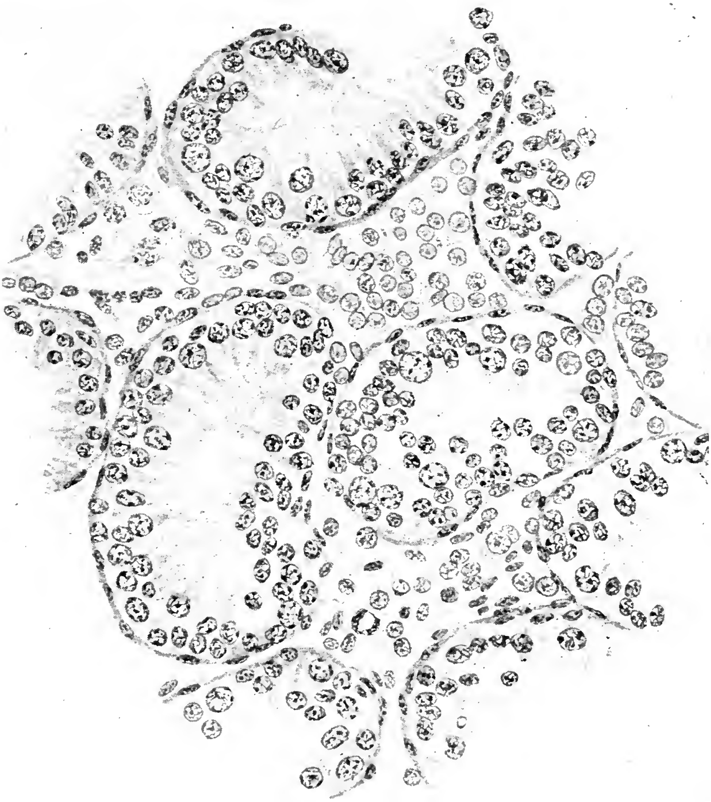


FIG. 57C.—*Development of interstitial tissue in guinea pig.* Six days old (Prot. Nr. 71).

generative cells. From the generative epithelium formed by the mesoderm would be derived not only the generative cells,

FIG. 57D.—*Development of interstitial tissue in guinea pig.* Two to three weeks old.

Note the gradual transformation of the spindle-shaped cells of the interstitial tissue into epithelioid cells. They are few in A and B; they fill up almost the whole intertubular space in C and D.—Prepar. and design of Wagner.

but also the elements which are to be found between the generative parts; such a suggestion has been already made by several authors. . . . Generative cells and interstitial cells would be of the same mesothelial origin and in a relation similar to that of nerve cells and neuroglia cells."

To the question whether the interstitial cells originate from mesenchyme, or from other primitive tissue giving origin to epithelium, great importance has been attached by some authors. They think that by demonstrating that the interstitial cells are derived from mesenchyme, and have the character of connective tissue cells, it is proved that these cells cannot have a glandular function. But I think that no conclusion concerning the function of the interstitial cells can be drawn from the embryological data. First of all, the mesenchyme is a part of the mesoderm. Secondly, as was mentioned above, it is possible that the connective tissue cells, which after birth may be transformed into interstitial cells, are not common connective cells, but a peculiar type of epithelial origin. Thirdly, even if the interstitial were really identical with common connective tissue cells, this would not preclude the possibility of their being glandular cells. On the contrary as we have shown above, there is little doubt that the interstitial cells histologically are glandular elements. After all, it seems to me undesirable, when discussing the question as to which part of the testicle produces the internal secretion, to attach much weight to evidence as to the origin of these cells. The question as to the functions of the different parts of the testicle can be decided only by experiment, which may be supplemented by pathological observation.

It has been demonstrated by various workers that the interstitial tissue has a different appearance at different ages. *Bouin and Ancel* (1904 a, f) showed in the horse that the interstitial tissue present in the embryonic testicle diminishes in the later stages of intrauterine life, and that the formation of a new interstitial tissue begins after birth, to be completed when spermatogenesis commences. Similar observations have been recently made by *Aron* (1921) on the pig and the sheep. According to Aron, the interstitial cells formed after birth, have a different cytological appearance from those present during intrauterine life. As regards rabbits and guinea pigs, some observations have been made in our Institute by Dr. Wagner. The figures 57 and 58 show in a very striking way the gradual transformation of the tissue between the tubules in the testicle of the guinea pig into cords of well-developed interstitial cells soon after birth. The puberal development of the sexual characters begins in the guinea pig a few weeks after birth. In the rabbit puberty does not

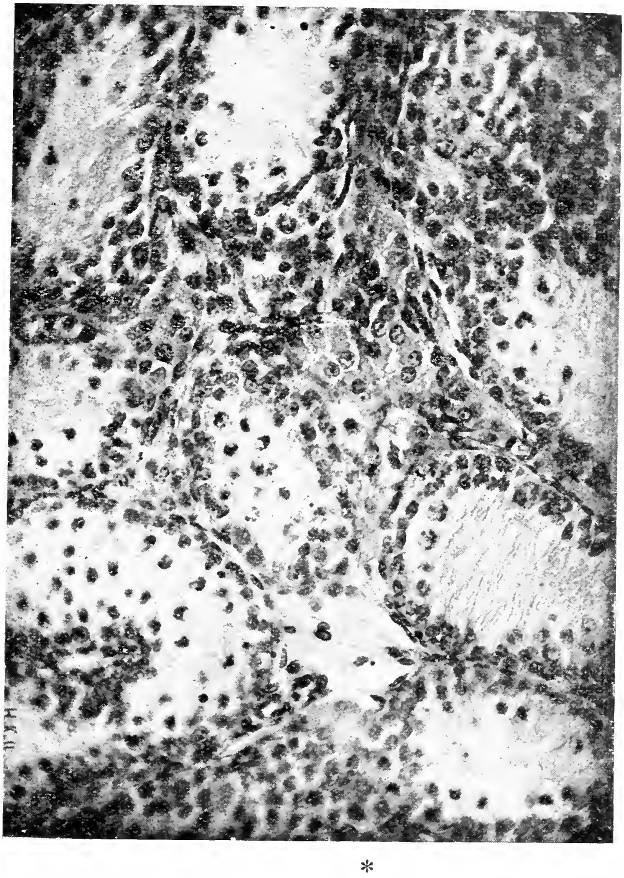


FIG. 58.—*Section through testicle of guinea pig, 2 to 3 weeks old* (Prot. Nr. 32). x 280. Interstitial cells rich in protoplasm with big spherical nucleus. Above the * the granular mass is visible.—Prepar. of Wagner; photo of Kull.

begin until about three or four months after birth, and until this time we find the whole testicle in an infantile condition. Each interstitial cell is very small—a narrow band of protoplasm surrounding a small spherical nucleus (*Fig.* 59). The protoplasm does not stain well with eosin. At about three and a half months after birth the interstitial cells become fully developed We have in the guinea pig and the rabbit a close correspondence between the state of the interstitial cells and the development of the sexual characters. Are the latter caused by the former?

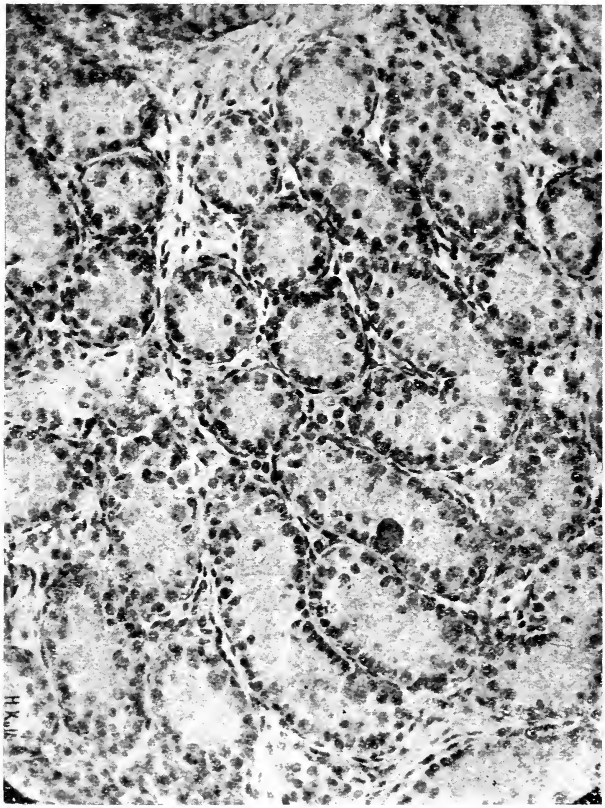


FIG. 59.—*Section through testicle of rabbit, 2 months old* (Prot. Nr. 46). x 280. Seminal tubules with mostly one stratum of cells; spermatogonia are present. Small spherical nucleus. At many places cells with spindle-shaped nucleus prevail.—Prepar. of Wagner; photo of Kull.

And is there also a close correspondence between the state of the seminiferous tubules and the development of the sexual characters? For deciding this question it would be necessary to study the time relations concerned in a more detailed manner than we have done hitherto.

We have not personally investigated the question whether well developed interstitial cells are temporarily present in the guinea pig and the rabbit during intrauterine life.

The development of the interstitial tissue has also been studied in man. We shall record here the results of *Kasai* (1908), in whose paper the older literature on this question is to be found. Kasai examined testicles of different ages, the youngest being in the fourth month of intrauterine life, the oldest being 84 years of age. In accordance with other authors Kasai stated that in the testicle of a human embryo of four months (*Fig.* 54a) the interstitial cells are present in a relatively great quantity; they occupy the greater part of the testicle; the cellular masses are well vascularized. In the seventh and in the following months of intrauterine life the relative quantity of the interstitial tissue diminishes, whereas the space occupied by the seminiferous tubules increases. In the new-born individual one finds fewer interstitial cells than in the embryo. According to Kasai this does not change till the age of 14. In most cases examined by Kasai there was a remarkable increase of interstitial cells at the time of puberty. After puberty Kasai records a decrease of interstitial cells. They are, however, always present in the testicle of the adult man, but sometimes they are not very numerous. It seems that the decrease after puberty is a relative one only, caused by the enlargement of the seminiferous tubules and distribution of the interstitial cells in a large space. It must be mentioned, that the statements of the different authors do not agree with one another in regard to the quantity of interstitial cells in the testicle of the adult man. But there can be no doubt that the interstitial cells are always present in the normal testicle of the adult man. In old age the interstitial tissue increases relatively, as the space occupied by the seminiferous tubules undergoing degeneration is diminished. It may be that even the absolute quantity of the interstitial cells is increased in old age (*Goddard*, 1920; a man of 78).

The *condition* of the interstitial cells at different ages is of a still greater interest for us. In the foetus of four months they generally contained protoplasm which stained well; the nucleus was big and spherical. In the following months the size of the cells and of the nucleus was diminished and the protoplasm less well stained. At the time of puberty when, as mentioned, the number of interstitial cells is increased, they are of the same type as in the foetus. Later on a pigmentation of the interstitial cells takes place; this seems to begin at about 21, and increases with age. In old age the pigmentation is especially remarkable. The pigmentation is a brownish-yellow one. Kasai speaks of the pigmentation as due to atrophy because the pigment is absent in those cells which have just divided. But it must be said that the question as to whether the number of interstitial cells in the testicle increases by division, is not yet decided. It is probable, however, that, in general, increase of interstitial tissue implies transformation of *quiescent* cells, which are more or less like common connective tissue cells, into true interstitial cells. There has been much discussion as to whether mitosis occurs in interstitial cells. Although we observed numerous testicles of different mammals in our Institute, Wagner only twice found mitosis, both times under experimental conditions (*Fig.* 66). The transformation of the quiescent cell into a true interstitial one is characterised, as already said, by changes in the nucleus; the spherical nucleus of the embryonic interstitial cells becomes elliptic later, and at puberty the nucleus becomes again spherical and maintains this shape.

In considering all the changes the interstitial tissue undergoes throughout life from the foetal condition till old age, we see that there are evidently two summits or climaxes in the development of the interstitial cells: the first being in man at about the fourth foetal month, the second at the time of puberty. As we have seen above the same seems to be true for other mammals, and it may be that this is the general rule for all mammals, as Aron has pointed out. We shall see how this may be understood from a functional point of view. The histological side of the question, however, needs still further thorough investigation, especially in man.

Attempts have been made to prove that the interstitial cells can perform the endocrine function of the sexual gland in mammals, especially by experimental destruction of the generative part of the testicle. But in all these experiments the interstitial tissue in reality has not been isolated, as the cells of Sertoli and possibly also the generative cells at certain stages generally survive. Attempts based upon clinical observations also have been made to establish the theory that the interstitial cells have an endocrine function. We shall deal with these experiments in the following sections of this chapter, as well as with some of the clinical observations, leaving the others over for consideration in Chapters IX. and X. It may be pointed out here, however, that there are discrepancies between the views of the various authors in regard to the endocrine functions of the testicles, those who have studied the question experimentally usually holding the view that the endocrine function resides in the interstitial cells, while those who have based their position on pathological observations are disposed to regard the germinative cells as those which elaborate the hormone.

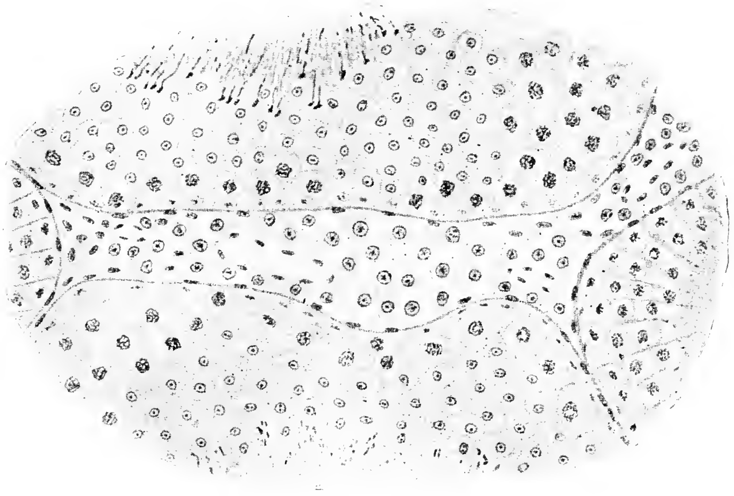


FIG. 60.—*Section through testicle of adult guinea pig.* x 400. Complete spermatogenesis; interstitial cells surrounding capillaries.—From Bouin and Ancel.

2. THE LIGATURE OF THE VAS DEFERENS.

We owe the first information concerning the function of the interstitial cells of the testicle to Bouin and Ancel, who ligatured the vasa deferentia in dogs, rabbits and guinea pigs. *Bouin and Ancel* (1903 a, 1904 f, g) recorded that spermatogenesis ceases some time after the ligature is made (*Figs.* 60, 61), whereas the cells of Sertoli and the interstitial cells survive. The interstitial tissue may even increase. As there are no signs of castration in the sexual characters in animals whose vasa deferentia have been ligatured, and in whose testicles the seminiferous tubules underwent degeneration, one must conclude that a normally developed generative tissue is not necessary for the performance of the endocrine function of the testicle. The experiments of Ancel and Bouin were repeated with other animals: by *Tandler and Gross* (1913) on roe-deer, by *Steinach* (1912) and *Myers* (1915) on rats, by *Sand* (1918) on rats, rabbits and guinea pigs, by *Berblinger* (1921) on guinea pigs, and by *Kuntz* (1921) on rabbits and dogs. These investigations have confirmed the statements of Ancel and Bouin.

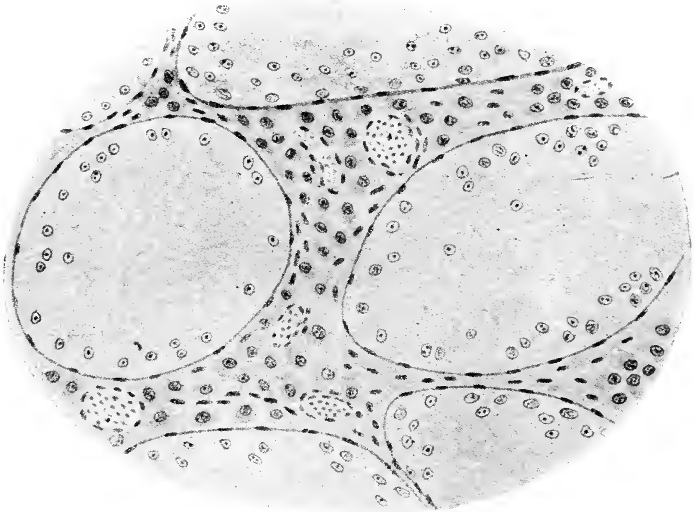


FIG. 61.—*Section through testicle of guinea pig 78 days after ligature of vas deferens.* x 400. No spermatogenesis; seemingly only cells of Sertoli present. Interstitial cells well developed.—From Ancel and Bouin.

The degeneration of the seminiferous tubules takes place a considerable time after the ligature is made, and it seems that several months later a regeneration of seminiferous tubules may occur. This was shown to be probable by *Steinach* (1920), and confirmed by *Tiedje* (1921) on guinea pigs, whereas there seems to be no regeneration in the rabbit. According to *Sand* (1918) spermatogenesis in young animals (guinea pigs and rats) is not completely stopped by ligature of the vasa deferentia. In guinea pigs, in which I sectioned the ductus epididymidis for other experimental purposes at a very early age, I even observed formation of spermatozoa. In mice, *Miss Kropman* (1923) and I found full spermatogenesis in the seminiferous tubules throughout both testicles seven weeks after sectioning the vasa deferentia. By puncturing the testicle *Posner* (1922) showed that as much as thirty years after occlusion of the spermatic duct in gonorrhoeal epididymitis spermatozoa may be present in the seminal tubules. It may, therefore, be objected that the action of the generative part of the testicle was not wholly excluded in the experiments of Bouin and Ancel. Tandler and Gross tried to overcome this objection by experiments on roedeer. The observation of the antlers of the roe is a good means of judging whether the sexual gland was performing the internally secretory function or not, because the antlers do not grow again in a castrated animal after being shed. In these experiments Tandler and Gross found that in a roebuck whose vasa deferentia had been ligatured and cut, and whose seminiferous tubules—as shown by microscopical examination—had degenerated, the antlers grew again a year after the operation. *Retterer* (1923) has, however, objected to Tandler and Gross that the state of spermatogenesis in their operated roebuck was like that in an animal just before puberty.

The following objections to the conclusions of Bouin and Ancel were recently made by *Tiedje* (1921). He ligatured the vasa deferentia in adult guinea pigs and recorded some weeks afterwards a decrease in sexual ardour; this decrease lasted for some time, but subsequently the ardour increased again. Tiedje explains these changes in the psycho-sexual behaviour as due to changes in the seminiferous tubules; degeneration of the generative tissue leads to a decrease, regeneration to a restitution of the sexual ardour. My opinion is that it is not possible to make statements about such rapid changes in the psycho-sexual ardour of laboratory animals. Even when castrated the animal shows for weeks and even months no changes in sexual behaviour. Only morphological changes can be taken into consideration as sure indications of the state of the endocrine function of the sexual glands. Although I saw about 40 animals on which I performed partial castration (see below) with section of the ductus epididymidis, I observed only once temporary morphological changes such as Tiedje's theory would suggest. The horny styles in the blind sac of the guinea pig degenerated and regenerated some months later. Unfortunately in this case we did not find the testicular fragment, and therefore we cannot say whether there was really a regeneration in the seminiferous tubules. Finally, *Ancel and Bouin* (1923) kept vasectomized rabbits for *four years after the operation*, the sex characters remaining normal.

Although there is no proof that the seminiferous tubules are involved in the internal secretion of the testicle, one must, indeed, recognise, that this question is not decided negatively by the experiments of Bouin and Ancel in a definite manner. Even when regeneration of the tubules does not take place, cells of Sertoli, and possibly also spermatogonia, are present in the tubules. As regards spermatozoa and cells in late stages of spermatogenesis, we shall see below that there can be no doubt that they are not directly involved in the endocrine function of the testicle. As regards cells of Sertoli and spermatogonia, *Bouin and Ancel* (1903 b, 1904 c) tried to show by the following experiments that they have nothing to do with the internal secretion of the testicle. They performed a unilateral castration on rabbits and ligatured on the other side the vas deferens so as to evoke a compensatory hypertrophy of those elements which perform the internal secretory function. The result was that only the interstitial cells proliferated, whereas the cells of Sertoli remained unaltered. The interstitial cells in these cases, according to Bouin and Ancel, show signs of great secretory activity. They are obviously situated around the blood vessels in thick layers. *Sand* (1918) has repeated this experiment of Bouin and Ancel on rabbits, rats and guinea pigs. He also claims to have shown that unilateral castration was followed by an enormous hypertrophy of the cells of Leydig in the remaining testicle, the vas deferens of which was ligatured, whereas the spermatozoa disappeared and the cells of Sertoli became partly degenerate. But a considerable hypertrophy of the interstitial tissue occurred only in two out of six experiments of *Sand* (1921 b). The sexual characters were normally developed.

In section 6 of this chapter we shall return to the question of compensatory hypertrophy of the interstitial cells, and shall show that it is very improbable that they undergo a compensatory hypertrophy for endocrine purposes. The same is true also for the generative part of the testicle.

Whereas it seems impossible by means of ligature of the vasa deferentia to exclude the possibility that some parts of the tubules are involved in the internal secretion of the testicle, other experiments of *Bouin and Ancel* (1904 d) of the same kind showed beyond doubt that the cells of Sertoli and spermatogonia *in the absence of fully developed interstitial cells* are unable to perform the internal secretory function. They ligatured the vasa deferentia in rabbits seven to eight weeks old. Some of these animals developed as "castrates," as was shown by their penis. On examining the testicles of such animals Bouin and Ancel found that the generative part remained in an infantile condition; this means that the tubules were in a state like that in adult animals with ligatured vasa deferentia after degeneration has taken place. Further, Bouin and Ancel found in these cases that the interstitial cells were infantile. We were able to confirm this observation of Bouin and Ancel in experiments with partial castration of young rabbits in which only a fragment of a testicle was left in the body (1921 f, 1922 e, i) (*Figs.* 62 *to* 64). An animal operated on at an age of one month had, when about eight months old, the infantile penis of a "castrate"; the tubules in the testicular fragment were infantile, but their diameter was enlarged, and they were full of cells of Sertoli and spermatogonia; the interstitial tissue was in an infantile stage (*Figs.* 65, 66). Ancel and Bouin consider observations of this kind as evidence for their theory that only the interstitial cells are involved in the internal secretion of the testicle. It would be safer to conclude merely from the experiments here recorded, that they are sufficient to show that the interstitial cells are necessary for the internal secretion of the testicle (1922 h, i). The same result was obtained by *Lipschütz and Wagner* (1922 g and h; *Wagner,* 1922) and by *Wagner and Loeper* (1923) with two rabbits which had a normal testicular weight with normally

FIG. 62.—*Testicle of adult guinea pig* (Prot. Nr. 77; 450 gr.). Nat. size. The small caput epididym. covered by the fatty body which covers also the ductus epidid. The cauda epidid. is attached to the gubernaculum. To be compared with Figs. 63 and 64.

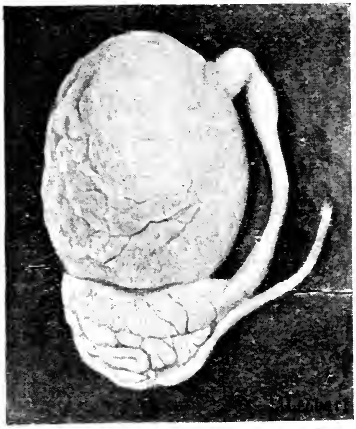


FIG. 63.—*Testicle of adult guinea pig, about* 18 *months old.* The animal died of tuberculosis and was very thin. The fatty body disappeared, and the relations between testicle and epididymis become apparent. To be compared with Fig. 64.

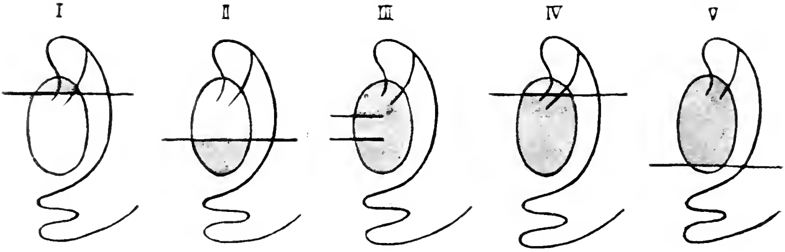


FIG. 64.—*Diagram of different operations performed in the Physiological Institute on the testicle of mammal.* Black: part of the testicle left in the body; white: part removed. I., upper partial castration (one testicle removed, from the other an upper fragment left); II., under partial castration; III., horizontal incisions not touching the epididymis; IV., horizontal incision, by which an upper fragment is formed without the total testicular mass being reduced; V., horizontal incision near the under pole of the testicle by which almost the whole testicle is transformed into an upper fragment.

developed seminiferous tubules full of spermatozoa, but with underdeveloped interstitial cells. These animals had the penis of a "castrate" (*Figs.* 67 *to* 72).

Lacassagne (1913, p. 213) tried to support the view that the endocrine function of the testicle is performed by the interstitial cells, by the observation that the sexual ardour of the rabbit becomes intensified after ligature of the vasa deferentia. One might suppose that this was due to the proliferation of the interstitial cells. Also *Sand* (1918, p. 104) and *Kuntz* (1921) remark that the sexual impulse is of a particular intensity when there is a striking hypertrophy of the interstitial cells. Further, *Ancel and Bouin* (1904 b) have found a proportional relation between the quantity of the interstitial cells in the retained testicles and the degree of the development of the copulatory apparatus in pigs in such a condition. Similar observations have been recorded by Steinach and Sand in experiments on rats with engrafted testicles (see Section 4). We shall see that all these quantitative observations are insufficient for proving the internal secretory function of the interstitial cells. First, an increase of interstitial tissue after ligature may be sometimes only apparent, as was pointed out by *Myers* (1915), who ligatured the vas deferens in white rats; the same may be often true also for other experiments where an operative interference with the testicle itself took place. Further, a normal development of the sexual characters may be observed when an extremely small number of interstitial cells is present, as we showed in our own experiments. These two objections will be discussed later. Thirdly, it seems to me impossible, as already mentioned above, to make any certain statements as to the intensity of the sexual ardour of small laboratory animals.

The question as to why ligature of the vas deferens leads to a degeneration of the seminiferous tubules is by no means decided. One might suppose that degeneration is caused by an interference with the blood supply of the testicle. This seems very improbable, since in the rabbit and in the guinea pig the ligature of the vas deferens can be made without any difficulty and without interfering with the arteria spermatica interna. An interference with the innervation of the testicle is more probable. It is known (*Brack*, 1921) that in cases of aplasia of the vas deferens and of the cauda epididymidis in man there may be full spermatogenesis. On the other hand, some workers have

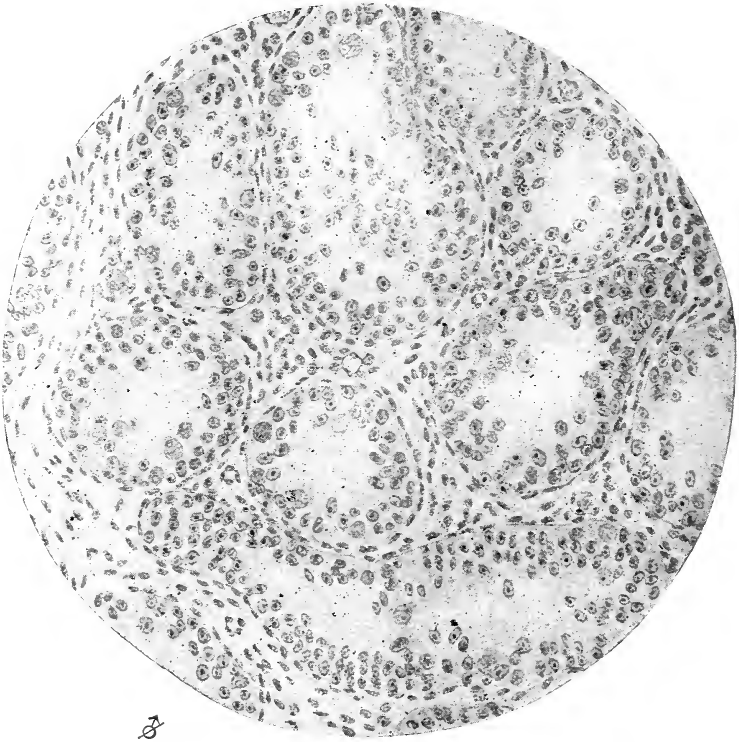


FIG. 65.—*Section through testicle of rabbit 8 months old, with eunuchoid penis* (Prot. Nr. 4; under partial castration—compare Fig. 64—at age of 2 months). Seminal tubules further developed than in an animal of 2 months. Great quantity of cells of Sertoli and spermatogonia. Desquamation. Infantile interstitial tissue; small interstitial cells with small nuclei; cells with spindle-shaped nuclei prevail.—Prepar. and design of Wagner.

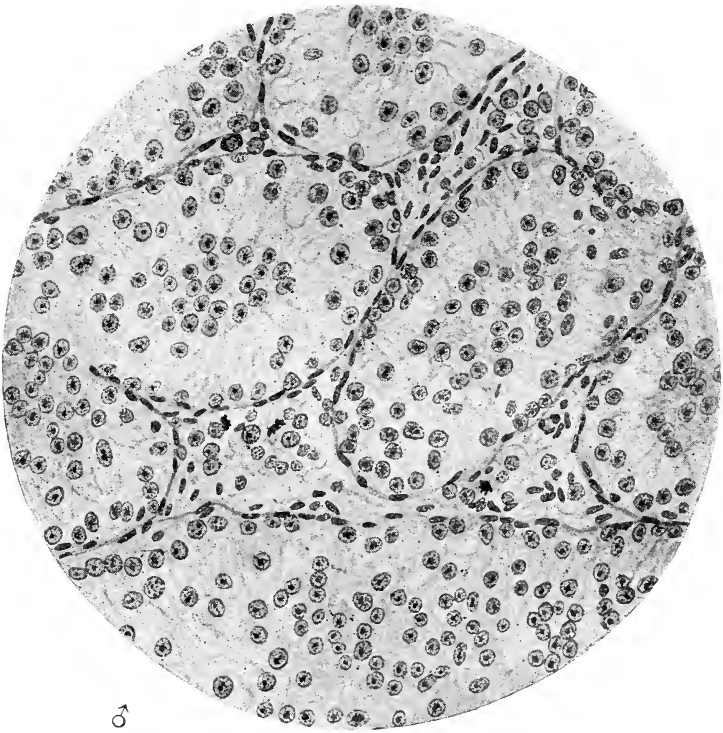


Fig. 66. *Section through testicle of rabbit about 8 months old, with normal sex characters* (Prot. Nr. 49; horizontal incisions on the testicle performed at an age of 2 months). Same magnification as Fig. 65. Puberal transformation of penis took place only at an age of 7 months (normally at 4 months). Only beginning of spermatogenesis; great quantity of cells of Sertoli in the tubules, possibly also spermatogonia, but no spermatocytes. Pronounced desquamation. Big interstitial cells with big spherical nuclei; several mitoses. To be compared with Fig. 65.—Prepar. and design of Wagner.

Fig. 67.—*Section through testicle of rabbit 6½ months old, with eunuchoid penis* (Prot. Nr. 95, unilaterally castrated at age of 6 weeks; of *same litter as Fig.* 68.) Complete spermatogenesis; spermatozoa present in the epididymis. Interstitial cells with little protoplasm; nucleus smaller than in Fig. 68; cells with spindle-shaped nuclei prevail.—Prepar. and design of Wagner.

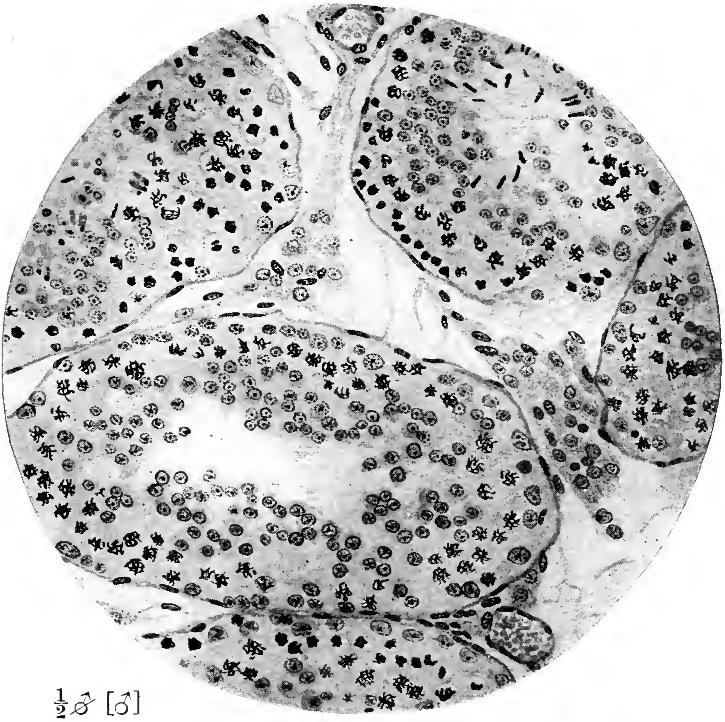


FIG. 68.—*Section through testicle of rabbit 6½ months old, with normal sex characters* (Prot. Nr. 94; unilaterally castrated at age of 6 weeks). Complete spermatogenesis; spermatozoa present in epididymis. Well developed interstitial cells (big spherical nucleus, big area of propotoplasm).—Prepar. and design of Wagner.

Fig. 69.—*Interstitial cells of rabbits with normal and eunuchoid penis* (Prot. Nr. 94 and 95). Stained with Heidenhain. Compare with Figs. 67 and 68.—Prepar. design of Wagner.

A. Triangular groups with about equal quantity of interstitial cells.
B. Quadrangular groups with about equal quantity of interstitial cells.
C. Two interstitial cells. Greater magnification.

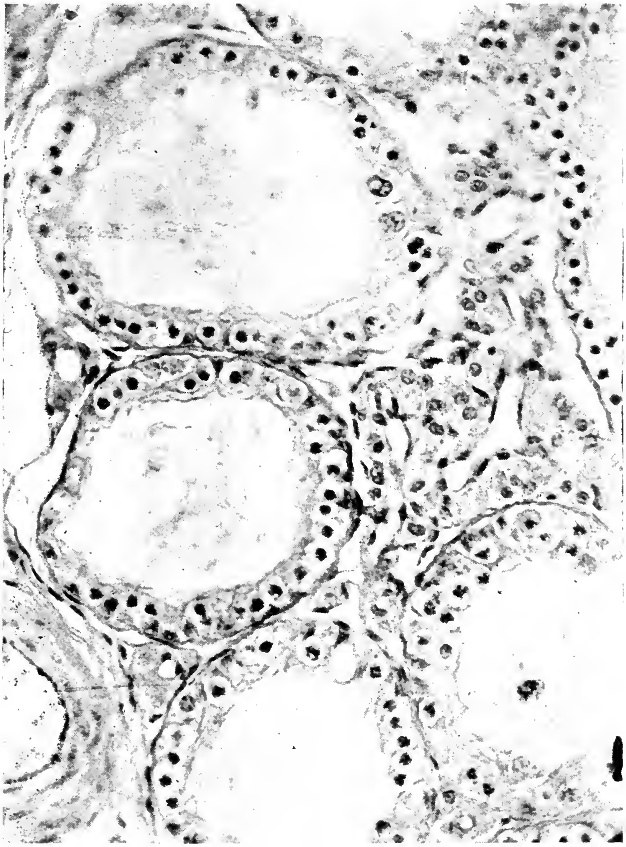


FIG. 70.—*Section through testicle of rabbit 6 months old, with normal penis.* Same litter as Figs. 71 and 72. Seminal tubules with one stratum only. Well developed interstitial cells.—Photo of Kull; from Wagner and Loeper.

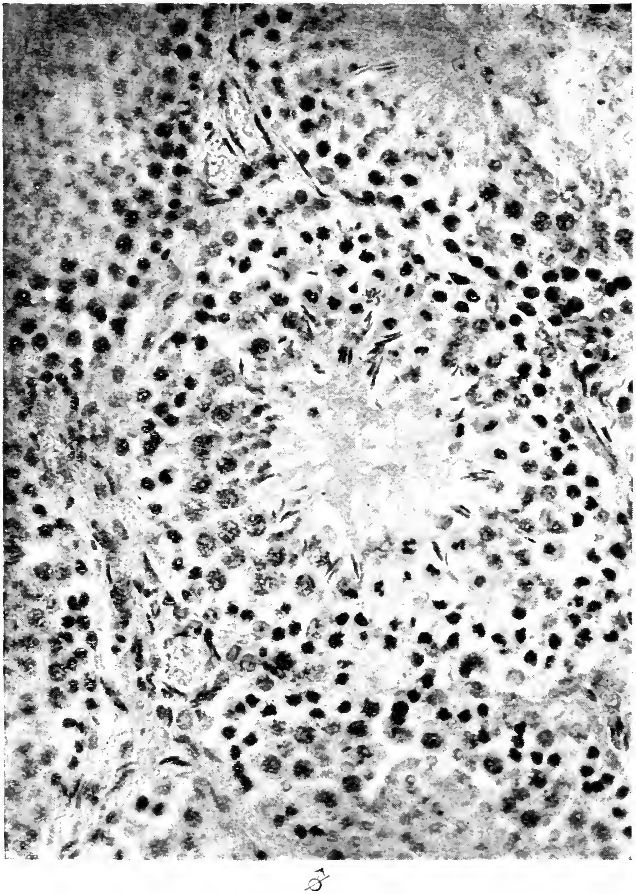


FIG. 71.—*Section through testicle of rabbit* 6 *months old with eunuchoid penis.* Complete spermatogenesis. Few small interstitial cells; connective tissue prevails. To be compared with Fig. 70. Photo of Kull.—From Wagner and Loeper.

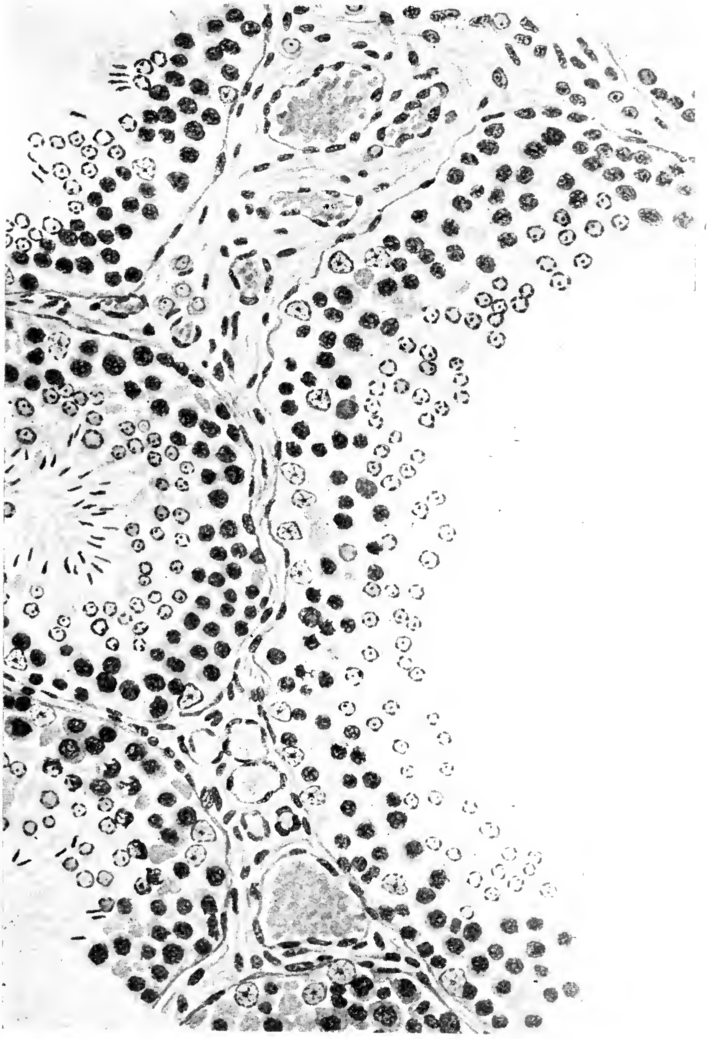


FIG. 72.—*Section through testicle of rabbit 6 months old with eunuchoid penis.* Complete spermatogenesis. Few small interstitial cells; connective tissue prevails. To be compared with Fig. 70. Design of Wagner.—From Wagner and Loeper.

caused degeneration of the tubules by operative interference with the nervous system; *Ceni* (1914) observed degeneration of the tubules after an experimentally produced cerebral commotion; *Houssay and Hug* (1923) found that a lesion of the infundibulum and of the hypothalamic region in the dog does not interfere with the development of the testicle and of the sex characters; there was only one out of a great number of operated animals which exhibited testicular atrophy; *Takahashi* (1922) claims to have caused testicular atrophy by extirpating the lumbosacral part of the sympathetic nerve in guinea pigs. But it may be mentioned that the testicle of the guinea pig is very sensitive to all abdominal operations. I am not aware whether the experiments of Takahashi, which gave contradictory results, justify the conclusion that the sympathetic nerve has some kind of trophic influence on the testicle. In cats I removed the fifth and sixth lumbar ganglia on one side without any disturbance of spermatogenesis being caused by the operation.

The papers of *Bolognesi* (1921 a, 1921 b) also may be referred to here.

3. The Retained Testicle.

It has long been known that with men having both testicles retained in the abdominal cavity a condition of sterility may be present whereas the somatic sexual characters and the sexual libido are normal. Similar observations have been made on animals, especially on the horse. A stallion with a unilaterally retained testicle preserves the behaviour of a stallion when only the normal testicle is removed, becoming a gelding when the retained testicle also is extirpated. Numerous investigations have shown that the seminiferous tubules in the retained testicle of men and animals are often in a state of degeneration. The retained testicle consists in some cases only of interstitials cells and cells of Sertoli, whereas in other cases generative cells in different stages may be observed (*Michon and Porte*, 1920). Sometimes a condition of eunuchoidism exists when both testicles are retained. In these cases there is a complete sclerotization of the testicles, in which the interstitial cells are absent. Retention of testicle has been produced also experimentally in rats, guinea pigs and dogs by different workers; all record the atrophic state of the testicle or of the tubules (quoted from *Sand,* 1921 c). Some investigators especially Kyrle, mention also an hypertrophy of the interstitial cells. Very detailed investigations on this question have been made by *Sand* (1918, p. 109; 1921 c), who caused in rabbits, guinea pigs and rats retention of both testicles by loosening the testicle from the gubernaculum and closing the processus vaginalis. He observed a degeneration of the seminiferous tubules and an hypertrophy of the interstitial cells; there were no signs of castration.

Crew (1922), suggested that the degenerative changes occurring in the undescended testicle are due to the difference of temperature in the scrotum and the abdominal cavity. The testis is adapted to the lower temperature of the scrotal sac; the temperature of the abdominal cavity (the difference is of several degrees) is not that at which the final stages of spermatogenesis normally develop.

The observations made on men and animals with retained testicles show with complete certainty that full development of sexual characters is possible without spermatogenesis proceeding to production of spermatozoa.

Ancel and Bouin (1904 b) further record an observation made on a pig killed at an age of six months with normally developed sexual characters, in which animal in the retained testicles even the cells of Sertoli were absent. So one may suppose that the internal secretion of the retained testicle is produced only by the interstitial cells. This was already suggested in 1901 by *Regaud and Policard* (1901). Detailed investigations on this question were made by Bouin and Ancel on pigs, in which retention of testicles is very frequent. The degree of development of the genital organs in pigs with retained testicles is very variable. According to *Ancel and Bouin* (1904 g) the interstitial tissue in the retained testicle of the pig is the better developed the greater the weight of the testicle, and there is, as already mentioned, a proportional relation between the quantity of the interstitial cells and the degree of development of the genital apparatus. It is clear that such a quantitative statement is of the greatest importance in relation to the question of the endocrine function of the interstitial cells, and it was these most important observations of Bouin and Ancel which first led me to plan out quantitative investigations on the internal secretion of the testicle. As a result of our

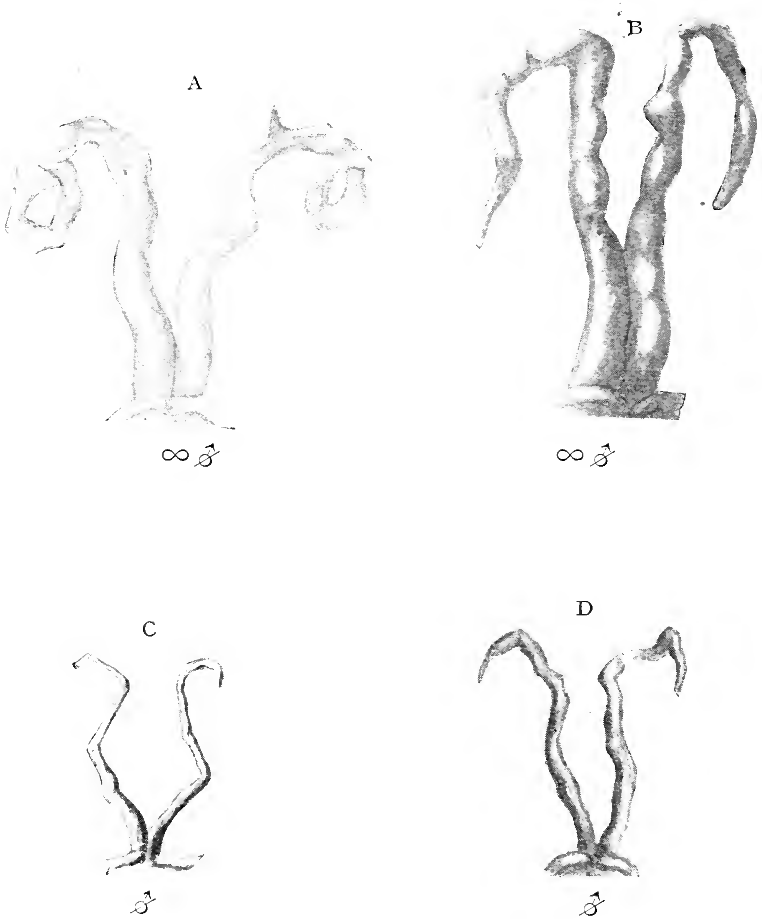


FIG. 73.

A. *Seminal vesicles of guinea pig with testicular fragment of about* 60 *cmm.* (instead of normal testicular weight of about 2·0–2·5 gr). Nat. size. Prot. Nr. 34. Operation at age of about 2–3 weeks; drawn 11 months later. Highly developed seminal vesicles; to be compared with C.

B. *Seminal vesicles of guinea pig, with testicular fragment of about* 35 *cmm.* (instead of about 2·0–2·5 gr.). Nat. size. Prot. Nr. 35. Operation at age of 4½ months; drawn 7 months later. Highly developed seminal vesicles; to be compared with D.

C. *Seminal vesicles of guinea pig,* 21 *months old, castrated at the age of* 2 *weeks* (Prot. Nr. 23). Nat. size.

D. *Seminal vesicles of guinea pig castrated at the age of* 4½ *months* (Prot. Nr. 27). Drawn 11 months later. Nat. size.

experiments, we met with the following objections to the conclusions of Bouin and Ancel. In experiments (*Lipschütz and coworkers,* 1922–23) where only very small testicular fragments were left in the body (young guinea pigs), and where sometimes a very small quantity of interstitial cells was present, an almost or quite normal development of the sexual characters occurred (*Fig.* 73). In some cases where we left small testicular fragments, we observed a retardation in the development of the sexual characters. First, I supposed (1920, 1921 c) that this retardation was due to the quantity of the hormone being diminished, and that the velocity of the reaction of the somatic substratum was diminished somewhat after the manner of enzyme reactions. But as we have already seen, an underdevelopment of the testicular fragment occurs sometimes (*Fig.* 65), and the underdevelopment of the sexual characters, or the eunuchoidism, can be explained as due to the underdevelopment of the testicle (1921 f). In another case (*Lipschütz, Wagner and Bormann,* 1922 e) we found that a retardation in the development of the testicle can really be determined experimentally. I made horizontal incisions of the testicles (*Fig.* 64, III.) of a young rabbit, the penis of which remained infantile till about the seventh month, when a rapid puberal development began. The microscopical observation showed that spermatogenesis was stopped by desquamation occurring, whereas the interstitial cells were well developed (*Fig.* 66). In view of these observations I am inclined to explain the quantitative statements of Bouin and Ancel on pigs with retained testicles in a different way from them. I think that the differences they observed in the sexual characters were caused by a different degree of retardation in the development of the retained testicle in individual cases. (See also Section 4 of this chapter.)

Bouin and Ancel (1904 d) made also quantitative experiments on pigs with retained testicles. On pigs with one retained testicle they removed the normal testicle at an age of six weeks. They stated that in the retained testicle a marked hypertrophy of the interstitial cells took place, whereas the number of cells of Sertoli remained unaltered (*Figs.* 74, 75). The weight of such a retained testicle was about twice as great as that of a retained testicle in the presence of a second normal testicle. These statements of Ancel and Bouin were confirmed by *Sand* (1918, pp. 117, 118, 212). Sand caused retention of the testicle in rabbits and guinea pigs on one side, and removed the other testicle. In these experiments the retained testicle weighed two and a half times as much as a retained testicle in the presence of a second normal testicle. Like Bouin and Ancel, Sand found the interstitial tissue in a state of hypertrophy, whereas the cells of Sertoli in the degenerated tubules were not increased in number. But these statements of Bouin and Ancel, and of Sand are, in view of our own experiments, insufficient to prove that a compensatory hypertrophy of interstitial cells for endocrine purposes occurs (see below).

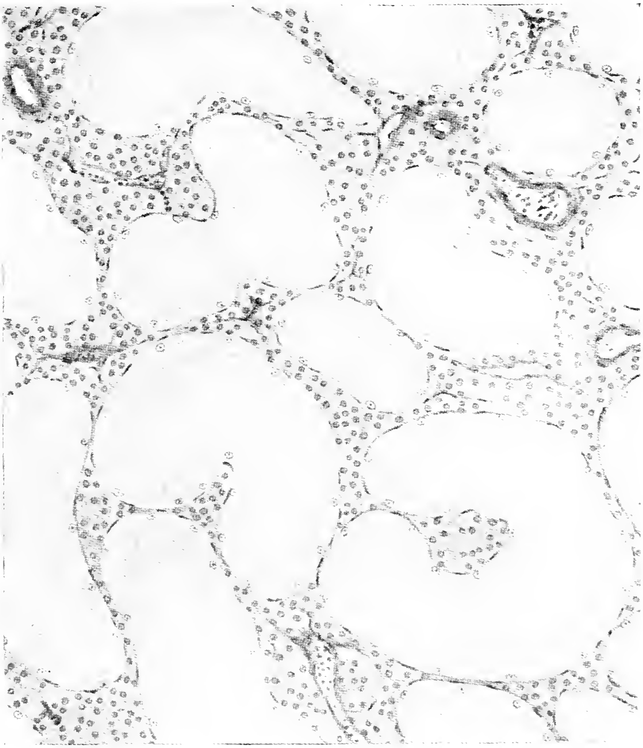


FIG. 74.—*Retained testicle of pig* (bilateral cryptorchism). x 200. No spermatogenesis; seemingly only cells of Sertoli present. Normal quantity of interstitial cells. —From Ancel and Bouin.

All the observations made on man and animals with retained testicles and recorded here supply evidence that the spermatozoa or other cells in late stages of spermatogenesis are not necessarily involved in the internal secretion of the testicle. But they do not afford conclusive evidence for the suggestion that the interstitial cells only represent the endocrine apparatus in the testicle. The observations of Bouin and Ancel alone, where the sexual characters were normally developed, although there was a complete disappearance of cellular elements of the tubules, can be regarded as a proof of the theory that the interstitial cells are the only testicular internal secretory organs. But here, also, we are confronted by an objection. It takes some time for the effects of castration to become visible after the disappearance of the endocrine testicular elements. It is

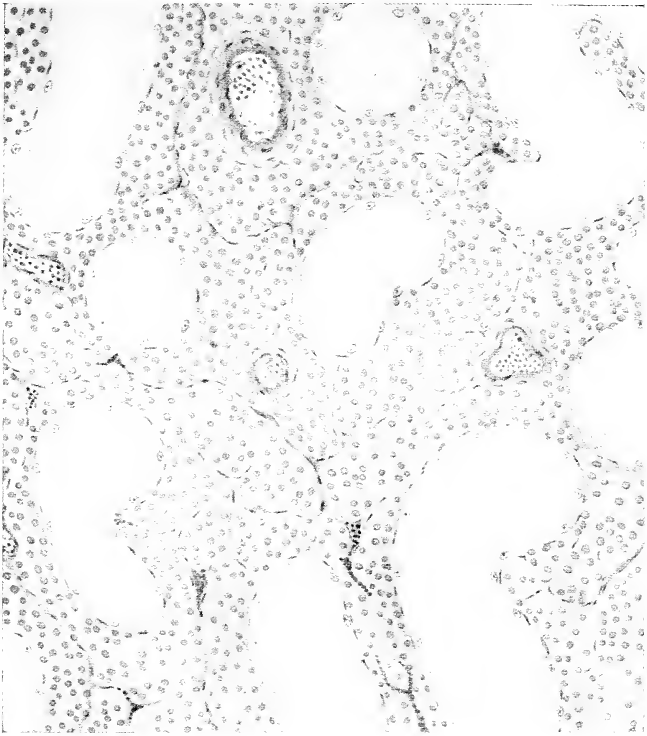


FIG. 75.—*Retained testicle of pig with unilateral cryptorchism; the normal testicle has been removed.* x 200. Increased number of interstitial cells; no change of number of cells of Sertoli.—From Bouin and Ancel.

not impossible, therefore, that in the animals mentioned testicular secretory products were no longer present, though the effects of castration were not yet visible.

The knowledge of the fact that the absence of the higher stages of spermatogenesis or of spermatozoa in the retained testicle does not hinder the normal endocrine function of this organ, has found practical application in human pathology. We learned in Chapter III. that the results of castration can be counteracted by the implantation of a retained testicle. In a case reported by Lichtenstern, the microscopical examination of a particle of the engrafted testicle showed that the seminiferous tubules were atrophic, and that no spermatozoa were present. *Thorek* (1923) succeeded in restoring potency in an ape previously castrated a year ago by engrafting a human cryptorchic testicle.

4. The Engrafted Testicle.

We referred above (p. 82) to the experiments of Steinach on rats where testicles were transplanted; in many cases the transplantation was successful, and the animals reached full maturity. But the histological examination (*Steinach*, 1916) of the engrafted testicle showed that the generative part was not normally developed. If there are originally fully developed seminiferous tubules, or if these develop, they degenerate afterwards. This is shown by the histological examination of grafts at different intervals after transplantation. The greater the interval after transplantation the greater the atrophy of the generative part. The diameter of the atrophying seminiferous tubules decreases. According to Steinach the cells of Sertoli are finally the only part of the cellular elements of the seminiferous tubules which persists (*Fig.* 76). It may be, as *Benda* (1921) has pointed out, that the cells forming the wall of the degenerate tubules are really not cells of Sertoli, but primitive cells of a generative character, which can enter into a new phase of spermatogenesis. I sometimes found degenerate tubules in a condition identical with that of young tubules. This is why I suggested that degeneration of seminiferous tubules implies really something which might be characterised as "*backward development*" (1921 d, 1922 c), to use an expression of the Russian zoologist, *Eugen Schultz* (1908) The changes observable in a degenerating tubule are, indeed,

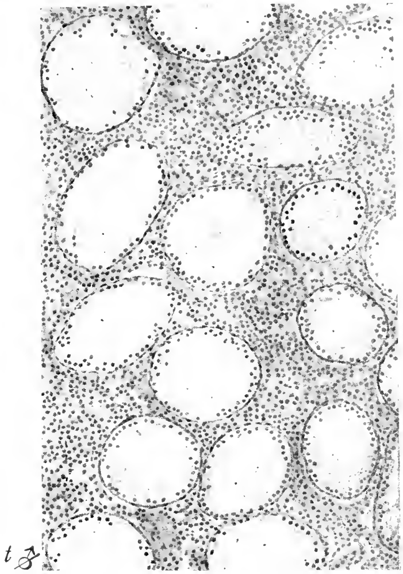


FIG. 76.—*Section through testicle which 8 months previously had been subjected to autotransplantation (rat).* x 100. From the same litter as Fig. 77. No spermatogenesis. Hypertrophy of interstitial tissue.—From Steinach.

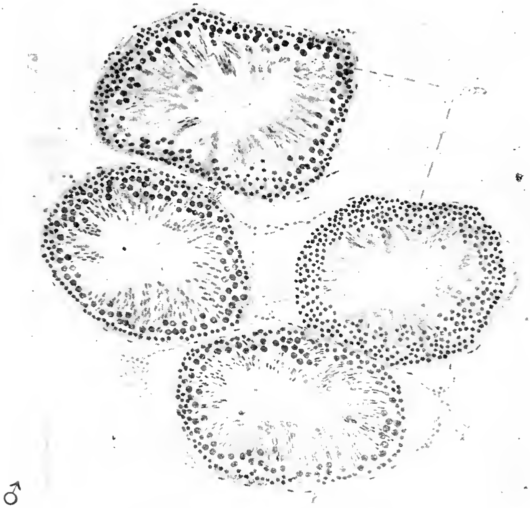


FIG. 77.—*Section through normal testicle of a rat about 9 months old.* x 100. Complete spermatogenesis; small quantity of interstitial cells.—From Steinach.

very different in each case. But the differences seen are possibly caused by other factors interfering with the backward development (1921 c).

Wholly different from the behaviour of the tubules is that of the interstitial tissue. In the normal testicle of the mouse or the rat (*Fig.* 77) we find between the seminiferous tubules a fine net of connective tissue, and between the fibres of the latter here and there single cells of Leydig or little nests of these cells. In the transplanted testicle the number of the cells of Leydig is enormously increased (*Figs.* 76 *and* 77). The cells of Leydig now form a compact mass of thick cords situated between the degenerate seminiferous tubules. The network of connective tissue fibres between the proliferated interstitial cells is very insignificant. It seems that the number of the interstitial cells in the transplanted testicle is several times greater than in the normal one. It was objected that there is no real increase of interstitial tissue between degenerating tubules, the increase being only an apparent one. This may be true in some cases. But various observations certainly show that this objection is not always justified. From our own experiments I realised that it is not difficult to determine whether the hypertrophy of the interstitial tissue is real or only apparent. And in our experiments with partial castration there was often an enormous hypertrophy of the interstitial cells in small fragments of the upper pole of the testicle (*Figs.* 78 *and* 79). It would be out of place to discuss this question more fully here. My paper (1923) may be referred to.

As the animals with an engrafted testicle reached full maturity, although the seminiferous part of the graft ceased to develop further, or else degenerated, we must conclude that the internal secretion of the sexual gland does not depend on the accomplishment of spermatogenesis or upon the presence of spermatozoa. Full sexual maturity is possible without any spermatoza in the graft. According to Steinach, the graft does not remain always in the same condition. A few months after the transplantation the cells of Sertoli also undergo a degeneration, and according to Sand this may occur very early. The seminiferous tubules lose their structure and disappear; the testicle now consists almost entirely of interstitial cells representing, according to Steinach, an "isolated puberty gland." I made a similar observation in our experiments with partial castration. But after a short time further changes take place in the graft. There is an increase of connective tissue. Although the interstitial cells surrounded by connective tissue persist for months, they, nevertheless, finally undergo degeneration.

FIG. 78.—*Section through testicle of normal adult guinea pig* (Prot. Nr. 228, 600 gr.). x 70. Full spermatogenesis. Normal quantity of interstitial cells; the latter often surrounded by granulated mass (especially at the *). To be compared with Fig. 79.—Prepar. of Wagner; design of Lehbert.

FIG. 79.—*Upper testicular fragment of a partial "castrate"* (guinea pig. Prot. Nr. 30). x 70. Operation at age of 10 days; fragment removed at age of 4½ months. Fragment represents about 1 per cent. of total normal testicular mass. Seminal tubules with one stratum only; diameter of some tubules remains normal. Number of interstitial cells in general increased; besides this, very pronounced local increase. Sex characters normal.—Prepar. of Wagner; design of Lehbert.

We have already mentioned that the number of interstitial cells in the graft can be sometimes greatly increased. Steinach argues that if the interstitial cells are the endocrine apparatus of the testicle, one might expect that where there is an increased number of interstitial cells there would also be signs of an increased action on the part of the puberty gland. As we have already seen above, Ancel and Bouin have argued in the same manner, when dealing with the proportion between the number of the interstitial cells in the retained testicle and the development of the sexual characters. Observations of Steinach seemed to corroborate this. He records that several rats, in which both transplanted testicles had "taken," showed an abnormally great sexual activity. In other cases where the engrafted testicle was diminished in size the sexual characters were midway between those of a castrated and those of a normal animal; the genital organs had continued their development to a certain degree, but there was no sexual activity. Thus, according to Steinach, the experiments with transplanted testicles corroborate the view that the degree of development of the sexual characters depends upon the degree of development attained by the interstitial tissue. A series of experiments with transplantation performed by *Sand* (1918, pp. 74–95) on rats seemed to give further evidence for a proportionality existing between the number of interstitial cells and the degree of development of the sexual characters. When in the transplanted testicle only a few interstitial cells were present, the animals developed into "castrates"; the spermatogonia and cells of Sertoli, which were present in great quantities, were unable to prevent eunuchoidism. When more interstitial cells were present, the animals showed almost normal genital organs, although in the tubules only cells of Sertoli were to be found. When the interstitial tissue was well developed or hypertrophied, the sexual characters were normal, or even in some respects hypertrophied.

Steinach concluded from his experiments on rats that in the higher animals the individual differences in the development of the somatic sexual characters and in the sexual activity are caused by differences in the quantity of interstitial cells. This suggestion cannot, I think, be accepted without reserve.

Kyrle (1911), amongst others, has pointed out that the increase in the interstitial cells is of the nature of a local reaction to the tubules degenerating.

5. THE INFLUENCE OF X-RAYS ON THE TESTICLE.

Since X-rays have been used in medicine it is known that sterility can be caused by them without any visible changes in the somatic and psychical sexual characters. A number of authors have experimented on this question with animals also and there is general agreement among them that X-rays can cause sterility without interfering with sexual activity (*Albers-Schönberg*, 1903). Later it was shown by *Bergonié and Tribondeau* (1904, 1905) that X-rays cause a degeneration of the seminiferous tubules, whereas the interstitial cells and the cells of Sertoli are not altered. Even a single irradiation could produce this effect provided the irradiation was strong and long enough. The authors also called attention to the fact that simultaneously with the atrophy of the tubules there is a proliferation of the interstitial cells, their number being sometimes two or three times greater than normally. Also a proliferation of the cells of Sertoli was reported. *Villemin* (1906 a) confirmed the statements of Bergonié and Tribondeau. An investigation upon this question was made also by *Tandler* (1913) on the roedeer. Several months after irradiation the seminiferous tubules were in a state of degeneration, whereas the interstitial cells were normal. The roedeer treated with X-rays cast and regrew their antlers like normal animals.

Objections may be made to the assumption that in these experiments a complete suppression of the activity of the seminiferous tubules had taken place. *Bergonié and Tribondeau* (1904) and *Villemin* (1906 b) found that a regeneration of the degenerated tubules can occur if the irradiation was not too strong. Villemin showed that this result takes place only when besides the cells of Sertoli the spermatogonia also are resistant to X-rays. The question of regeneration was studied further by *Simmonds* (1909), who records that some tubules may persist unaltered even after radiation of long duration; in regenerated tubules he found spermatozoa. Simultaneously with the regeneration of the tubules the interstitial tissue decreases. This latter observation might be taken as further evidence that the increase of interstitial tissue after degeneration of tubules is often only apparent, the extension of this tissue being only greater in comparison with the diminished extension of the seminiferous part of the testicle. As was shown by Simmonds, mesothorium acts like X-rays.

In view of these phenomena of regeneration, Simmonds concluded that the internal secretion is produced by the spermatozoa, and that the interstitial cells take up this function only when the seminiferous tubules of the testicle are partially destroyed. I do not deny that these experiments with X-rays are insufficient for demonstrating that the occurrence of different stages of developing spermatic cells is not correlated with the production of the internal secretion of the testicle; irradiation seems to be a very uncertain means of destroying the seminiferous tubules, depending greatly upon strength and duration. We have no guarantee that in all the experiments with X-rays recorded hitherto a more or less extended regeneration has been avoided. But in 1916 a Russian author, *Nemenov*, published a paper which has not yet been taken into consideration in the criticism directed by different authors against the theory of the "interstitial" or "puberty" gland. Nemenov irradiated dogs *repeatedly* and examined the testicles and the prostate a long time after the last irradiation. Nemenov stated that even more than eight months after the last irradiation only cells of Sertoli were present in the seminiferous tubules. Nevertheless, the prostate was very well developed, many mitoses were present and the tubules of the prostate were full of secretion. The paper of Nemenov is of great importance in its bearing upon the question, and taken in conjunction with the experiments with ligation and transplantation recorded above, together with our experiments with partial castration, the observations of Nemenov supply further evidence that seminal cells are not directly involved in the internal secretion of the testicle. Further, *Ancel and Bouin* (1923) irradiated young guinea pigs and kept them till *nine months after irradiation*. Though the seminal tubules were in an infantile stage and generative cells were totally absent, the sex characters were normal; the fluid of the seminal vesicles coagulated as in a normal animal. The objection may, however, be made that spermatogonia were still present in the tubules, or that the cells of Sertoli represent some kind of primitive generative cells. But if it is so, it nevertheless remains true that these generative cells alone would be unable to produce the internal secretion of the testicle; we have seen in a preceding section that in the experiments where cells of Sertoli and spermatogonia were present in the tubules eunuchoidism occurred when interstitial cells were underdeveloped. In view of these considerations the criticism directed against the evidence provided by the X-ray experiments in support of the theory of the interstitial cells is deprived of its importance.

Thorek (1923) has made testicular homoiotransplantation in apes (*Cynocephalus* and *Macacus*) one to two years after castration; immediately following this implantation, the animals were subjected to the action of X-rays. Removal of specimens proved that generative tissue was absent. Nevertheless, out of five animals four revealed a return of sexual potency.

6. The Relation between the Quantity of Interstitial Tissue and the Hormonic Effect.

(*a*) *Is there a compensatory hypertrophy in the testicle?*

We have seen that the number of interstitial cells may be greatly increased under certain conditions. It may be, as already pointed out, that in some cases with retained testicles, ligature or irradiation, this increase is only an apparent one. But no doubt in certain of Steinach's transplantation experiments, and in many of our own with partial castration, the hypertrophy of the interstitial tissue was very great (*Figs.* 78 *to* 81).

We do not know the real cause of this hypertrophy. It seems that it always occurs when a degeneration or a retrograde development of the tubules takes place. My observations agree with *Kyrle's* (1911) in regard to the hypertrophy of the interstitial cells which often occurs in the same testicle or testicular fragment in the neighbourhood of the degenerated tubules only, and not in that of the normal ones. This is an indication that the cause of this hypertrophy is often local rather than general. Further, I observed an enormous hypertrophy of the interstitial cells in a small testicular fragment (*Fig.* 82) in a guinea pig, notwithstanding that the second testicle was present (1922 c, f). There was an hypertrophy of interstitial cells also in those experiments in which both testicles were transformed into upper fragments without reducing the total testicular mass (*Fig.* 83). From these observations one must conclude that the hypertrophy of the interstitial cells occurring in small testicular fragments is not a compensatory one, i.e., that this hypertrophy has nothing to do with the function of the testicle in relation to the organism as a whole. In a number of cases with partial castration we observed full development of sexual characters without any increase of interstitial cells, or only an insignificant one having taken place in the small testicular fragment (*Fig.* 84).

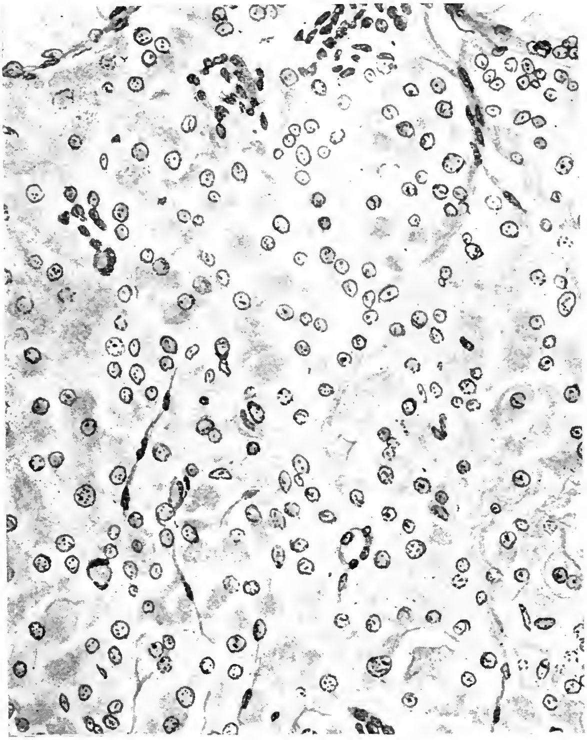


FIG. 80.—Same age as Fig. 79. High magnification. x 300. At the top the walls of two tubules visible. To be compared with Fig. 81.—Prepar. of Wagner; design of Lehbert.

Further, we found in numerous experiments that the behaviour of a testicular fragment is different according to the pole of the testicle to which it belongs (see *Fig.* 64, I. or II.)

(*Lipschütz, Ottow and Wagner*, 1921 d, e). In an upper pole we often found a great hypertrophy of the interstitial cells, whereas in the under pole hypertrophy was rather the exception. The blood is supplied to an upper fragment by the arteria spermatica interna, to an under fragment by the arteria deferentialis; the blood supply of an upper pole is better than that of an under pole. It seems likely, therefore, that the hypertrophy depends upon the greater blood supply.

FIG. 81.—*Interstitial cells of a normal adult guinea pig* (Prot. Nr. 27). Same age as Fig. 80. Same magnification. The interstitial cells are disposed between five seminal tubules and surround various small and one bigger blood vessel. To be compared with Fig. 80; there is in the latter an increase also of the size of the int. cells.—Prepar. of Wagner; design of Lehbert.

In view of these considerations I think that the hypertrophy of the interstitial cells as observed under different experimental conditions is not a compensatory one. At first sight this conclusion may seem to weaken our theory concerning the endocrine function of the interstitial cells, in view especially of other observations which one might consider as evidence of a compensatory hypertrophy of the seminiferous part of the testicle. Since the experiments of *Ribbert* (1890) it has been known that unilateral castration leads to an hypertrophy of the remaining testicle, the seminiferous tubules attaining a greater diameter than in a normal testicle. The hypertrophy of the remaining testicle was observed later by Sand and by myself. Similar observations have been made in studying human pathology. But is this hypertrophy really a compensatory one, i.e., is this hypertrophy related to an increased endocrine function of the testicle necessary for the organism as a whole? That this is not the case is shown by our experiments, in which

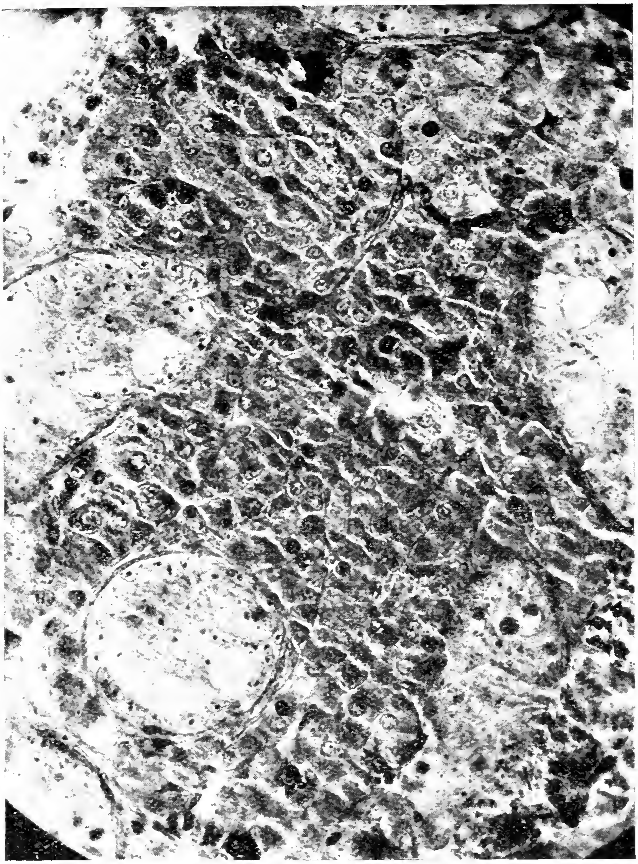


FIG. 82.—*Section through upper testicular fragment of guinea pig subjected to "complex" testicular section* (Prot. Nr. 76; operation IV., Fig. 64). x 280. Stained with Heidenhain. Operated at weight of 400 gr.; fragment removed about 4 months later. Increased number of interstitial cells. Seminiferous tubules with only one stratum of cells (cells of Sertoli).—Prepar. of Wagner; photo of Kull.

very small testicular fragments were sufficient for a normal development of the sexual characters. One might, indeed, object that the seminiferous tubules are as a rule degenerate, and the result is that the fragment is diminished in size; in reality the size estimated by weighing or by microscopical observation indicates a far greater "potential" volume of the fragment. But we observed a case where in the testicular fragment (of the under pole—a guinea pig) almost all the tubules were fully developed, and nevertheless the volume of

FIG. 83.—*Section through testicle of guinea pig subjected to operation* V. *of Fig.* 64 (Prot. Nr. 72). × 280. Operated at weight of 516 gr.; testicle removed about 4 months later. Backward development of seminiferous tubules. Increased number of interstitial cells.—Prepar. of Wagner; photo of Kull.

this fragment was calculated to be only about 20–25 mgr., or about 1 per cent. of the weight of two normal testicles (1921 a, b, c; 1922 d). The sexual characters were fully developed. Together with Miss Kropman, I made a similar observation on the mouse (1922 k). This showed that the hypertrophy of the testicle or of the seminiferous tubules after unilateral castration is not a compensatory one. This view is supported by the fact that in adult animals only a slight hypertrophy or no hypertrophy at all occurs after unilateral castration (*Nothnagel*, see *Exner*, 1903; *Kyrle*, 1911, p. 13; *Lipschütz*,

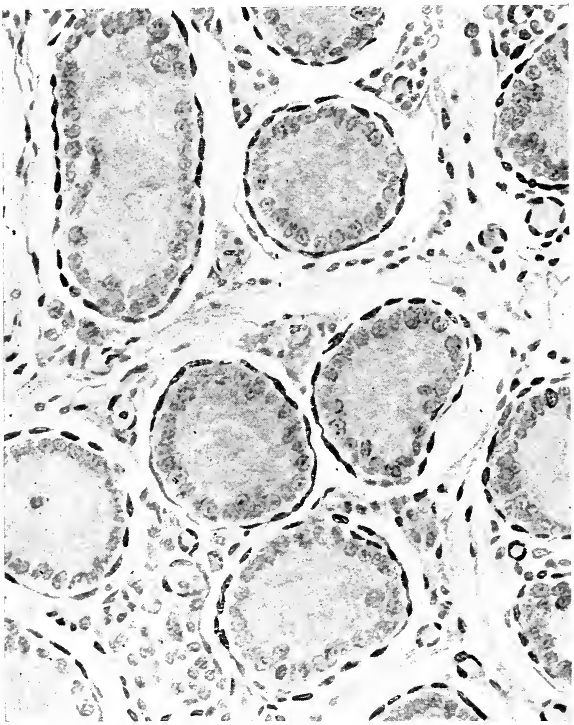


FIG. 84.—*Section through upper testicular fragment* (guinea pig. Prot. Nr. 39). Same magniffcation as Figs. 80 and 81. Operated at age of 3 weeks; died at age of 3½ months. Fragment of about the same volume as Figs. 79 and 80. Backwardly developed (or infantile?) seminal tubules. No increase of number or size of interstitial cells. No signs of castration, but development somewhat retarded.—Prepar. of Wagner; design of Lehbert.

1922 a, 1923 e). From the results of a detailed study made on the hypertrophy of the testicle after unilateral castration it seems further very likely that the increase of weight observed in young animals in this experimental condition is not an hypertrophy at all but a phenomenon of a very different kind (1922 c). (*Fig.* 85). Further, *Lipschütz and Ibrus* (1923 c, d) have shown that no change in the quantity of the interstitial cells takes place after unilateral castration. The remaining testicle reveals a structure (*Fig.* 86) quite identical with that of a normal one. It may be mentioned that in the frog the testicle or the testicular fragment seems to react differently from the way it does in the mammal (*Lauche,* 1915); in the frog the testicular fragment undergoes hypertrophy.

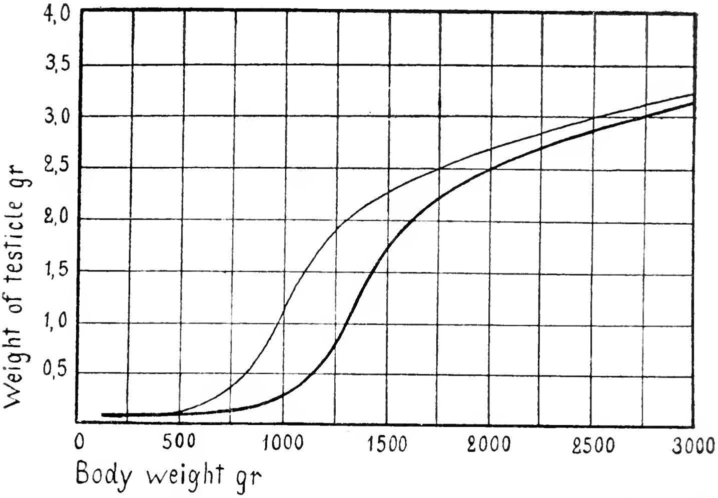


FIG. 85.—*Diagram to illustrate the hypothesis that the so-called compensatory hypertrophy of the remaining testicle is only an accelerated growth.* The thick line indicates the real curve of growth of testicle in the normal rabbit ; the thin line shows the supposed curve of growth of the remaining testicle after prepuberal unilateral castration; this curve is the normal one removed to the left. The difference between a normal and a remaining testicle is supposed to increase gradually and after a maximal difference is attained at time of puberty, to decrease again gradually. Different points of the supposed curve have been verified by experiments.

No matter where the seat of the endocrine function of the testicle is situated, no compensation seems necessary in the mammal for the performance of the normal internal secretory function even when the testicular mass is greatly reduced (*Lipschütz*, 1922 d, 1923 b).

Yet the fact remains that in many animals at any rate an hypertrophy of the interstitial cells takes place, and that the number and the size of the interstitial cells are really increased under different conditions affecting the testicle. If now the interstitial cells are an endocrine apparatus, one might suppose that under conditions of hypertrophy there should be also an increased hormonic action. As already mentioned above, Steinach records having observed an abnormally great sexual

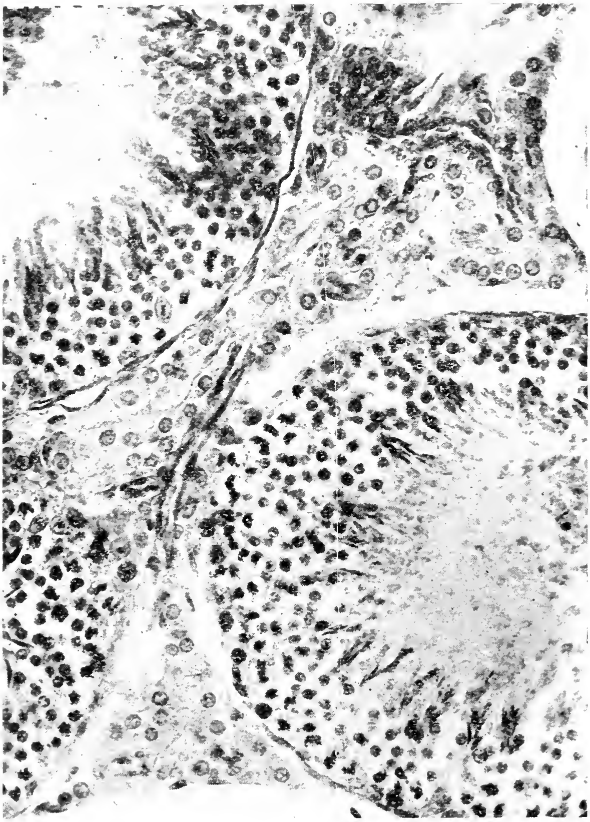


FIG. 86.—*Section through testicle of rabbit* 14 *months old, unilaterally castrated when* 1½ *months old* (Prot. Nr. 86). × 280. The biggest testicle we observed in rabbits; the weight was 3·8 gr. Normal quantity of interstitial cells. To be compared with Fig. 52. —Prepar. of Wagner; photo of Kull.

activity in animals with highly hypertrophied interstitial tissue in transplanted testicles. Similar observations have been recorded by Lacassagne and Sand in animals with ligature of the vasa deferentia. On the contrary *Alfred Kohn* (1914 a) points out that in cases of retained testicles there are no such results, notwithstanding the hypertrophy of the interstitial cells. There is a disproportion between virility and interstitial tissue. But against all these contradictory statements manifold objections may be made. First of all, in view of my own observations, I cannot but repeat that I have little confidence in quantitative statements concerning sexual activity in rats, guinea pigs and rabbits; secondly, it is still an open question whether there is always in a retained testicle a real hypertrophy of the interstitial cells (the hypertrophy being possibly in many cases only an apparent one); thirdly, the functional state of the interstitial tissue must also be taken into consideration. Fig. 87 (*Lipschütz,* 1923 a) may serve as an example. Horizontal sections through the testis and the ductus epididymidis were made on both sides at an age of two months. The animal was observed for about six months. It remained eunuchoid as shown by the observation of the penis. Spermatogenesis had ceased at a somewhat earlier stage than in Fig. 66. No differential stain for fat was employed, but the large vacuoles occupying the enormous interstitial cells and separated only by very small threads of protoplasm are most probably remains of droplets of fat. In some places interstitial cells of the usual appearance were present. Were the interstitial cells normal or not, and is the eunuchoidism in this case to be explained by an abnormality of the interstitial cells? Another case is also of high interest (*Lipschütz,* 1921 c; 1922 d). There was an underdevelopment of sex characters in a guinea pig with a very small upper testicular fragment (*Fig.* 88) in which quite normal interstitial cells were to be found. It is most probable that there was in this case a *retarded* development of the testicle and of sex characters, due to the operative interference in the former, and that the animal would have attained some time later full sexual development. But quite apart from all this, the question remains whether it is justifiable to expect an increased hormonic effect when the interstitial tissue is hypertrophied. By taking into account certain general physiological and pharmacological observations a negative answer is arrived at. We know that if an excess of certain compounds which play a part in the metabolism is introduced into the organism, this excess will be oxidized or excreted, as, for instance, proteins and salts of which only small quantities can be stored.

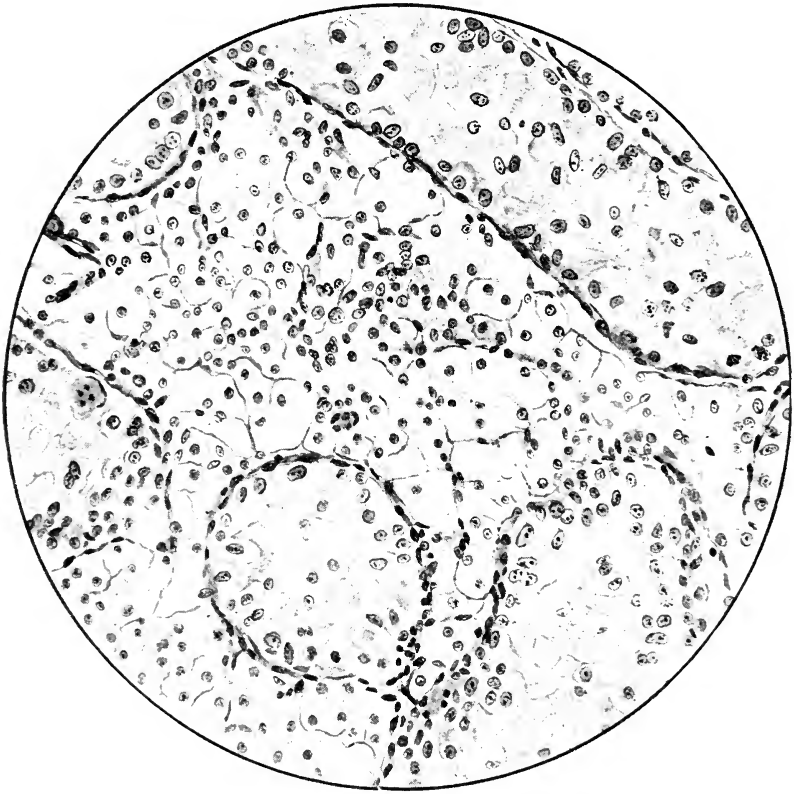


FIG. 87.—*Section through testicle of rabbit, 8 months old, with eunuchoid penis* (Prot. Nr. 41, same litter as Fig. 66; horizontal incisions on the testicle at age of 2 months). Seminal tubules in a state of degeneration; they seem to be less developed than in Fig. 66. Interstitial cells of extraordinary dimensions packed, full evidently with fat.—Prepar of Wagner; design of Lehbert.

Although these substances, such as amino-acids or some ions, have definite biochemical properties, their introduction in increased quantity does not necessarily augment these functions or affect the metabolism in general, provided that certain limits are not surpassed; all we observe is that in such cases there is an increased demand on the organs of digestion, absorption, circulation and excretion, and that eventually there is an increase of oxidation in general. We know further that some toxic substances such as morphine can be introduced in relatively great quantities without any specific effect in cases

FIG. 88.—*Section through upper testicular fragment* (guinea pig. Prot. Nr. 29). Operation at age of 1 week; fragment removed at age of 4½ months. The smallest fragment ever observed. Some tubules of normal diameter; one stratum only. Highly increased number of interstitial cells. Sex characters underdeveloped, but no signs of castration.—Prepar. of Wagner; design of Lehbert.

of abuse. I do not intend to deny that flooding the organism with a particular hormone may have an increased specific effect, and cause some disturbance or trouble, such a result being known to occur in the case of certain internal secretions. And in the same manner it is probable that a sudden temporary flooding of the organism with sexual hormones may have an increased specific effect, as, for instance, a greater sexual activity during heat. It may also be that this increased effect will last a considerable time, as in Steinach's transplantation experiments, and those of Lacassagne and Sand with ligature of the vas, referred to above. But this is very different from supposing that with an increased quantity of hormone there will be always and necessarily an increased specific hormonic effect. On the other hand, it must not be forgotten that the result of an increased hormonic influence depends, not only upon the actual hormones and the quantity present, but also upon the substratum affected thereby. Take for instance the psycho-sexual behaviour or certain somatic sexual characters such as the uterus and the mammary gland, on the one hand, and the prostate, the vesiculae seminales and the penis on the other. The former are probably in a very labile state, easily influenced, as it seems, by the quantity of erotizing hormones temporarily present; whereas the latter organs are more stable, and in their case, it may be, the quantitative laws which hold are of a different kind.

(*b*) *The Law of "All or Nothing."*

We mentioned in a preceding chapter that it had been already suggested by Foges that small particles of gonad suffice to produce a normal development of the sexual characters, but that these fragments must not be too small. Further we discussed above the suggestion of Bouin and Ancel that there is a proportionality between the quantity of interstitial tissue and the stage of development of the genital organs in pigs with retained testicles. Steinach reported a similar proportionality in his experiments with testicular transplantation. The observations of Sand seemed to corroborate those of Steinach. I showed in preceding sections of this chapter that our own new experiments make it possible to explain all these observations without assuming a proportionality between the quantity of the hormone and the degree of the hormonic effect. In the first edition of this book I attempted to formulate quantitative laws on the basis of all the different data, notwithstanding that these data were at first sight contradictory. I suggested that the hormonic effect is in a certain measure proportional to the quantity of the hormone, but that beyond this measure the proportionality does not exist. I tried to illustrate these quantitative relations by the following diagram (*Fig.* 89). The quantities of the hormone secreted in the blood are given on the abscissa; the intensity of the effects on the ordinate. The normal development of the somatic sexual characters, *N*, seems to be brought about by a quantity of hormone, q_1, the *threshold quantity* which is smaller than that normally secreted and entering the blood; the latter assumption is supported by the fact that castration results do not appear when small particles of the testicle are present. When the quantity of the hormone is greater than q_1, the hormonic effect is not increased, and an excess of the quantity, for instance, q_2, will cause only a temporarily increased effect such as at the "heat." Within the limits of o and q_1, the intensity of the hormonic effect might be proportional to the quantity of the hormone, beyond q_1 this proportionality will not exist excepting under certain special conditions (heat, pregnancy). Further, I suggested that an excess in the quantity of the hormone of the sexual glands prior to puberty might have an accelerating effect on the development of the somatic sexual characters and the psycho-sexual behaviour, i.e., that this excess might cause a pubertas praecox. Basing himself on his own experiments and on observations of *Houssay* (1907) on fowls, *Pézard* (1918, 1919) suggested that the relations between the hormonic quantity and the hormonic effect may be somewhat different. Pézard stated that not only did small quantities of testicular tissue cause development of sexual characters, but that this development was always a *complete* one, when a certain minimal quantity of testicular tissue was present. When this minimal quantity is

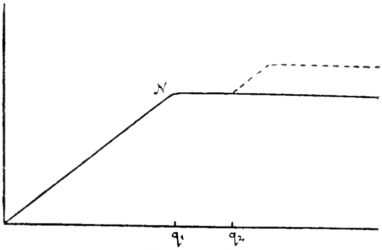


FIG. 89.—*Diagram: Dependence of hormonic effect upon the quantity of testicular hormones.* Abscissa: quantity of hormone; ordinates: hormonic effect as expressed by somatic sex characters *e.g.*, length of comb). q_1—quantity of hormone sufficient for normal hormonic effect (*N*). q_2—quantity of hormone normally present. It is assumed that there is between o and q_1 proportionality between the quantity of hormone and the hormonic effect, whereas no such proportionality exists beyond q_1 and q_2. Further increase of the quantity of hormone may temporarily cause an increase of the hormonic effect as during heat (as indicated by dotted line); but this increased hormonic effect does not last.

present, there are no intermediate stages in regard to development of sexual characters; they are either fully developed or else they are in the same state as in the "castrate." *Pézard suggested that the hormonic action of the sex gland is regulated by the law of "All or Nothing,"* applied already in the case of the heart (Marey) and nerve (Lucas and Adrian, Verworn, Vészi), and probably true also for skeletal muscle (Lucas, Adrian). This law affirms that when the strength of the stimulus is increased beyond that of the liminal or threshold stimulus the effect is not varied (*Fig.* 90). The difference between the suggestion of Pézard and that developed by myself in the first edition of this book and represented in the above diagram (*Fig.* 89) is, that according to Pézard only the horizontal part of this curve is correct and, further, that this horizontal part must be much displaced to the left. Our own experiments with partial castration justify us in discussing this quantitative problem more fully. In confirmation of Pézard's statements on fowl we have shown in mammals that the testicular particles which can admit of full development of somatic sexual characters may be so small that it is impossible to lay down any practical limit to the minimal quantity sufficient for the growth of the sexual characters. In other words, the horizontal part of the curve will begin not far from 0, in our experiments near one per cent. or even less. But this does not necessarily imply that no proportionality between hormonic quantity and hormonic effect exists in the limits between 0 and one per cent. In our

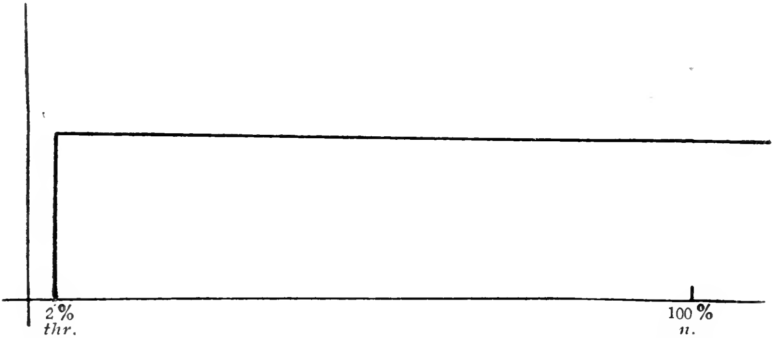


FIG. 90.—*Diagram to illustrate the law of "All or Nothing."* The maximal hormonic effect (ordinates) is brought out when the threshold quantity (*thr*) of sex hormones is produced. The threshold quantity is supposed to be very small as compared with the average normal quantity (*n*).

experiments with partial castration, as already mentioned, we did observe intermediate stages between castration effects and normally developed somatic sexual characters. In one of these experiments we found that the weight of the fragment was much less than one per cent. of the normal testicular mass. At first sight one might take these observations as being contrary to the law of "All or Nothing." But on the other hand we have shown from our own experiments that by injuring the testicle it is possible to retard its development. In view of these observations it seems justifiable to assume that the intermediate stage is in reality due to retarded development of the testicle or the testicular fragment, and that any animal representing an intermediate stage in the development of sexual characters may attain to full puberty provided no detrimental changes occur in the operated fragment. These observations of our own confirm Pézard's view, as represented in the law of "All or Nothing." *Pézard* (1922 a) gave full experimental evidence of his suggestion in remarkable experiments on fowls.

The objection that in small fragments the interstitial cells are often really in a state of hypertrophy, is not justified, as it was shown above that this hypertrophy has no relation to functional compensation in regard to internal secretion. Another objection might, however, be made; it might be said that a small testicular fragment is possibly producing as much hormone as both the normal testicles, without there being any visible histological or cytological changes in the fragment. We are not in a position to discuss such an objection, since there is no indication of the functional state of the testicle other than that provided by microscopically visible changes.

There is yet another objection. One might suppose that retardation of development of sexual characters as observed in some cases with partial castration is caused by the time normally necessary for the development to puberty being lengthened on account of a diminished quantity of sexual hormone. This assumption would, as already said, be in accordance with what we know about ferment action. Such a dependence of the development of the sexual characters upon a time factor would not be contrary to the law of "All or Nothing," although, at first sight, one might suppose it.

Whatever the truth about these questions may be, we are now far removed from the original quantitative standpoint adopted by Bouin, Ancel, Steinach and Sand as a result of their experiments, and which I had adopted in the first edition of this book No doubt the view taken by Pézard and myself in regard to the quantitative law in the action of the sexual hormones will undergo further development as a consequence of subsequent experimental research. Future experiments must, I think, relate especially to the question as to whether by diminishing the quantity of the hormone the time necessary for puberal development is lengthened.

7. On Cyclic Changes in the development of the Interstitial Tissue.

Cyclic changes in sexual activity occur in some species in the male as well as the female. It is of interest to enquire whether, corresponding to the transitory increase in the sexual activity during rut, there is any augmentation of the interstitial tissue in the testicle. It is clear that this question is of great importance in relation to the function of the male "puberty" gland.

It has long been known that the interstitial tissue of the testicle in some animals undergoes seasonal changes. *Hansemann* (1895, 1896) stated that in the woodchuck the interstitial cells are hardly represented at all during hibernation, whereas in the spring after awakening the interstitial tissue is as highly developed as in the wild boar, the cat, the mole, etc. This question has been studied also by several other investigators on mammals and on amphibians (see *Rasmussen,* 1917, 1918). We shall deal in this paragraph with mammals only. Ganfini found, like Hansemann, that the interstitial tissue in the testicle of the woodchuck was apparently reduced during hibernation; but he points out that in reality there is no decrease in the number of interstitial cells, the latter being only reduced in size. Detailed investigations on the hedgehog were made by *Marshall* (1911); he found a simultaneous development of the interstitial cells and seminiferous tubules in the period of heat, and a simultaneous diminution of both during the time of sexual inactivity. The statements of the different observers on the hedgehog and the woodchuck are represented in the following diagram taken from the paper of Rasmussen (*Fig.* 91). The curve of spermatogenesis and the curve of development of the interstitial tissue are more or less parallel. Similar results have been obtained lately by Rasmussen in the woodchuck. Rasmussen emphasized the discrepancies between the older observations and his own, but I think that no serious discrepancy exists. Rasmussen finds that spermatogenesis attains its maximum about a month sooner than the interstitial tissue, and further that the interstitial tissue remains several months at its maximal state of development, whereas the curve of spermatogenesis is lowered long before. But I think that it is impossible to draw from such observations *detailed* conclusions in regard to time and quantity of interstitial tissue or tubules, especially as all these conclusions are naturally derived from different individuals which may show much variation. On the other hand all these observations are a sufficient basis for the general conclusion that in the woodchuck and in the hedgehog the interstitial

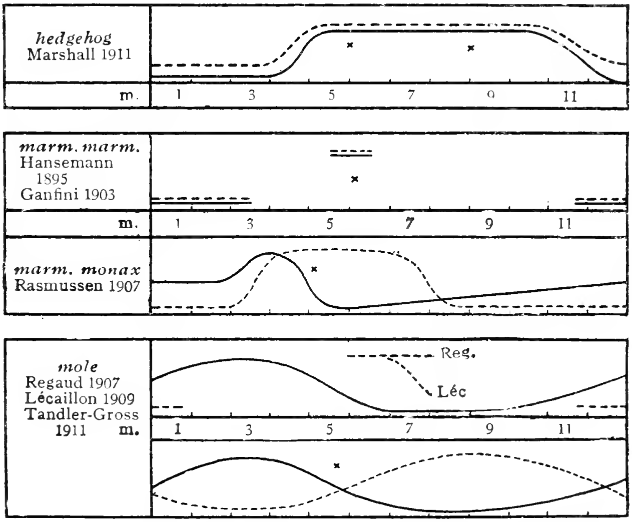


FIG. 91.—*Cyclic development of generative and interstitial tissue of the testicle of hibernating mammals.* Plain lines indicate generative tissue ; dotted lines, interstitial tissue. Climax of spermatogenesis during heat, hibernation from November till March; birth of young indicated by *x*.—Parallel development of generative and interstitial tissue in the hedgehog and in *Marmota marmota* (for marm. marm. data available only for some months). Some deviations between both tissues in *Marm. monax*; no parallelism in the mole.—From Rasmussen (with changes).

tissue attains its minimum during hibernation or in the time of sexual inactivity, and that it attains its maximum during heat. Marshall concluded from his experiments that the characteristic features during heat are caused in the hedgehog by an increased internal secretion of the interstitial cells.

In disagreement with the statements concerning the woodchuck and the hedgehog are those relating to the mole. The mole experiences heat once in the year about the beginning of March, and at this time the generative part of the testicle attains its maximum. Regaud found the interstitial tissue well developed in June and July, when the generative part is already at its minimum. In December only a few interstitial cells are to be found; at the same time the tubules enter upon new spermatogenesis. The statements of Lécaillon on the mole are somewhat different from those of Regaud, as seen in the diagram. Finally a detailed investigation on the cyclic changes in the testicle of the mole was made by *Tandler and Gross* (1912, 1913, p. 117). Their results were again somewhat different from those of Regaud and Lécaillon as concerns the time of development of the interstitial tissue. They stated that the maximum of the generative part corresponds to the minimum of the interstitial tissue, this being reduced at the period of heat. In the time of sexual inactivity, in the autumn, when the generative part is at its minimum, the interstitial tissue attains its maximal development. Tandler and Gross never found mitoses in the interstitial cells when at their maximal number,· and they suggested that the connective tissue cells in the testicle are mostly inactive interstitial cells, which can be activated at a given moment and assume the morphological character and the function of interstitial cells. Evidently the cyclic increase of the number of interstitial cells does not imply a cyclic proliferation of cells.

Courrier (1923 a) made an investigation on the cyclic changes in the bat. He insists on the very important fact that the generative part of the testicle is inactive during the autumn and winter, and, nevertheless, the accessory genital glands (the epididymis, the vas deferens, the seminal vesicles and the prostate) are in full secretory activity; likewise sexual intercourse can take place during that time. The interstitial cells have at that time the appearance of highly active glandular cells. The interstitial cells undergo a pigmentation at the end of May and concomitantly the secretion of the epididymis ceases. From all these observations, and likewise from those on other mammals with a periodic spermatogenesis (1923 b), Courrier concludes that the cyclic changes of the interstitial gland are in a striking correspondence with the cyclic changes of the sex characters. The cells of Sertoli, however, also undergo concomitant changes. On the contrary, the accessory genital glands may be in a state of rest when the seminal tubules are active.

The statements of Regaud, Tandler and Gross on the mole disagree with those made about the hedgehog, the woodchuck and the bat. They are also opposed to the view that heat is caused by an increased activity of the interstitial tissue. But, as already mentioned, the statements of Lécaillon about the mole are somewhat different from those of the other authors. It is also possible that the decrease of the interstitial tissue in the mole during heat is only an apparent one. The nearer the time of heat, the greater the room occupied by the seminiferous tubules in the testicle and the greater also the space in which the interstitial cells are distributed. If the total volume of the interstitial tissue is not increased in the same measure as the total volume of the seminiferous tubules, a microscopical preparation will give the impression that the interstitial tissue is reduced, even though in reality there is a very marked increase of the latter. One will understand the weight of such an objection, if one takes into consideration how enormously the volume of the testicle is increased in heat owing to the augmentation of the tubules. As said already in the first edition of this book, it is absolutely necessary to know the real number of interstitial cells, or the real volume of the interstitial tissue in the testicle during heat and during sexual inactivity; we learn nothing about this question when we merely count the cells in one or another preparation. We shall meet with the same difficulties in dealing with amphibians as we here encounter in mammals (see below in this chapter).

Tandler and Gross concluded from their observations that the interstitial cells play a leading rôle in causing the condition of heat. They suggested that the interstitial cells are a factor in the spermatogenesis of the next heat, influencing the generative part of the testicle as they influence the somatic characters. If this were true, it would follow that the generative cells are a "secondary" sexual character genetically dependent upon the interstitial cells. This may seem at first sight wholly inacceptable. But there are some facts which support this view. Ancel and Bouin stated that the interstitial cells in the embryo of the pig are present before spermatogenesis begins. The interstitial cells in the embryo of 30 mm. can be recognised with certainty. Bouin records having observed signs of secretory activity in the interstitial cells during embryonic development (1903 c). In view of these facts *Bouin and Ancel* (1903 d) suggested that the interstitial cells determine in some measure the sex of the generative cells. In accordance with Bouin and Ancel one might suppose that the cyclic spermatogenesis under the influence of the increased or hypertrophied interstitial cells occurring before heat is nothing else than the recapitulation of what happens during embryonic life. The suggestion of Bouin and Ancel has lately been supported by *Witschi* (1921), who made observations on the frog. There has been much discussion about a so-called "trophic" function, the suggestion being that the interstitial cells prepare some kind of material necessary for the nutrition of the spermatic cells. This view is supported by many histologists, especially by Plato, *Kyrle* (1911), Winiwarter, and recently by *Kohn* (1914 a, 1920). Kyrle expressed the belief that the increase of the interstitial cells in the neighbourhood of degenerated tubules (or backwardly developed tubules, as I should prefer to say) indicates that the interstitial cells have something to do with the regeneration process which occurs in these tubules. Such an assumption is in reality not very different from what Bouin and Ancel suggested. But no sufficient proofs exist for this assumption, although some histologists claim that it is definitely proved that the interstitial cells are no more than a trophic organ in relation to the seminiferous tubules. It may be useful to compare what such a critical histologist as Alfred Kohn pointed out about this question. He claimed in 1914 that there is "absolutely no proof" and that it is very "improbable" that the interstitial cells of the testicle should be necessary for the development of the seminiferous tubules. Later (1920), without any new fact having been added, the same author declared that the interstitial cells are probably a "trophic" apparatus for the generative part of the testicle. Quoting these two contradictory passages from Kohn, I should like to make it clear that, in my judgment, all the statements based on "definite" proofs that the interstitial cells have nothing to do with the internal secretion of the testicle, and that they are nothing else than a nutritive organ for the seminal tubules, are without any foundation.

8. The Phases of Puberty in the Male.

It is generally assumed that "puberty" marks the time when a developmental process takes place in the organism of a different kind from that going on previously. But in reality it is not so. At the time of puberty we have only an acceleration of processes culminating in the full development of the sexual characters. Such a suggestion will be especially acceptable if one takes into consideration the fact that the development of the sexual characters, as we must now assume, has begun already during embryonic life. The first steps towards sexual maturity are made in the embryo; maturity is consummated at the time known as puberty in the ordinary sense of the word. In man and other mammals there is from birth to puberty a relatively long period when the development towards sexual maturity proceeds very slowly, or even for a time ceases altogether. I showed experimentally with rabbits that in all probability no internal secretion of the testicle is produced at all for about three months after birth, the development of the penis in the rabbit prepuberally castrated at an age of one to two months being, until the commencement of the time when puberty would otherwise occur, exactly like that in the normal animal. So one may suppose that there are in reality two great phases of puberty; the first at a certain time of embryonic development, the second one several months (rabbit) or years (man) after birth, and that these two great phases or climaxes of puberty are separated by an intermediate phase. Such an assumption is necessary to the theory of the existence of an asexual or indifferent state of the somatic substratum of the sexual characters before the internal secretion of the gonads enters into activity.

We must now ask ourselves whether we have any knowledge of the condition of the testicle at the indicated phases, so as to explain the true correlation of the latter with corresponding changes in the endocrine function of the testicle. As we have seen at the beginning of this chapter, the interstitial cells seem to show a first climax of development during embryonic life and a second climax at sexual maturity. So it should be possible to explain the sequence of the phases of puberty by a sequence of phases in the development of the interstitial tissue. One might, indeed, object that synchronously with the development of the interstitial tissue, at the time of sexual maturity, we have also a rapid development of the generative part in the seminiferous tubules, and more or less synchronously with the first appearance of interstitial cells we have the formation of the generative part. But if we take into consideration the fact that a testicle with cells of Sertoli and spermatogonia, but without fully developed interstitial cells, is not capable of producing the internal secretion, we shall understand that, if there is any internal secretion of the testicle during embryonic life, it cannot be due to the primitive generative cells. This will be especially clear if we consider how in the rabbit, for instance, as already mentioned, there is in the first three months no internal secretion of the testicle, although numerous spermatogonia, and even spermatocytes, may be present in the seminiferous tubules. After all it cannot be denied that there is a correspondence between the sequence of changes in the interstitial tissue and the phases of puberty, whereas no such correspondence exists in relation to the phases of spermatogenesis. In the time between the two great phases of puberty the interstitial tissue is possibly in an "intermediate" stage, the cells being quiescent.

The further question arises as to whether also the changes which take place in sexual activity with advancing age are related to changes in the interstitial tissue.

9. THE "FOLLICULAR THEORY" OF HORMONE-PRODUCTION IN THE TESTICLE.

If we compare figures 65 and 66, figures 70, 71 and 79, and if we take into consideration only the actual state of the interstitial tissue and of the seminiferous part in all the above-mentioned cases, it is impossible to avoid the conclusion that well developed interstitial cells represent the organ of internal secretion in the testicle of mammals, and that the generative part is not involved in this function. A condition of eunuchoidism may occur in the presence of full spermatogenesis and a normal development of sexual characters may be brought about by testicular tissue where the tubules are in an infantile stage, but where the interstitial cells are of the adult type. But if we consider the state of the testicle or of the testicular fragment in these cases from a dynamical point of view, together with all the resulting processes, it is difficult to avoid the conclusion that spermatogenesis is possibly involved in the puberal development of the interstitial cells, and so is *indirectly* involved in the internal secretion of the testicle. Spermatogenesis proceeding to a certain degree may be necessary for the transformation of the quiescent form of the interstitial cells into the puberal form. Our knowledge, however, of the time relations between spermatogenesis and puberal development of the interstitial cells is at present incomplete.

There is a further consideration of a more general character which supports such a theory. As we shall see in Chapter V., it is almost unanimously agreed that the follicle is an endocrine apparatus in the ovary. Follicular development is connected with development of the ovum. But the ovum itself is not necessary for the production of the internal secretion of the follicle, as is shown by the fact that the follicle or the corpus luteum which persists after the death or the exodus of the ovum, continues to elaborate internal secretions. Cells (of epithelial or connective tissue origin) hitherto not involved in internal secretion are transformed into endocrine cells during the process of ripening of the germinative cells of the ovary. The same is possibly true for the testicle. So the theory suggested above has its analogy in what is known in regard to the ovary. The term "follicular theory" may be conveniently used in this connection.

Such a follicular theory of the endocrine function of the testicle cannot be based on proof, at any rate at present. Nevertheless it may serve as a convenient working hypothesis.

The assumption of *Berblinger* (1921), that the interstitial cells serve for the storing of hormones produced by spermatic cells, seems to me unjustified by the facts described in this chapter.

10. The Condition of the Interstitial Cells in Intoxication and Disease.

It is known that degeneration of the seminiferous tubules can also be caused by certain poisons. The influence of chronic alcoholic intoxication on the tubules, as noted by various observers on alcoholic subjects, is of great practical interest. *Simmonds* (1898, quoted from *Kostitch*) showed that 60 per cent. of cases of azoospermia are caused by chronic alcoholic intoxication. The histological investigations of *Bertholet* (1909, *Kost.*) and *Weichselbaum* (1910, *Kost.*) revealed that in the testicle of alcoholic subjects spermatogenesis may decrease or even disappear, whereas the interstitial cells are increased in number. The same was demonstrated experimentally on animals under conditions of chronic alcoholic intoxication by *Bouin and Garnier* (1900, *Kost.*), *Kyrle and Schopper* (1914, *Kost.*). Lately, *Kostitch* (1921), a pupil of Bouin, has performed new experiments and published a detailed paper on this question. *Adler* (1914) has shown that similar degenerative processes in the testicle can be caused by subcutaneous application of different compounds of iodine; *Hofstätter* (1923) has demonstrated the same for nicotine.

The changes which the interstitial cells undergo in different diseases may also be considered as due to toxic substances. As far as I know, *Hansemann* (1895, p. 544) was the first to draw attention to this question. He found the interstitial cells in a state of hypertrophy in chronic diseases, such as tuberculosis of the lungs and cachexia caused by cancer or syphilis. *Thaler* (quoted from *Kasai*, 1908) records having observed in many cases of acute diseases that the interstitial cells were rather numerous, whereas in some cases the interstitial tissue was not well developed. The increase of the interstitial cells in cachectic diseases, according to Thaler, is not a constant one. A marked increase of the interstitial cells was observed by *Cordes* (quoted from *Kasai*, 1908) in seven out of twelve cases of tuberculosis. The question was studied also by *Bouin and Ancel* (1905 a). They record an hypertrophy of the interstitial tissue in acute diseases such as pneumonia and tuberculosis, which progress rapidly. But this hypertrophy is not always of the same degree, neither does it always take place. They observed also the hypertrophy of the interstitial cells in chronic diseases such as in tuberculosis of the lungs. They record that this hypertrophy may be very marked, the bands of cells of Leydig between the tubules being twice as large as normally; there are signs of an intense secretory activity in the cells. But, on the other hand, a degeneration or a complete atrophy of the interstitial cells may take place in diseases, especially in cachexia of long duration. The interstitial cells are decreased in number and size, they are filled with pigment, and their edges are serrated. *Bouin and Ancel* (1905 b) observed also an hypertrophy of the interstitial tissue in cases of experimental infection or great loss of blood experimentally produced, where the hypertrophy occurs after a few days; in the final stage of a chronic infection or intoxication (general experimental tuberculosis or alcoholic intoxication during several months) an atrophy of the interstitial cells may occur. The same point was observed in the final stage of an acute mortal infection. In opposition to these statements are those of Kasai, who found no changes in the interstitial tissue in pneumonia and acute tuberculosis; in septicaemia and in purulent peritonitis the interstitial cells were sometimes visibly increased in number, whereas in other cases the interstitial tissue showed no abnormality. In chronic diseases of the organs of circulation or bronchi an increase of interstitial cells was observed only exceptionally. In cancer no increase of the interstitial cells was found by Kasai even when the tubules were atrophied. But a marked increase of the interstitial cells was observed by Kasai in seventeen out of twenty-two individuals who died of tuberculosis. The tubules were mostly more or less atrophied. In some cases also the interstitial tissue was in a state of degeneration, the cells having only a little protoplasm ("quiescent interstitial cells," according to Kasai). The question of the behaviour of the human testicle under different pathological conditions has been very carefully studied by *Kyrle* (1911, 1920), who examined for this purpose more than a thousand testicles. As Kyrle points out, the testicle in man is sensitive to such a degree that it is hardly ever possible to find a normal testicle in adults who died of acute infectious diseases, such as pneumonia, or acute septic infection. But sometimes the number of tubules affected by degeneration is very restricted. More pronounced are the degenerative changes in chronic diseases. Kyrle says that out of 1000 testicles examined by him he found none which could serve as an example of the wholly normal testicle. Kyrle is of the opinion that most of the new-born have underdeveloped testicles. This is surely an exaggeration. If most of the new-born who die from accidents during birth have testicles of a certain structure, it is most likely that this is the *normal* state. As to the degenerative changes in the adult testicle which Kyrle so often met, they relate to a very restricted number of tubules. I found the same several times in our "normal" laboratory rabbits and guinea pigs. It may be that this backward development of seminal tubules, occasionally occurring in normal men and animals, has some kind of genetic relation with the cyclic changes which occur regularly in other species.

Notwithstanding all the contradictory reports related above, it seems that in general there is an atrophy of the seminal tubules, and an increase of the interstitial cells, in serious acute and chronic diseases, and, further, that an atrophy of the interstitial cells may occur when the organism is very much injured by the disease. Two objections must be taken into consideration; first, that the increase is only an apparent one, caused by the degeneration of the tubules, and, secondly, that the increase, if really present, is not caused by a direct influence of toxic substance, but represents only a reaction to the degeneration of the tubules. The first objection, which we have already met with several times in other connections, could be advantageously studied in microscopic detail, and by taking into consideration the total volume of the interstitial cells. Kasai's statement is of importance here; he sometimes observed mitotic figures, which shows that the increase in the number of cells is not always merely an apparent one. The second objection is of a rather different order. There is no doubt that the increase of the interstitial tissue is in many cases merely a local reaction to changes occurring in the tubules, and may be a process related to the regeneration of the seminal tubules, as was pointed out by *Kyrle* (1911). But, on the other hand, certain observations have been made showing that the increase of the interstitial cells can take place independently of changes in the tubules. An observation of *Hedinger* (1920) must be mentioned here. He observed a man of 29 with a chorion-epithelioma of the right testicle. The tumour occupied almost the whole testicle, only a few atrophic tubules and isolated interstitial cells being visible in some sections. The man died some time after the extirpation of the right testicle on account of multiple metastases. The microscopic examination of the left testicle was of great interest; the seminiferous tubules were well developed and in a state of full spermatogenesis, and, nevertheless, any microscopical preparation, whatever place it was taken from, showed an increase of interstitial cells disposed in large groups or nodules of 1 to 1·5 mm. in diameter between loose connective tissue. To control this statement Hedinger examined the testicles of about 100 men, mostly robust and healthy individuals of 25 to 35 years of age, who died of Spanish influenza; he never found groups of interstitial cells which could in any way be compared with those in the left testicle in the case described above. This shows that an increase of interstitial cells cannot be considered merely as a reaction to local changes in the tubules; hypertrophy of the interstitial tissue can occur independently of any change in the tubules. That hypertrophy of the interstitial cells, although very often only a local reaction to the degeneration of tubules, is not always so, is rendered probable also by some experiments of our own. Horizontal incisions were made on the testicle of adult guinea pigs without touching the ductus epididymidis ("incomplete testicular section" [*Fig.* 64, III.]). We observed in most of these cases a degeneration of tubules only near the level of the incision; but I have the impression that some hypertrophy of the interstitial cells occurred, nevertheless, throughout the whole testicle between normal tubules in a state of active spermatogenesis (*Fig.* 92). We have not yet made a detailed examination of the total volume of the interstitial tissue in these cases. Our experiments with partial castration, as reported above, showed further that not only the tubules, but other local conditions also, such as a rich blood supply, are to be taken into consideration in studying the hypertrophy of the interstitial cells.

In view of the hypertrophy of the interstitial cells in disease, Alfred Kohn objected that no relation has been observed between virility and the interstitial cells, as one might expect on our theory. I have already tried to show that an increased quantity of hormone in the blood need not necessarily have an increased hormonic effect. On the other hand, it must not be forgotten, that the hormonic effect depends not only upon the quantity of hormone, but also upon the sensitiveness of the substratum; in this case upon that of the central nervous system. No doubt the sensitiveness of certain parts of the latter is much diminished in acute and chronic diseases. It is easy to understand that in such conditions even an increased quantity of the hormone will not lead to a normal

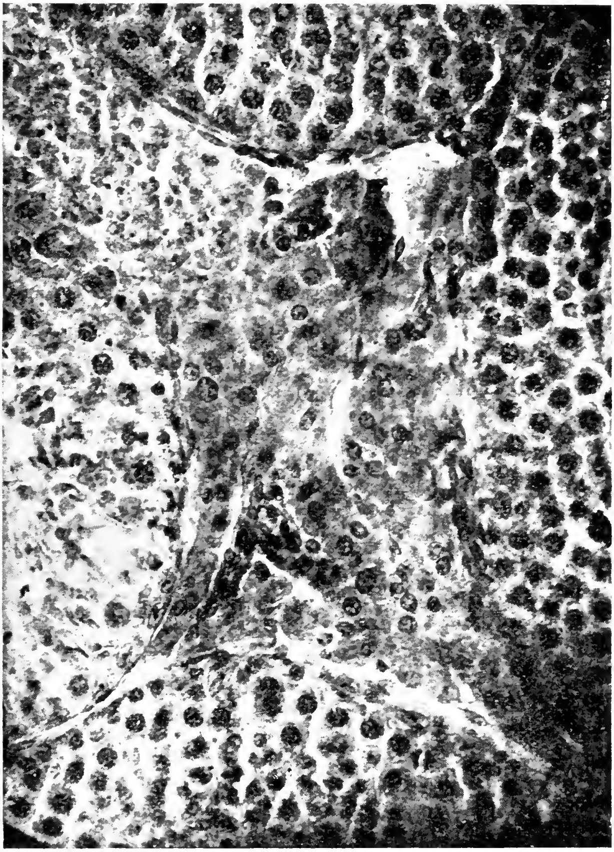


FIG. 92.—*Section through testicle cut horizontally.* (Operation III., Prot. Nr. 76, left testicle) x 280. The testicle was adherent to the abdominal wall. Spermatozoa were not to be found in the epididymis, but there was spermatogenesis in many tubules. Great quantity of hypertrophic interstitial cells between four tubules in complete spermatogenesis.—Prepar. of Wagner; photo of Kull.

erotization. Moreover, as has been shown, especially by Kasai, there is sometimes a degeneration of the whole testicle, as, for instance, in tuberculosis; the interstitial cells are often of the so-called quiescent type, with a little protoplasm and with an elliptic nucleus.

Bouin and Ancel suggested that the hypertrophy of the interstitial cells in diseases represents a means of defence for the organism. As a result of various experiments, *Voinov* (1905) put forward the theory that the interstitial cells produce certain chemical substances for the protection of the generative part of the testicle. A similar view is held by *Kitahara* (1923), being based upon embryological evidence. Kitahara and *Čejka* (1923) consider it possible that the interstitial cells act also as a kind of chemical transformer of substances produced in the generative part. Although it cannot be denied that there is, perhaps, some truth in all these hypotheses, they are none of them based on sufficient evidence. The papers of *Goette* (1921), *Jaffé* (1922), and *Berberich and Jaffé* (1922), who deal with a great number of pathological observations, and of *Brack* (1922), may also be referred to here.

In any case there can be no justification for urging the disproportion between the number of the interstitial cells and the very low level of erotization in certain diseases as evidence against the theory that the interstitial cells elaborate an internal secretion.

According to *Steinach and Kammerer* (1920) the quantity of interstitial cells is increased when animals are kept for a long time under a higher temperature. They claim that there was in these animals an hypertrophy of sex characters such as the seminal vesicles and the prostate.

As was shown recently by *Tsuji* (1920) a degeneration of the seminiferous tubules may occur when rats are fed on a diet poor in vitamines, such as a mixture of casein, starch, cane sugar, lard and salts; the degeneration of the tubules can be prevented when small quantities of milk are added to the standard diet. No changes were found in the interstitial cells surrounding the degenerated tubules. As Tsuji points out, the changes in the testicle are evidently due to a diminished activity on the part of the thyroid gland, which showed considerable changes in the experimental animals, the weight of the thyroid per 100 gr. body weight not reaching even half of that of the control animals. It has been ascertained from former experiments (for references see Tsuji's paper) that thyroidectomy causes degeneration of the generative part of the testicle. No data are given by Tsuji as to the sexual characters of his experimental animals. In fully grown white mice, fed for a long time without any experimental object in view with a uniform diet of oats and bread, we observed great changes in the seminiferous tubules, many of them being in different stages of degeneration; the penis was normally developed. According to *Mattill and Carman* (1923), even a uniform milk diet can cause in rats degenerative changes in the testicle; desiccated preparations of kidney, spleen, thymus, etc., were unable to prevent these changes.

The theoretical value of all these observations concerning the behaviour of the testicle under different conditions (disease, intoxication, diet and operative interference), seems to be very small. But every practitioner will agree that these observations are of the greatest practical interest. It is very probable that intoxications are much more commonly the cause of sterility in man than admitted hitherto. Since degeneration of the seminiferous tubules does not lead to signs of castration, many cases of sterility in man remain undetected without special examination. The practitioner is as a rule disposed to explain the existence of sterility in the wife as due to an abnormality when he hears that the sexual behaviour of the husband is normal. I am of opinion that one of the greatest mistakes a gynæcologist can make is to refrain from repeated examination of the semen of the husband when a woman is supposed to be sterile. Every practitioner will agree that the difficulties in this field of practical medicine are much greater than is publicly admitted. There are cases where intellectual people suffer for many years from not having progeny, and yet are unable to decide upon consulting a doctor. I regard it as absolutely necessary that the general practitioner should be well trained in this matter both in theory and in practice. In many cases of sterility a properly trained medical man is better able to assist his patients by sound advice and simple explanation than by having recourse to a severe operation on the uterus. And he may be sure that the success and the gratitude he will obtain will often be incomparably greater.

CONCLUSIONS.

The experiments recorded in the preceding sections supply evidence that in mammals

(1) Underdevelopment of interstitial cells is connected with eunuchoidism.

(2) Signs of castration are absent when the seminiferous tubules undergo manifold changes, and even when the tubules undergo retrograde development to the infantile stage, provided that the interstitial cells are fully developed.

(3) Complete sexual maturity is possible even when spermatozoa were never present in the testicle.

(4) On the other hand, eunuchoidism is not excluded in the presence of spermatozoa.

It follows that in mammals

(*a*) the interstitial cells are a necessary part of the endocrine apparatus of the testicle;

(*b*) no proof exists of a direct hormonic action by the cells of Sertoli or by other constituents of the wall of the tubules independently of the interstitial cells.

It might be assumed as a working hypothesis that the transformation of the interstitial cells after birth into an endocrine apparatus is connected with spermatogenesis ("follicular theory") or with some stages of this process.

It is probable that the hormonic apparatus of the testicle in man and other mammals during ontogenetic development reaches a culminating point twice; the first in embryonic development, the second at the time of puberty. It is certain that in the rabbit the endocrine apparatus does not function in the first three months after birth, and it is possible that in man also the hormonic apparatus of the testicle is, until puberty, in such an "*intermediate*" state, when the secretory activity of the interstitial cells is much reduced or even ceases completely; the latter is the more probable.

What we generally call the "age of puberty" is on this view really *the second great phase of puberty*. The *first great phase of puberty* should be placed at the time of embryonic development when the embryonic asexual or indifferent soma turns over to the male side. An *intermediate phase of puberty* may be said to occur between the first and the second great phases; it is the time when the sexual characters cease to develop further, or continue to develop in so far only as they do so "concordantly" with the general growth of the body and independently of the hormonic apparatus of the testicle, or when they continue their "discordant" growth at a very low level.

* * *

These conclusions are founded mostly on *experimental* evidence taken in conjunction with clinical evidence such as that derived from the study of cryptorchism. Further clinical evidence, as, for instance, that afforded by some cases of eunuchoidism in man, and especially cases of hermaphroditism, seem to militate against the theory elaborated above. This evidence will be discussed later on.

B. INTERSTITIAL CELLS IN THE TESTICLE OF OTHER SPECIES.

We have so far confined our discussion of the question as to the seat of the endocrine testicular function to the mammals. It is, however, a matter of great interest to go deeper into the problem from the standpoint of comparative physiology, as we have indicated when comparing the rabbit and the guinea pig (Section A1). We shall now consider the question as to whether there are other animals besides mammals, in which the generative cells of the testicle can be considered as having no direct connection with the internal secretion of the testicle, and in which certain other elements of the latter can be regarded as endocrine organs. As we said above, systematic investigations on this question have been made only recently upon fishes, amphibians and birds.

1. Invertebrates.

We know that in the earthworm the development of the male sexual characters depends upon the sexual gland. As in the testicle of the earthworm, besides the generative cells, only connective tissue can be found, *Harms* (1914, pp. 117, 158) has concluded that in this animal the generative cells alone produce the sexual hormones.

2. Fishes.

Observations on interstitial cells in fishes have recently been made by *Courrier* (1921, 1922) and by *Kolmer and Scheminzky* (1922), who state that they are present in numerous species.

It has been shown by different observers that the interstitial tissue in vertebrates other than mammals undergoes cyclic changes.

Among fishes observations have been made by *Courrier* (1921, 1922) on *Gasterosteus aculeatus*. According to this observer the connective tissue cells of the interstitial tissue in April begin to assume the appearance of glandular cells surrounding the blood vessels. This transformation of connective tissue cells into true interstitial cells takes place only after spermatogenesis is accomplished. Spermatogenesis begins long before, and as early as the end of March spermatozoa are to be found in great number in the seminiferous tubules. In May and June *Gasterosteus* assumes the features characteristic of heat, i.e., long after spermatogenesis has been accomplished, and when the testicle contains a well developed tissue of glandular cells. From these observations Courrier concludes that the interstitial cells produce the internal secretion upon which the nuptial transformations depend. It is also of great interest that in cases where spermatogonia and spermatocytes only were found in the testicle, and no interstitial cells, the nuptial transformations fail to take place. Further, Courrier concluded that the interstitial tissue cannot be considered as a trophic organ in relation to the seminiferous tubules, as the former does not develop until after the latter. *Van Oordt* (1923) and *Champy* (1923), however, consider that these statements are insufficient to prove the dependence of the nuptial changes upon the interstitial cells. It may be pointed out that Courrier's observations can be explained also in the light of the "follicular theory" developed in the foregoing section of the chapter.

3. Amphibians.

For amphibians the statements are very contradictory. The question has been studied both histologically and experimentally. *Harms* (1914, p. 117) claimed to have demonstrated that in *Bufo vulgaris* the Bidder's organ is a factor in the development of the finger callosities. As this organ can be considered as a rudimentary female sexual gland, in which, according to Harms, interstitial cells do not occur, one might conclude that in this case the degenerating female generative cells present in Bidder's organ produce male sexual hormones.

But *Guyénot and Ponse* (1923) have made a detailed experimental study of this question and they have come to a conclusion definitely opposite to that of Harms. According to Guyénot and Ponse the Bidder's organ has no influence at all on the sex characters, the testicle alone being responsible for hormone production in the male toad.

According to *Champy* (1921), who has studied the changes in the testicle of *Triton alpestris* for two years, real interstitial cells are absent. But Champy found in the testicle connective tissue cells which can store lecithin; they are regarded as homologous with the interstitial cells of other amphibians and vertebrates. The lecithin is not stored until after the spermatozoa are formed, and after the external signs of heat have already appeared. Champy inhibited in *Triton alpestris* the completion of spermatogenesis experimentally by inanition during the summer. In this case the external signs of heat also were absent. Champy concluded from his observations that in the triton the interstitial cells have not the endocrine function such as was demonstrated by Ancel and Bouin in other vertebrates, but that in the animal in question this function is performed by the generative part of the testicle only. The same conclusions were drawn by *Champy* (1908) for *Rana esculenta*. He found that the interstitial tissue in the testicle of this animal attains its climax in autumn when spermatogenesis ceases. The interstitial cells assume at that time the appearance of glandular cells, which they lose more or less suddenly in the following July when spermatogenesis begins again. The statement made by Champy about *Rana esculenta* does not agree with those of various authors about other frogs and *Bufo vulgaris*, where the curve of growth of the interstitial tissue is more or less parallel to the curve of the generative part (*Fig.* 93). The difficulties in the way of our theory arising from observations like those of Champy, which diverge so much from those on other amphibians, are the same as those already dealt with in discussing the seasonal changes in the testicle of mammals. The objection may also be made that the decrease of interstitial tissue during heat in *Rana esculenta* is only an apparent one. Champy's observation that the interstitial cells assume the character of glandular cells only after the completion of spermatogenesis does not justify this objection.

Similar observations were made by *Humphrey* (1921) on the Urodele testis. He stated that lipoid inclusions appear in the interstitial cells only after the spermatozoa have left the testicle; after the degeneration of the seminiferous part the interstitial cells disappear. Like Champy, Humphrey concluded that the interstitial cells in the Urodele testis have no bearing either on the spermatogenesis or on the nuptial changes. Pérez considers the interstitial cells of the triton as phagocytes without any relation to the internal secretion.

A statement which is in complete contradiction to that of Champy and Humphrey was lately made by *Aron* (1921), a pupil of Bouin, on another triton, *Molge cristata*. Here the male assumes in spring a nuptial apparel, consisting of a comb on the back, and other characteristics concerning the colouring of the skin; the nuptial characters disappear in May or June. No interstitial cells of a glandular nature are to be found in the testicle. But at the time of heat there is near the hilus of the testicle a tissue with rich fatty inclusions, which can be easily recognised by its reddish-yellow colour.[1] This tissue is formed of spermatic cysts in which the cells of Sertoli had undergone a peculiar transformation. These cells proliferate,

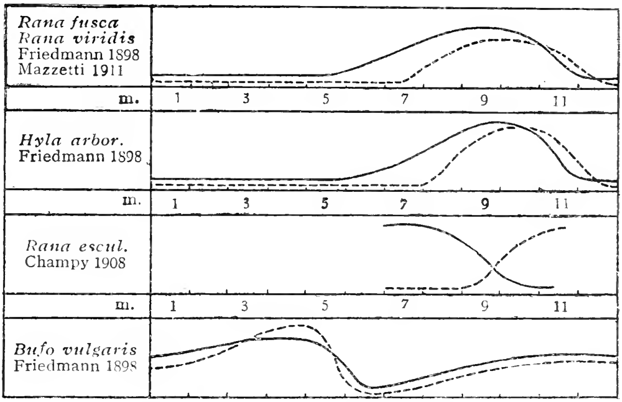


FIG. 93.—*Diagram: Cyclic development of generative and interstitial tissue of the testicle of amphibians.*—Plain lines indicate generative tissue; dotted lines interstitial tissue. Parallelism in Rana fusca and viridis, in Hyla arborea and Bufo vulgaris. No parallelism in Rana esculenta (as in the mole, see Fig. 91.)—From Rasmussen.

---

[1] I am indebted to Dr. Wagner for having demonstrated this fatty body to me both *in situ* and microscopically.

and their protoplasm becomes filled with big granulations staining with osmic acid. Finally the whole cyst is charged with these cells. As was previously observed by Champy, "corpora lutea" of some kind are formed in the testicle. As Aron points out, this glandular paratesticular tissue develops and persists during the whole time of heat, and its regression begins at the same time as regression of the nuptial features sets in. Experiments performed by Aron on this species are of great interest. It has already been shown in the triton that castration leads to rapid disappearance of the nuptial characters. Now Aron succeeded in destroying the glandular paratesticular tissue by galvanocauterization at the beginning of heat. This operation was successful in several cases; a rapid and complete regression of the nuptial characters followed. The histological examination showed that the spermatic part of the testicle was intact. We see that the latter alone is not sufficient to prevent castration effects from occurring. If only an incomplete destruction of the paratesticular tissue was made, there were no changes in the nuptial characters.

Objections have been made by Champy to the experiments of Aron. The various papers of *Champy* (1922) and *Aron* (1922) may be consulted.

Lately *Kolmer and Koppányi* (1923 a, 1923 b) have demonstrated that in *Pleurodeles Waltli* there is a special organ near the testicle consisting almost exclusively of interstitial cells, though islets of generative tissue can be found also in this special organ. It is scarcely possible to say anything about the physiological bearing of this organ.

The results obtained by *Lauche* (1915) in experiments with partial castration on the frog must also be mentioned. A small testicular fragment left in the body hypertrophied and attained the volume of two normal testicles; in reality there was an hypertrophy up to about the volume of one testicle, as the tubules of the regenerated organ were very distended. In other experiments only one testicle was removed; the remaining testicle showed no hypertrophy. Also no signs of hypertrophy occurred when one whole testicle and a fragment of the second testicle were left in the body. We thus see that the case of the frog is very different from that of the mammal, in which there is no hypertrophy of a testicular fragment, but in which an apparent hypertrophy of the remaining testicle after unilateral castration may be observed. As Lauche points out, the hypertrophy of the testicular fragment in the frog is caused especially by a proliferation of the generative cells within the seminiferous tubules. He concludes from his experiments that this hypertrophy of the generative elements is to be considered as compensatory in regard to the endocrine function of the testicle. But I think that the great difference in the behaviour of the remaining testicle, or of the testicular fragment in mammals and in the frog, is sufficient to show that the factor here involved is not simply the need of hormones, but something else which is not yet known to us; it seems very likely that a variety of factors come into play.

Patzelt (1923) has observed a frog with testicular atrophy and far-going degenerative changes in the seminiferous tubules. The interstitial cells were well developed and likewise the sex characters such as the pads and the vasa deferentia with their enlargements. The fatty bodies were abnormally voluminous.

4. Birds.

For the purpose of a comparative physiological study of the problem before us, investigations on birds should be of special interest, since in this class the dependence of the sexual characters upon the sexual glands is particularly striking. There is, moreover, in many species of birds a cyclic change in the appearance of the external sexual characters. Those who have described the histology of the testicle in birds do not agree upon the question as to the quantity in which interstitial cells are present, or indeed as to whether they occur at all. They disagree also in regard to the data concerning time relations. Detailed investigations on all these questions have been made in the last few years by Boring and Pearl, by Pézard, Morgan, Nonidez, Massaglia, Punnett and Pease, and still more recently by Courrier and Benoit in Bouin's laboratory.

One of the first studies on the interstitial cells in the testicle of the cock was made by *des Cilleuls* (1912). He found the interstitial tissue in the first weeks to be not very well developed; this is the time when the sexual characters which depend upon the sexual glands have not yet manifested themselves. Des Cilleuls reports that at about the forty-fifth day the connective tissue cells begin *en masse* to transform themselves into polyhedric interstitial cells disposed around the blood vessels. At this time the development of such sexual characters as the head apparel also begins. Des Cilleuls concluded from his observations that there is in the cock a parallelism in the development of the interstitial tissue and that of the sexual characters.

The detailed investigations made by *Boring and Pearl* (1917) are opposed to these observations of des Cilleuls. Boring and Pearl examined more than 60 birds from chickens just hatched to eighteen-months-old cocks. In the former they found a small number of interstitial cells, whereas in older birds interstitial cells were never detected. According to Boring and Pearl the interstitial cells in the testicle of the cock disappear at the age of about six months. They think that the observers who found interstitial cells in the testicle of the cock (des Cilleuls, Mazzetti and Reeves) were misled by small pieces of tubules surrounded by connective tissue. Boring and Pearl observed in their preparations several places which resemble the illustrations of groups of interstitial cells. They point out "that the only way to be sure of interstitial cells is to use a differential stain." Boring and Pearl claim to have used such a stain, since they employed osmic acid for blackening the fat and several differential stains for secretion granules of a protein nature, and they say that there is "no possibility of missing secreting cells when these stains are used, if there are any present." Boring and Pearl conclude from their observations that true interstitial cells are not a necessary or a constant element in the testicle of the cock. Basing their position on these histological and other observations made by them on the gonads of hermaphrodite birds (1918) they concluded that the interstitial cells have probably no influence on the development of the sexual characters in the fowl.

The question was examined also by *Pézard* (1918, pp. 109–117) who confirmed the statement of des Cilleuls, Reeves, Boring and Pearl as to the presence of interstitial cells in the testicle of the young chicken. But like Boring and Pearl, Pézard states that at the end of the second and at the beginning of the third month the interstitial tissue decreases; as he points out, this decrease is possibly only an apparent one, as by this time the generative part is more markedly increased than the interstitial tissue. The interstitial tissue continues to decrease, whereas the seminiferous tubules increase further and enter upon spermatogenesis. At the age of eight months the interstitial cells have almost disappeared. Pézard supposes that the development of the sexual characters in the cock is not parallel to the development of the interstitial tissue: the discordant growth of the comb and the development of the sexual instincts take place at a time when the interstitial tissue is already nearly at the minimum. As the discordant growth of the comb and the development of the sexual instincts can take place only when the hormones of the testicle enter without interruption into the blood, Pézard concluded from his observations that the sexual characters in the cock are formed and preserved by hormones arising not in the interstitial cells but in the generative part of the testicle.

Against the conclusions of Boring, Pearl and Pézard the same objection can be made as in the cases of the mole and *Rana esculenta,* i.e., that the decrease of the interstitial tissue in the testicle of the growing cock is only an apparent one. The testicle increases enormously owing to the development of the seminiferous tubules, and if the volume of the interstitial tissue remains unaltered or even markedly increases, a single microscopical preparation will always give the impression that the insterstitial tissue decreases as compared with what is found in the just hatched or young chicken, whereas there may be in reality only a distribution of the interstitial tissue in an enlarged space.

A detailed study of the interstitial tissue in the cock as made by *Benoit* (1922) showed that this objection is justified. Benoit claims that the investigators drew erroneous conclusions about the interstitial cells in the cock, owing to an insufficiency in their methods. According to Benoit the interstitial cells of the cock acquire the appearance of glandular cells at an age of about three months. A quantitative study of the question reveals that the total mass of interstitial tissue increases enormously, though there is seemingly a decrease when judged from a single microscopical preparation. *Benoit* (1922 d) stated that at an age of two and a half months when, according to Pézard, the interstitial tissue decreases, there is in reality an increase of about three times compared to that at an age of two weeks. At about seven months the total mass of glandular interstitial cells is about 24 times greater, and in the fully-grown cock the increase may be one of 86 times. But there *seems* to be less interstitial tissue as the generative tissue has increased more than 1000 times. The result is contrary to what was supposed by Pézard; the discordant growth of the sex characters is concomitant with the development not only of the generative tissue but also with that of the interstitial cells.

Lately *Massaglia* (1921) repeated the experiments of Bouin and Ancel on the rooster. He performed ligation and resection of the vas deferens in birds of different ages. Contrary to the authors mentioned above, he stated that interstitial cells are present also in the testicle of the adult normal cock. He found in the interstitial cells numerous small fatty granules and mitochondria well stained by acid fuchsin. After ligation and resection of the vas deferens a marked atrophy of the seminiferous tubules occurred, whereas the interstitial cells remained normal or increased in number. Nevertheless the sexual characters of the animals remained normal, or in the case of young birds developed normally. In some experiments Massaglia removed the degenerated testicle; after this signs of castration became visible. Massaglia considers the elaboration of the fatty granules and of mitochondria as a proof of the conception that the interstitial cells have the character of secretory cells, and he concluded from his experiments that the endocrine function of the testicle in the cock is performed by the interstitial cells. Further Massaglia points out that no fact exists which supports the conception that the endocrine function is carried out by the spermatogenetic cells.

Against the experiments of Massaglia the objection might be made that the seminiferous tubules still contained spermatogenetic cells after ligation, and that these produced the hormones; it is the same objection as that which we have dealt with in describing the experiments on mammals. But I should like to repeat here that it is very improbable that such deep-seated changes as those occurring in the seminiferous tubules after ligation could have no effect on the organism, if the seminiferous tubules were really endocrine in function. This is why I consider the conclusions of Massaglia to be justified, although I think it is still necessary to continue the experiments further.

A degeneration of the seminiferous tubules associated with an enormous increase of the interstitial tissue was observed also by *Guyer* (1912) in hybrids between the guinea and the common fowl, and by *Poll* (1920 a, 1920 b) in hybrids between pea and guinea fowl. It would be difficult to say whether the hybrids showed a "normal" plumage or a "normal" sexual behaviour, both having been different from those of any other race; only a detailed analysis and experimental investigation could give evidence on this point. But it seems that in the cases of both Guyer and Poll the sexual behaviour of the hybrids was different from that of the ordinary "castrate," and that there was consequently an internal secretion of the testicle.

We have no detailed knowledge of the changes the testicle of the cock undergoes after transplantation. According to Foges and Pézard the seminiferous tubules in the engrafted testicle of the cock do not degenerate. Also Massaglia found in one case numerous spermatozoa in the seminiferous tubules in small fragments transplanted on to the peritoneum; the interstitial cells were normal. The bird showed diminished sexual instincts; Massaglia is disposed to explain this by the small number of interstitial cells which were present in the body. It may be that the quantity was so small that the effect produced was beneath the threshold, and that the bird was on the way to become a capon.

As to the function of the interstitial cells in birds the experiments of *Ceni* (1909) on drakes should also be recorded here. *Ceni* (quoted from *Boring and Pearl,* 1917) removed the cerebral hemispheres from drakes; the interstitial tissue increased, whereas the seminal tubules underwent a decrease. The sex characters remained undeveloped. He does not state whether this hypertrophied interstitial tissue consisted of connective tissue or of epithelioid interstitial cells. The "interstitial tissue" is a very complex formation, in which cells of Leydig are intermingled with simple connective tissue cells. More "interstitial tissue" does not imply more active epithelioid glandular cells of the type of Leydig, and by ignoring this fundamental consideration the discussion of the problem becomes impossible.

We have some further knowledge of the interstitial cells derived from the study of other birds such as the sparrow, canary, pheasant and jackdaw. The data accumulated concern the cyclic changes in the testicle occurring during heat, when the testicle in many birds increases to a very considerable degree. (For details see *Marshall*, 1922, p. 22). *Loisel* (1902 b) recorded that in the house sparrow and in another species of sparrow from Madagascar the spermatogenetic cells and the cells of Sertoli, when heat is approaching, are full of fatty granules, whereas no signs of secretory activity are to be seen in the interstitial cells. From these and similar observations on other species of birds Loisel concluded that the endocrine function of the testicle must be ascribed to the spermatogenetic cells and to the cells of Sertoli, and that heat is brought about by the endocrine function of these cells only, not by that of the interstitial cells. But, on the other hand, Loisel himself mentioned that in the canary fatty granules occur also in the interstitial cells, which are present in small numbers. Further, Loisel observed signs of secretory activity in the interstitial cells of the sparrow during embryonic development. Long before the formation of seminiferous tubules, long before the sexual differentiation of the sexual gland, he found interstitial cells packed full with fatty granules besides the cells of the germ epithelium. But he records that these cells eventually decrease in number and disappear finally in the testicle of the adult (1902 a).

Observations on the interstitial cells in the testicle of the silver and the golden pheasant have been made by Pézard. Before puberty the interstitial cells are very numerous, but as in the cock they disappear almost completely when the first spermatogenesis is completed, i.e., when puberty is attained; this takes place during the first great moult in spring and summer. Observations on the interstitial cells of the pheasant are all the more interesting as the sexual behaviour of this bird undergoes cyclic changes from the time of rest to that of heat. Pézard stated that in the golden pheasant the interstitial cells again increase in number during sexual inactivity when the generative part of the testicle assumes an almost embryonic appearance. But I think that here we have to do with an apparent change in the number of the interstitial cells. This is why I do not agree with Pézard, who thinks that in birds the interstitial cells are merely a factor in spermatogenesis, whereas the other sexual characters of birds are formed and preserved, according to Pézard, by an hormonic action of the spermatogenetic cells or of the cells of Sertoli.

Lately *Benoit* (1922 a), a pupil of Bouin, has made observations on different species of birds, and concluded that there is a close correlation between the nuptial plumage and the interstitial cells, whereas no such correlation exists between the sex character and the generative part of the testicle. Different objections have been made by *Pézard* (1923 a).

Investigations on the cyclic changes of the interstitial tissue in birds have been made by *Watson* (1919). The histological observations of Watson on the greenfinch are of interest in this connection. As in the mole, the greenfinch shows a relative decrease in the number of interstitial cells during oestrus. But it seems that marked cyclical changes of a *cytological* nature take place also in the interstitial tissue. This question must be investigated in greater detail and by special cytological methods; but what Watson stated, indicates that the fibrous tissue cells gradually disappear in the interstitial tissue, and are replaced by another type of cell. These seem to be the true interstitial cells massed together in the angles formed by the greatly increased tubules. Similar statements were made by *Benoit* (1923 a).

Certainly more detailed histological investigations are necessary. First, it is essential to define in a stricter sense what kind of cells precisely are understood under the name "interstitial cells," and in every case. Differential histological methods should be applied more closely. Secondly, further criticism is necessary in regard to all questions concerning the quantity of the interstitial cells.

On the other hand it is unjustifiable and arbitrary to declare that some tissue cannot be considered as having an endocrine function because it is "connective tissue." The notion of connective tissue is very indefinite, and where such tissue is present it may undergo cyclic changes like the interstitial cells in mammals. It suffices to glance at *Fig.* 57 where a tissue which seems to be simply connective step by step becomes transformed into an agglomeration of interstitial cells. There is no fundamental reason why cells which are connective tissue cells by origin should not form an organ of internal secretion, and if further embryological investigation should show that, contrary to Rubaschkin's view, the interstitial cells are really mesenchyme cells, as supposed by Bouin and Ancel, this need not modify our conclusions as to the endocrine function of the interstitial cells of mammals, based especially on the experimental observations which are above recorded.

A new point has lately been made by Goodale. As the interstitial cells containing granules are eosinophile cells, *Goodale* (1919) is disposed to consider them as leucocytes. He remarks that similar cells are to be found also in other organs, such as the thymus of the moulting drake, where they are abundant, and in the thyroid, pineal and pituitary glands, where they have been found, though they are not common. The question has been taken up by *Nonidez* (1920). He studied the gonads of embryos and young chicks by differential staining methods; he concluded from his observations that the granule-laden interstitial cells are derived from primitive blood cells or hæmocytoblasts, or in other words from mesenchyme cells. The granule-laden interstitial cells are connected with typical eosinophile granulocytes (or leucocytes) by a graded series of stages. Besides these interstitial cells primitive undifferentiated mesenchyme cells and small lymphocytes are also present in the intertubular space of the testicle of the adult bird. These may become transformed, according to Nonidez, in the adult bird into several types of cells, also into cells closely resembling the interstitial cells in the testicle of mammals; these cells have a finely granular acidophile cytoplasm; they are vacuolated and contain fat; the nucleus is round. They are not, however, a constant element in the testes of the adult bird, and may be absent. Nonidez considers them to be wandering cells. As to the function of all these different types of cells Nonidez thinks that neither the granular cells, nor the interstitial cells derived from the small lymphocytes, can have a specific endocrine function. The granulocytes and the modified small lymphocytes are not restricted to the gonads occurring elsewhere in the general mesenchyme; Nonidez says that the small lymphocytes may perhaps have some bearing on the development of the sex characters in the young bird, but their inconstancy in the testis of the adult bird shows that they are not necessary for the maintenance of these characters. It seems likely to Nonidez that the fat stored in the interstitial cells derived from the small lymphocytes may be used by the cells within the seminal tubules, or even transformed into a specific hormone which exerts its influence on the sex characters. It may be remembered that *Bouin and Ancel* (1905 c) consider the interstitial cells of the mammal to be derivatives of the cells of lymphoid nodules disposed between the seminal tubules. A similar view was held by *Champy* (1913) for the frog, and by *Courrier* (1922 b) for the *Gasterosteus*.

I should like to point out certain objections of a general order to Goodale and Nonidez's conception. I have myself no experience of birds, but what we learned in our laboratory for mammals conforms with some of Nonidez's observations. First, the interstitial cells in the testicle of the mammal seem to be of very different types; a glance at *Fig.* 56 (especially G) conveys this idea. The size, shape and inclusions of the interstitial cells are manifold. Further, a detailed research on the inclusions of the interstitial cells of the mammals, which Wagner has undertaken in our laboratory, also gave some cytological results very similar to those of this author. But we may still ask whether there is sufficient evidence for the claim that the different types of interstitial cells are merely elements common to all other organs. What is proved by Nonidez is only the fact that the different types of interstitial cells may be derived, like the blood cells, from mesenchyme cells, and further that the interstitial cells are cytologically very similar to cells common to other organs. This does not mean that the interstitial cells can be *identified* with certain types of blood cells or with similar cells in other organs *in regard to their function*. I agree that the question as to the function of the interstitial cells in birds and their bearing on the internal secretion of the testicle is a very complex one, more complicated than it might seem at first. The cytologist will play an important part in the elucidation of this question. But it would be a great mistake to build up a theory as to the seat of hormone production in the testicle on the basis of morphological observations only. It may be also mentioned that according to *Nonidez* (1922) certain interstitial cells in birds are formed from young seminiferous tubules which undergo degeneration. *Benoit* (1923 b) is even of the opinion that possibly *all* interstitial cells arise in the cock during embryonic development and during youth in a similar manner, i.e., that they are all of an epithelial origin.

A new paper of *Ceni* (1922) may be mentioned here. He claims to have given new proofs of the endocrine function of the generative part of the testicle in the cock.

BIBLIOGRAPHY FOR CHAPTER IV.

[* *Not seen in the original.*]

Adler (Leo) 1914. Über Jodschädigungen der Hoden. *Arch. f. Pathol. u. Pharmakol.*, 75, p. 362.

Albers-Schönberg. 1903. Über eine bisher unbekannte Wirkung der Röntgenstrahlen auf den Organismus der Tiere. *Münch. mediz. Wochenschr.*, p. 1859.

Ancel *et* Bouin (*or* Bouin *et* Ancel). 1903a. Recherches sur les cellules interstitielles du testicule des mammifères. *Arch. de Zool. expérim.*, 1.

—— 1903b. Recherches sur le rôle de la glande interstitielle du testicule. Hypertrophie compensatrice expérimentale. *C. R. de l'Acad. Sc.*, 137, p. 1289.

—— 1903c. Histogenèse de la glande interstitielle du testicule chez le porc. *C. R. de la Soc. de Biol.*, 55, p. 1680.

—— 1903d. Sur la signification de la glande interstitielle du testicule embryonnaire. *C. R. de la Soc. de Biol.*, 55, p. 1682.

*—— 1904a. Sur l'existence de deux sortes de cellules interstitielles chez le cheval. *C. R. de la Soc. de Biol.*, 56, p. 81.

—— 1904b. Tractus génital et testicule chez le porc cryptorchide. *C. R. de la Soc. de Biol.*, I-er sem.; 56, p. 281.

—— 1904c. La glande interstitielle a seule, dans le testicule, une action générale sur l'organisme. *C.R.de l'Acad. Sc.*, 138, p. 110.

—— 1904d. L'apparition des caractères sexuels secondaires est sous la dépendance de la glande interstitielle. *C. R. de l'Acad. Sc.*, 138, p. 168.

—— 1904e. L'infantilisme et la glande interstitielle du testicule. *C. R. de l'Acad. Sc.*, 138, p. 231.

*—— 1904f. Recherches sur la structure et la signification de la glande interstitielle dans le testicule normal et ectopique du cheval. *Arch. de Zool. expér. et génér.*, 2.

—— 1904g. Recherches sur la signification physiologique de la glande interstitielle du testicule chez les mammifères. *Jl. de Physiol. et Pathol. Génér.*, 6.

—— 1905a. La glande interstitielle du testicule et la défense de l'organisme. 1. Hypertrophie ou atrophie partielle de la glande interstitielle au cours de certaines maladies chez l'homme. *C. R. de la Soc. de Biol.*, 58, I-er sem., p. 553.

—— 1905b. 2. Hypertrophie ou atrophie partielle de la glande interstitielle dans certaines conditions expériment. *C. R. Soc. Biol.*, 58, I-er sem., p. 554.

*—— 1905c. La glande interstitielle du testicule chez le cheval. *Arch. de zool. expér. et génér.*

—— 1923. Les cellules séminales ont-elles une action sur les caractères sexuels? *C. R. de la Soc. de Biol.*, 89, p. 175.

Aron. 1921a. Sur le conditionnement des caractères sexuels secondaires chez les Batraciens Urodèles. *C. R. de l'Acad. d. Sc.*, 173, p. 482.

—— 1921b. Sur l'existence et le rôle d'un tissu endocrinien dans le testicule des Urodèles. *C. R. de l'Acad. d. Sc.*, 173, p. 57.

—— 1921c. Sur la glande interstitielle du testicule embryonnaire chez les mammifères. *C. R. de la Soc. de Biol.*, 85, p. 107.

—— 1922a. Signification morphologique du tissu glandulaire end. du testic. des Urodèles. *C. R. de l'Acad. d. Sc.*, 174, p. 332.

—— 1922b. Sur le déterminisme des caractères sexuels second. chez les Urodèles. *C. R. de l'Acad. d. Sc.*, 174, p. 709.

—— 1922c. Sur le développement des caractères sexuels primaires chez les Urodèles. *C. R. de l'Acad. de Sc.*, 174, p. 1568.

Benda. 1921. Bemerkungen zur normalen u. pathol. Histologie der Zwischenzellen des Menschen u. der Säugetiere. *Arch. f. Frauenkunde*, 7.

Benoit. 1922a. Sur le conditionnement physiol. de la parure nuptiale périodique chez les Oiseaux. *C. R. de l'Acad. de Sc.*, 174, p. 701.

—— 1922b. Sur les cellules interstitielles du testicule du coq domestique. Evolution et structure. *C. R. de la Soc. de Biol.*, 87, p. 1382.

—— 1922c. Sur une méthode permettant de mesurer la masse absolue du tissu interstitiel testiculaire. *C. R. de la Soc. de Biol.*, 87, p. 1385.

—— 1922d. Sur les rapports quantitatifs entre le tissu interstitiel testiculaire, le tissu séminal et la masse du corps chez les oiseaux et quelques mammifères. *C. R. de la Soc. de Biol.*, 87, p. 1387.

—— 1923a. Sur les modifications cytologiques des cellules interstitielles du testicule chez les oiseaux à activité sexuelle périodique. *C. R. de la Soc. de Biol.*, 88, p. 202.

—— 1923b. Sur l'origine des cellules interstit. dans le testicule du coq domestique. *C. R. de l'Acad. d. Sc.*, 177, p. 412.

Berberich *und* Jaffé. 1922. Die Hoden bei Allgemeinerkrankungen. *Frankf. Ztsch. f. Pathol.*, 27, p. 395.

Berblinger. 1921. Über die Zwischenzellen des Hodens. *Verhandl. d. deutsch. pathol. Ges.*

Bergonié *et* Tribondeau. 1904. Action des Rayons X sur le testicule du rat blanc. *C. R. de la Soc. de Biol.*, 57, Sec. sem., p. 592.

—— See also *C. R. de la Soc. de Biol.*, 1904, 2 sem., p. 400, 592, 595; 1905, I. sem., p. 154, 155, 282, 678, 1078.

*Bertholet. 1913. *Action de l'alcoolisme chronique sur les organes de l'homme et sur les glandes reproductrices.* Lausanne.

*—— 1913. *Petit atlas manuel des altérations anatomo-pathologiques des organes dans l'alcoolisme chronique.* Paris.

BIEDL. 1913. *Innere Sekretion*, 2. Aufl. Berlin-Wien.

BOLOGNESI. 1921a. Sulla scontinuità delle vie spermatiche. *Arch. Ital. di Chirurgia*, 3, p. 207.

—— 1921b. Transplantations testiculaires séminifères et interstitielles. *Jl. d'Urologie*, 12, p. 153.

BORING *and* PEARL. 1917. Interstitial cells in the reproductive organs of the chicken. *Anatom. Rec.*, 13.

—— 1918. Hermaphrodite birds. *Jl. of Experim. Zool.*, 25, p. 1.

BOUIN *see* ANCEL.

BRACK. 1921. Über innere männliche Genitalmissbildungen bei einseitiger Nierenaplasie. *Zeitschr. für Urologie*, 15.

—— 1922. Zur pathologischen Anatomie der Leydigzelle. *Virchows Archiv*. 240, p. 127.

BUCURA. 1913. *Geschlechtsunterschiede beim Menschen*. Wien u. Leipzig.

ČEJKA. 1923. Eine Studie über die Genese und Funktion des Interstitiums auf Grund der Untersuchungen an seneszenten Hoden. *Arch. f. mikroskop. Anat.*, 98, p. 524.

*CENI. 1909. L'influenza del cervello sullo sviluppo e sulla funzione degli organi sessuali maschili. *Rivista sper. die Frenatria*, 35, p. 3.

—— 1914. Die höheren Genitalzentren bei Gehirnerschütterung. *Zeitschr. für Sexualwissenschaft*, 1.

—— 1922. Der Einfluss de Sehkraft auf die Funktion des Hodens und auf die äusseren Geschlechtscharaktere. *Arch. f. Entw.-Mech.*, 51, p. 507.

CHAMPY. 1908. Notes sur les cellules interstitielles du testicule chez les batraciens anoures. *C. R. de la Soc. de Biol.*, 64, p. 895.

*—— 1913. Recherches sur la spermatogénèse des Batraciens et les éléments accessoires du testicule. *Arch. Zool. exp. et gén.* (quoted from Courrier, 1922c).

*—— 1921. Sur les corrélations entre les caractères sexuels mâles et les divers éléments du testicule chez les amphibiens (étude sur triton alpestris). *C. R. de l'Acad. d. Sc.*, 172, p. 482.

—— 1922a. Sur le déterminisme des caractères sex. chez les Tritons. *C. R. de l'Acad. d. Sc.*, 174, p. 192.

—— 1922b. Sur les conditions de la genèse de l'harmozone sexuelle chez les Batraciens anoures. *C. R. de l'Acad. d. Sc.*, 174, p. 497.

—— 1922c. Etude expérimen. sur les différences sexuelles chez les Tritons (Triton alpestris Laur.). *Arch. de Morphol. Génér. et Expér.*

*—— 1923. Observations sur les caractères sexuels chez les poissons. *C. R. de la Soc. de Biol.*, 88, p. 414 (quoted from Van Oordt).

—— See also 1923. *C. R. de la Soc. de Biol.*, 88, pp. 55, 1007, 1186, 1275; 89, p. 223 (not mentioned in the text).

des Cilleuls. 1912. A propos du déterminisme des caractères sexuels secondaires chez les oiseaux. *C. R. de la Soc. de Biol.*, 73, p. 371.

Courrier. 1921a. Sur le conditionnement des caractères sexuels secondaires chez les poissons. *C. R. de la Soc. de Biol.*, 85, p. 486.

—— 1921b. Sur l'existence d'une glande interst. dans le testicule des poissons. *C. R. de la Soc. de Biol.*, 85, p. 939.

—— 1921c. Glande interstitielle du testicule et caractères sexuels secondaires chez les poissons. *C. R. de l'Acad. des Sc.*, 172, p. 1316.

—— 1922a. Sur l'indépendence de la glande séminale et des caractères sexuels secondaires chez les poissons. Etude expérimentale. *C. R. de l'Acad. des Sc.*, 174, p. 70.

—— 1922b. Etude préliminaire du déterminisme des caractères sexuels secondaires chez les poissons. *Arch. d'Anat., d'Histol. et d' Embr.*, 2, p. 115.

—— 1922e. Sur l'existence d'une glande interst. dans le testicule des Blennies. *Bulletin de la Soc. Zool. de France*, 47, p. 458.

—— 1923a. Cycle annuel de la glande interstit. du testic. chez les Chéiroptères. Coexistence du repos séminal et de l'activité génitale. *C. R. de la Soc. de Biol.*, 88, p. 1163.

—— 1923b. Sur le cycle de la glande interstitielle et l'évolution des caractères sexuels secondaires chez les mammifères à spermatogénèse périodique. *C. R. de la Soc. de Biol.*, 89, p. 1311.

Crew. 1922. A suggestion as to the cause of the aspermatic condition of the imperfectly descended testis. *Jl. of Anatomy*, 56, p. 98.

Exner. 1903. Physiologie der männlichen Geschlechtsfunktionen. *Handbuch der Urologie*, I., Wien, p. 288 u.ff.

Gley. 1922. Sénescence et endocrinologie. Extrait du *Bullet. de l'Acad. de Méd.*

Goddard. 1920. Hypertrophy of the interstitial tissue of the testicle in man. *Jl. of Anatomy*, 54, p. 173.

Goette. 1921. *Beitrag zur Atrophie des menschlichen Hodens.* Jena.

Goodale. 1919. Interstitial Cells in the Gonads of domestic fowl. *Anat. Rec.*, 16.

Guyénot *et* Ponse. 1923a. Inversion expérimentale du type sexuel dans la gonade du crapaud. *C. R. de la Soc. de Biol.*, 89, pp. 4–7.

—— 1923b. L'organe de Bidder du crapaud est-il indispensable à la vie? *C. R. de la Soc. de Biol.*, 89, pp. 63–65.

—— 1923c. Nouveaux résultats concernant le déterminisme des caractères sexuels secondaires du crapaud (Bufo vulgaris). *C. R. de la Soc. de Biol.*, 89, pp. 129–131.

*Guyer. 1912. Modifications in the testes of hybrids from the guinea and the common fowl. *Journ. of Morph.*, 23, p. 45.

HANSEMANN. 1895. Über die sogenannten Zwischenzellen des Hodens und deren Bedeutung bei pathologischen Veränderungen. *Virchows Archiv*, 142.

—— 1896. Über die Zwischenzellen des Hodens. *Arch. f. Physiol.*, p. 176.

HARMS. 1914. *Experimentelle Untersuchungen über die innere Sekretion der Keimdrüsen und deren Beziehung zum Gesamtorganismus.* Jena.

HEDINGER. 1920. Über Wucherungen der Leydigschen Zwischenzellen bei Chorionepitheliom des Hodens. *Zeitschr. f. angew. Anat. u. Konstitutionslehre*, 7, p. 55.

HOFSTÄTTER. 1923. Experimentelle Studie über die Einwirkung des Nicotins auf die Keimdrüsen und auf die Fortpflanzung. *Virchows Archiv*, 244, p. 183.

HOUSSAY. 1907. Variations expérimentales. Etudes sur six générations de poules carnivores. *Arch. de Zool. exp. et gén.*, 6, p. 137.

HOUSSAY *y* HUG. 1923. Influencia de las lesiones infundibulo-hipotalàmicas sobre el crecimiento. *Revista de la Asociacion Méd. Argentina*, 36.

*HUMPHREY. 1921. *Amer. Jl. of Anat.*, 29.

JAFFÉ. 1922. Path.-anat. Veränderungen der Keimdrüsen bei Konstitutionskrankheiten insbesondere bei der Pädatrophie. *Frankf. Ztschr. f. Pathol.*, 26, p. 250.

KASAI. 1908. Über die Zwischenzellen des Hodens. *Virchows Archiv*, 194.

KITAHARA. 1923. Über die Entstehung der Zwischenzellen der Keimdrüsen des Menschen und der Säugetiere und über deren physiologische Bedeutung. *Arch. f. Entw.-Mech.*, 52, p. 550.

KOHN (Alfred). 1914a. Morphologische Grundlagen der Organotherapie (Section "Generationsorgane," p. 84 u. 85). In Jauregg und Bayer, *Lehrbuch der Organotherapie.* Leipzig.

—— 1914b. Synkainogenese. *Arch. f. Entw.-Mech.*, 39, p. 112.

—— 1920. Der Bauplan der Keimdrüsen. *Arch. f. Entw.-Mech.*, 47, p. 95.

KOLMER *und* SCHEMINZKY. 1922. Finden sich Zwischenzellen nur bei den höheren Wirbeltieren? *Pflügers Arch.*, 194, p. 352.

—— *und* KOPPANYI. 1923a. Über den Hoden von Pleurodeles Waltli (Michah). *Anat. Anz.*, 56, p. 410.

—— —— 1923b. Über die Entwicklung des Pleurodeleshodens und der in ihm auffallenden Zwischenzellenbildungen. *Zeitschr. f. Anat. u. Entw.-Gesch.*, 69, p. 304.

KOSTITCH. 1921. *Action de l'alcoolisme expérimental sur le testicule.* Thèse méd. Strasbourg.

KRONFELD. 1921. Zur Morphogenese des Zwischengewebes der Keimdrüsen, nach den Untersuchungen *Guileras. Arch. f. Frauenkunde,* 7.

KROPMAN. 1923. Untersuchungen über Partialkastration an weissen Mäusen. *Skand. Arch. f. Physiol.,* 44, p. 76.

KUNTZ. 1921. Degenerative changes in the seminal ephithelium and associated hyperplasia of the interstitial tissue in the mammalian testis. *Endocrinology,* 5.

KYRLE. 1911. Über die Regenerationsvorgänge im tierischen und menschlichen Hoden. *Sitz.-Ber. d. Mathem.-Naturwissensch. Klasse d. Akad. d. Wissensch.,* Wien, 120, p. 3.

*—— *und* SCHOPPER. 1914. Untersuchungen über den Einfluss des Alkohols auf Leber und Hoden des Kaninchens. *Virchows Arch.,* 215.

—— 1920. Über die Hypoplasie der Hoden im Jugendalter und ihre Bedeutung für das weitere Schiksal der Keimdrüsen. *Wiener kl. Wochenschr.,* No. 9.

LACASSAGNE. 1913. *Etude histologique et des effets produits sur l'ovaire par les rayons X.* Thèse méd. de Lyon.

LAUCHE. 1915. Experim. Untersuch. an den Hoden, Eierstöcken u. Brunstorganen erwachs. u. jugendl. Grasfrösche (Rana fusca Rös.). *Arch. f. mikr. Anat.,* 86.

LEYDIG. 1850. Zur Anatomie der männlichen Geschlechtsorgane und Analdrüsen der Säugetiere. *Zeitschr. f. wissenschftl. Zool.,* 2, 1.

—— 1857. *Lehrbuch der Histologie des Menschen u. der Tiere.* Frankfurt a. M., p. 495.

LIPSCHÜTZ *et* OTTOW. 1920. Sur les conséquences de la castration partielle. *C. R. de la Soc. de Biol.,* 83, p. 1340.

LIPSCHÜTZ. 1921a. Quantitat. Untersuch. über die innersekretor. Funktion der Testikel. *Deutsche med. Wochenschr.,* No. 13.

—— OTTOW *et* WAGNER. 1921b. Nouvelles observations sur la castration partielle. *C. R. de la Soc. de Biol.,* 85, p. 42.

—— OTTOW *u.* WAGNER. 1921c. Über das Minimum der Hodensubstanz, das für die normale Gestaltung der Geschlechtsmerkmale ausreichend ist. *Pflügers Arch.,* 188, p. 76.

—— OTTOW *u.* WAGNER. 1921d. Sur des modifications histologiques subies par des restes du pole inférieur du testicule dans la castration partielle. *C. R. de la Soc. de Biol.,* 85, p. 86.

—— OTTOW *u.* WAGNER. 1921e. Sur des modifications histologiques subies par des restes du pole supérieur du testicule dans la castration partielle. *C. R. de la Soc. de Biol.,* 85, p. 88.

—— OTTOW *u.* WAGNER. 1921f. Sur le ralentissement de la masculinisation das la castration partielle. *C. R. de la Soc. de Biol.,* 85, p. 630.

Lipschütz 1922a. Sur l'hypertrophie du testicule dans la castration unilatérale. *C. R. de la Soc. de Biol.*, 87, p. 60.

—— 1922b. The so-called compensatory hypertrophy of the testicle after unilateral castration. *Jl. of Physiol.*, 56.

—— (*in collaboration with* Ottow, Wagner *and* Bormann). 1922c. On the hypertrophy of the interstitial cells in the testicle of the guinea-pig under different experimental conditions. *Proceed. Roy. Soc.*, 93, p. 132.

—— (*in collaboration with* Wagner, Tamm *and* Bormann). 1922d. Further experimental investigations on the hypertrophy of the sexual glands. *Proc. Roy. Soc.*, 94, p. 83.

—— Wagner *et* Bormann. 1922e. Ralentissement expérimental de la masculinisation. *C. R. de la Soc. de Biol.*, 86, p. 238.

—— *et* Wagner. 1922f. L'hypertrophie des cellules interstitielles, est-elle une réaction compensatrice endocrine? *C. R. de la Soc. de Biol.*, 87, p. 15..

—— *et* Wagner. 1922g. Nouvelles observations sur la fonction endocrine des cellules interstitielles du testicule chez les mammifères. *C. R. de la Soc. de Biol.*, 85, p. 306.

—— Bormann *und* Wagner. 1922h. Über Eunuchoidismus beim Kaninchen in Gegenwart von Spermatozoen in den Hodenkanälchen u. unterentwickelten Zwischenzellen. *Dtsch. medizin. Wochenschr.*, No. 10.

—— Ottow *und* Wagner. 1922i. Über Eunuchoidismus beim Kaninchen, bedingt durch Unterentwicklung des Hodens. *Arch. f. Entw.-Mech.*, 51, p. 66.

—— Wagner *et* Kropman. 1922k. Nouvelles observations sur la quantité minimale de masse testiculaire suffisante pour une masculinisation complète. *C. R. de la Soc. de Biol.*, 87, p. 122.

—— *und* Wagner. 1922l. Über die Hypertrophie der Zwischenzellen. Ihr Vorkommen und ihre Bedingungen. *Pflügers Archiv*, 197, p. 348.

—— 1923a. New experimental data to the question of the seat of the endocrine function of the testicle. *Endocrinology*, 7, p. 1.

—— 1923b. Über die kompensatorischen Reaktionen der Geschlechtsdrüsen. *Skandin. Arch. f. Physiol.*, 43, p. 45.

—— *et* Ibrus. 1923c. Sur la quantité de tissu interstitial dans le testicule du lapin après la castration unilatérale. *C. R. de la Soc. de Biol.*, 88, p. 1259.

—— *und* Ibrus. 1923d. Über die Menge des Zwischengewebes im Hoden des Kaninchens nach einseitiger Kastration. *Skand. Arch. f. Physiol*, 44, p. 237.

—— 1923e. Castration unilatérale chez la Souris blanche. *C. R. de la Soc. de Biol.*, 89, p. 1137. *See also* Kropman *and* Wagner.

LOISEL. 1902a. Sur l'origine embryonnaire et l'evolution de la sécrétion interne du testicule. *C. R. de la Soc. de Biol.*, 54, p. 952.

—— 1902b. Sur le lieu d'origine, la nature et le rôle de la sécrétion interne du testicule. *C. R. de la Soc. de Biol.*, 54, p. 1034.

LUDWIG *und* THOMSA. 1863. Die Lymphwege des Hodens u. ihr Verhältnis zu den Blut- und Samengefässen. *Sitz-Ber. Akad. Wissensch. Wien, Mathem.-Naturwissensch. Kl.*, 46, p. 221.

MARSHALL. 1922. *The physiology of reproduction.* 2nd Edition. London. Ch. IX.

MASSAGLIA. 1921. The Internal Secretion of the testis. *Endocrinology*, 4, p. 547.

*MATTILL *and* CARMAN. 1923. The degeneration of the testis of rats on a milk diet. *Proc. of the soc. f. exp. biol. a. med.*, 20, Nr. 7, p. 420.

MICHON *et* PORTE. 1920a. Etude histologique de six cas de testicules ectopiques. *Lyon Chirurgical.*

—— 1920b. Quelques faits concernant l'histologie du testicule ectopique. *C. R. de la Soc. de Biol.*, 83, p. 1438.

*MYERS. 1915. Histological changes in testes following vasectomy. *Anat. Rec.*, 10, p. 228.

NEMENOV. 1916. Sur l'influence de la roentgenisation des testicules sur la prostate. *Arch. des Sc. Biologiques*, 19.

NONIDEZ. 1920. Studies on the gonads of the fowl. I. Hematopoetic processes in the gonads of embryos and mature birds. *American Jl. of Anat.*, 28, p. 81.

—— 1922. Studies on the gonads of the fowl. III. *Americ. Jl. of Anatomy*, 31, No. 2.

VAN OORDT. 1923. Secondary sex-characters and testis of the ten-spined Stickleback (Gasterosteus pungitius L.). *Kon. Akad. v. Wetensch. te Amsterdam*, 26, p. 309.

PATZELT. 1923. Hypoplasie der Keimdrüsen und das Verhalten der Zwischenzellen bei Rana esculenta. *Arch. f. Mikrosk. Anat. und Entw.-Mech.*, 100, H. 1, 2.

PÉZARD. 1918. *Le conditionnement physiologique des caractères sexuels secondaires chez les oiseaux.* Edition du Bulletin Biologique de la France et de la Belgique. Thèse. Paris.

—— 1919. Castration alimentaire chez les coqs soumis au régime carné exclusif. *C. R. de l'Acad. d. Sc.*, 169, p. 1177.

—— 1922. La Loi du "Tout ou rien" et le gynandromorphisme chez les oiseaux. *Jl. de Physiol. et de Pathol. Génér.*, p. 200 and p. 495.

—— 1923a. Tissu interstitiel et caractères sexuels secondaires des Oiseaux (Réponse à Benoit). *C. R. de la Soc. de Biol.*, 88, p. 245.

—— 1923b. Critique de la théorie de Bouin et Ancel. *C. R. de la Soc. de Biol.*, 88, p. 333.

Poll. 1920a. Pfaumischlinge (Mischlingsstudien VIII.). *Arch. f. mikr. Anat.*, Festschrift Hertwig, p. 365.

—— 1920b. Zwischenzellengeschwülste des Hodens bei Vogelmischlingen. *Beitr. z. path. Anat. u. z. allgem. Pathol.*, 67, p. 40.

Rasmussen. 1917. Seasonal changes in the interstitial cells of the testis in the woodchuck (Marmota monax). *Amer. Jl. of Anatomy*, 21.

—— 1918. Cyclic changes in the interstitial cells of the ovary and testis in the woodchuck (Marmota monax). *Endocrinology*, 2.

Regaud *et* Policard. 1901. Etude comparative du testicule du porc normal, impubère et ectopique au point de vue des cellules interstitielles. *C. R. de la Soc. de Biol.*, 53, p. 450.

Retterer *et* Voronoff. 1923. Structure des testicules d'un chimpanzé et résultats physiologiques de leur greffe. *Journal d'Urologie*, 15, p. 417.

Ribbert. 1890. Über die kompensatorische Hypertrophie der Geschlechtsdrüsen. *Virchows Archiv*, 120.

Rubaschkin. 1912. Zur Lehre von der Keimbahn bei Säugetieren. Über die Entwicklung der Keimdrüsen. *Anatom. Hefte*, 46, p. 345.

Sand. 1918. *Experimentelle Studier over Kφnskarakterer hos Pattedyr.* Kopenhagen.

—— 1921a. Etudes experimentales sur les glandes sexuelles chez les mammiféres. *Jl. de Physiol. et Pathol. Génér.*, I. mem., 19, p. 305.

—— 1921b. II. mém.: Expér. sur la resection du "vas deferens." Ibidem, p. 494.

—— 1921c. III. mém.: Cryptorchidie expérimentale. Ibidem, p. 515.

Schultz (Eugen). 1908. Über umkehrbare Entwicklungsprozesse und ihre Bedeutung für eine Theorie des Vererbung. *Vortr. u. Aufs. üb. Entw.-Mech.*, Heft IV. Leipzig.

*Simmonds. 1909. Über die Einwirkung von Röntgenstrahlung auf die Hoden. *Fortschr. auf d. Gebiet d. Röntgenstrahlen*, 14 (quoted from Steinach, 1912, *Pflügers Archiv*, 144).

—— 1913. Über Mesothoriumschädigung des Hodens. *Deutsche mediz. Wochenschr.*

Steinach. 1912. Wilkürliche Umwandlung von Säugetier-Männchen in Tiere mit ausgeprägt weiblichen Geschlechtscharakteren und weiblicher Psyche. Eine Untersuchung über die Funktion und Bedeutung der Pubertätsdrüsen. *Pflügers Archiv*, 144.

—— 1916. Pubertätsdrüsen und Zwitterbildung. *Arch. f. Entw.-Mech.*, 42, p. 307.

—— 1920. Verjüngung durch experimentelle Neubelebung der alternden Pubertätsdrüse. *Arch. f. Entw.-Mech.*, 46, p. 553.

—— *und* Kammerer. 1920. Klima und Mannbarkeit. *Arch. f. Entw.-Mech.*, 46, p. 391.

TAKAHASHI. 1922. Untersuchungen über die tonisierenden und trophischen Funktionen des Sympathicus. *Pflügers Arch.*, 193, p. 322.

TANDLER *und* GROSS. 1912. Über den Saisondimorphismus des Maulwurfhodens. *Arch. f. Entw.-Mech.*, 33, p. 297.

—— 1913. *Die biologischen Grundlagen der sekundären Geschlechtscharaktere.* Berlin.

THOREK. 1923. Experimental investigations of the rôle of the Leydig, seminiferous and Sertoli cells. (Quoted from manuscript.)

TIEDJE. 1921a. Unterbindungsbefunde am Hoden unter besonderer Berücksichtigung der Pubertätsdrüsenfrage. *Deutsche mediz. Wochenschr.*, 1921, No. 13.

—— 1921b. *Die Unterbindung am Hoden und die "Pubertätsdrüsenlehre."* Jena.

TSUJI. 1920. On the function of thyroid gland with special reference to the effect of variations of diet upon it. *Acta Scholae Med. Univers. imper. Kioto*, 3, p. 713.

VILLEMIN. 1906a. Rayons X et activité génitale. *C. R. de l'Acad. Sc.*, 142, p. 723.

—— 1906b. Sur la régénération de la glande séminale après destruction par les rayons X. *C. R. de la Soc. de Biol.*, 60, I-er sem., p. 1076.

VOINOV. 1905a. Sur le rôle probable de la glande interstitielle. *C. R. de la Soc. de Biol.*, 58, I-er sem., p. 414.

—— 1905b. Les spermatotoxines et la glande interstitielle. *C. R. de la Soc. de Biol.*, 58, I-er sem., p. 688.

WAGNER. 1922. Über die Zwischenzellen und das spermatogene Gewebe in einem Fall von Eunuchoidismus beim Kaninchen. *Arch. f. Entw.-Mech.*, 52, p. 386.

—— 1923. Zur Zytologie der Zwischenzellen des Hodens. *Anat. Anz.*, 56, p. 559.

WAGNER *und* LOEPER. 1923. Über einen weiteren Fall von Eunuchoidismus beim Kaninchen bei normaler Spermatogenese. *Pflügers Archiv*, 198, p. 252.

WALDEYER. 1921. Anatomie der endokrinen Drüsen. *Arch. f. Frauenkunde*, 7, p. 1.

WATSON. 1919. A study of the seasonal changes in avian testes. *Jl. of Physiol.*, 53, p. 86.

*WEICHSELBAUM. 1910. Über Veränderungen der Hoden bei chronischem Alkoholismus. *Verhandl. der Deutsch. Path. Gesellsch.*

WHITEHEAD. 1912a. A microchemical study of the fatty bodies in the interstitial cells of the testis. *Anatom. Record*, 6, p. 65.

—— 1912b. On the chemical nature of certain granules in the interstitial cells of the testis. *Amer. Jl. of Anatomy*, 14, p. 63.

—— 1914. Vital staining of the interstitial cells of the testis. Anatom. Record, 8. (*Proceed. Amer. Assoc. of Anatomists*, 1913.)

WITSCHI. 1921. Der Hermaphroditismus der Frösche und seine Bedeutung für das Geschlechtsproblem und die Lehre von der inneren Sekretion der Keimdrüsen. *Arch. f. Entw.-Mech.*, 49, p. 316.

Chapter V.

The Seat of Production of the Internal Secretion of the Ovary.

A. MAMMALS.

Before entering into the question as to the parts of the ovary which elaborate the internal secretions, and before proceeding to a discussion of the different experiments made to elucidate this problem, we propose to give a short account of the histology and histogenesis of the ovary in so far as this concerns our problem. We do not intend however to discuss in detail questions which are purely histological.

1. The Interstitial Cells of the Ovary.

The histological appearances of the ovary are much more complex than those of the testicle. The subject has been examined by many authors, of whom Sainmont, Aimé, Winiwarter, Fraenkel and Schaeffer, Limon, Seitz, Wallart and Aschner may be especially mentioned. There have been many controversies about the interstitial cells in the ovary. But there can be scarcely any doubt that interstitial cells homologous with those in the testicle are to be found in the ovary of all the species of mammals which have been investigated. The number of these cells is, indeed, very different according to the species, to the age, and to the special condition of the individual. The interstitial cells (*Fig.* 94) are described as epithelioid and polyhedric, and as cells of a glandular nature grouped around the capillaries (*Fig.* 95). The cells may form nests or cords separated by thin threads of connective tissue (*Fig.* 96). The latter contains blood vessels from which capillaries enter into the nests. These cells are in no way similar to connective tissue cells; they resemble rather the cells of the liver or of the cortical substance of the adrenals. The protoplasm of these cells is granulated or vacuolated, and contains small droplets of fat. As to the presence of the yellow lutein pigment in these cells the different authors disagree. The cells are smaller than those of the corpus luteum (*Figs.* 94, 97). According to *Limon* (1901) these cells occupy in the bat and in the mole almost the whole ovary forming a parenchyma traversed only by blood vessels. The same is true for the rabbit, as seen in Fig. 98.

Interstitial cells may be found in the ovary already during embryonic life.

As mentioned above, most authors, especially Winiwarter, insisted that interstitial cells are present in the ovaries of all species. *Fraenkel* (1905) *and Schaeffer* (1911), who studied a great number of different species, concluded, on the contrary, that these cells are not always present in the ovary. But their material was very incomplete for many species, only one or a few ovaries having been investigated. Since the interstitial cells are not to be found always in different individuals of the same species, the absence of interstitial cells in one or some individuals of a given species is not sufficient evidence for concluding that these cells are really absent in that species. The interstitial cells in the ovary vary, indeed, very greatly in number and size, according to age. Anyone who examines a sufficient number of ovaries of the rabbit will confirm this (*Fig.* 99 A, B, C). The interstitial cells which are always present in the adult rabbit do not acquire the size characteristic of the adult animal until about the age of six months. Up

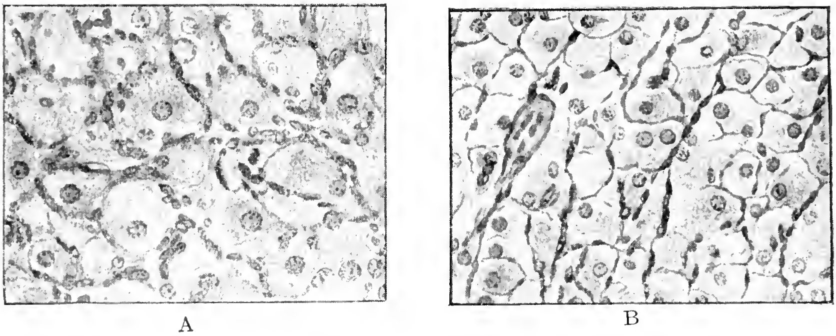


FIG. 94.—*Ovary of rabbit* 18 *months old* (Prot. Nr. 44). Fix. in the solution of Helly. A, Cells of Corpus luteum; B, Interstitial cells. The cells of the C.l. are bigger; the protoplasm of both is highly vacuolated. The cells are associated with closed capillaries.—Prepar. of Wagner; design of Lehbert.

to this age the stroma consists mostly of connective tissue cells (*Figs.* 99 A, 100; see also *Figs.* 102–103) and later of cells, having a spherical nucleus and a small quantity of protoplasm. Afterwards the ovary becomes transformed, long before corpora lutea appear, into an organ consisting almost entirely of interstitial cells, surrounded on the surface by a layer of follicles in different stages of development. That the number and the condition of the interstitial cells depend on the age of the animal was emphasized especially by *Aschner* (1914 c). Employing "Sudan" as a stain for fat, he was able to find interstitial cells in the ovaries of species in which they had not been detected by Fraenkel and Schaeffer, for instance, in the dog and in the cat. Aschner found the interstitial cells well developed before puberty in Rodentia, in the hedgehog, in the bat and in different species of Carnivora. He found that these cells increase in quantity till puberty. When puberty is attained and the first corpus luteum is formed, the space occupied by the interstitial cells is relatively smaller than before, as the corpora lutea now occupy the greater part of the ovary. According to Aschner, the quantity of the interstitial

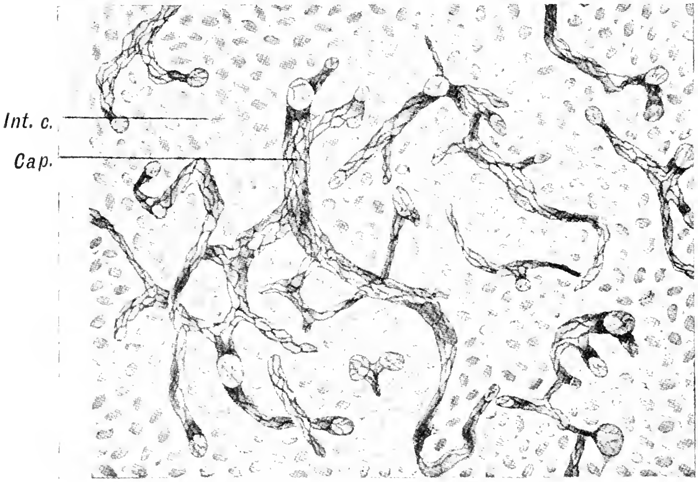


FIG. 95.—*Section through ovary of rabbit.* x 180. Injection of blood vessels by 1–300 nitrate silver. Impregnated endothelial cells of capillaries, which are surrounded by interstitial cells.—From Limon.

cells may even in some species decrease after the first corpora lutea have appeared; this he stated to be the case for the dog and for the cat (*Fig.* 101); he says that whereas the interstitial tissue in the ovary of the dog when stained with "Sudan" becomes gradually more accentuated till puberty, so that the ovary is full of cells with red granules of fat, these cells cannot be detected any longer by the usual methods at the time of the first heat. In the cow, sheep, goat, horse, ape and man there is, according to Aschner, only a rudiment of an interstitial tissue, if compared with that of the ovary in the species mentioned above. As Aschner points out, there seems to be a parallelism between fertility and quantity of interstitial cells in the ovary. Those species in which, as in the rabbit, hedgehog, bat and others, the number of the young in each litter is

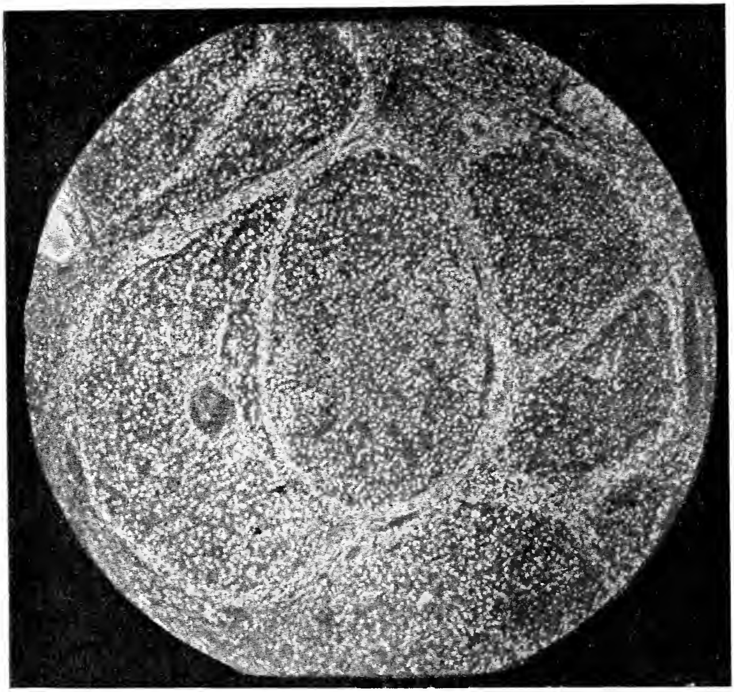


FIG. 96.—*Interstitial tissue in the ovary of Phascolomys* (*Marsupialia*). Photo, low magnif. The epithelioid cells of the stroma are disposed in the form of lobules. On the left a degenerated ovum is to be seen in the middle of a lobule, the lobules being nothing else than follicles undergoing atresia.—From L. Fraenkel.

large, have a well developed interstitial tissue. In these species the well developed interstitial cells are present not only up to puberty, but also afterwards, although the interstitial tissue is much reduced when corpora lutea appear. On the other hand, the interstitial tissue is rather rudimentary in the ovary of the cow, ape and man, where only one or two young are born simultaneously; in these species it hardly ever forms a parenchyma like the interstitial tissue in the ovary of the rabbit. Among Ungulata the pig is an exception, several young being present in a litter. Aschner stated that in the pig the interstitial tissue of the ovary is much more developed before puberty than in other Ungulata, although the nests of interstitial cells do not form an uninterrupted parenchyma as in the rabbit. Interstitial tissue in the ovary of the pig is transitional between

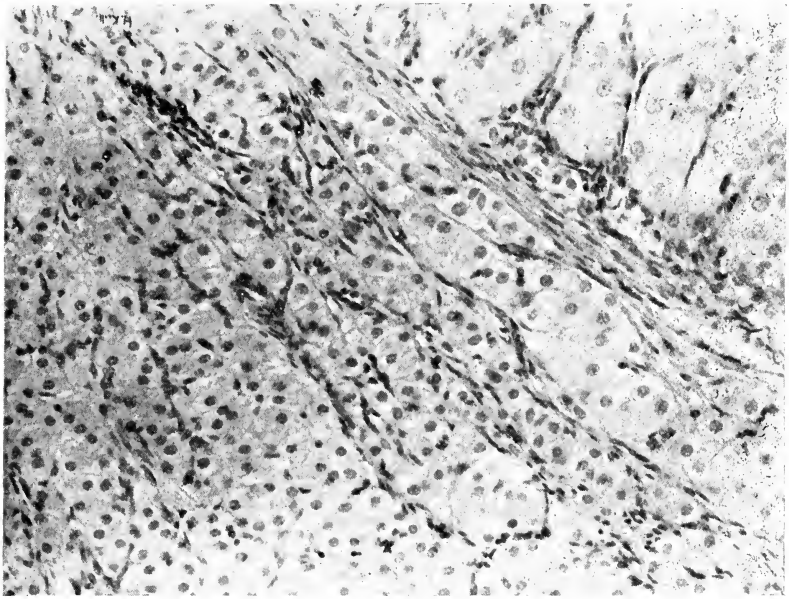


FIG. 97.—*Lutear and interstitial cells* (Prot. Nr. 104). x 250. Outer limit of the corp. lut. illustrated in Fig. 112. Big lutear cells; between them and the theca externa consisting of connective tissue, remains of the theca interna are to be seen. Then come the interstitial cells, which are of smaller size than the cells of the corp. lut.—Prepar. of Wagner; photo of Kull.

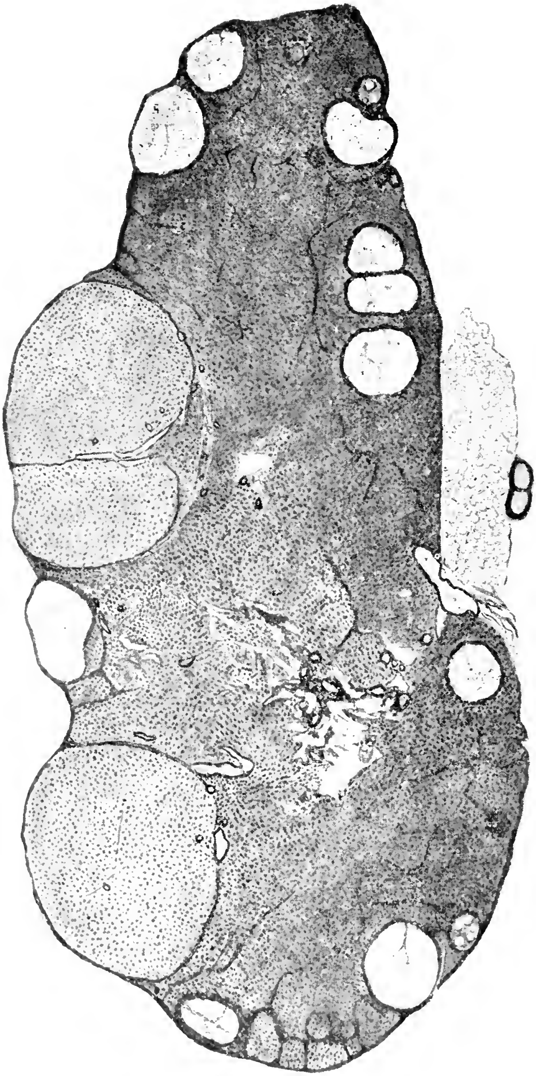


FIG. 98.—*Section through ovary of pregnant rabbit* (Prot. Nr. 280). Weight without embryos 2·7 kg. Ten embryos found in the uterus; total weight of embryos 230 gr. There were 11 corpora lutea in both ovaries and great quantity of Graafian follicles. Three corpora lutea surrounded by interstitial tissue occupying almost whole ovary.—Prepar. of Wagner; design of Lehbert.

that of the rabbit and that of the cow, ape and man. From his observations made on the ovaries of 250 females of very different species, Aschner concludes that the corpus luteum becomes more and more dominant over the interstitial tissue, the higher the position of the species in the class Mammalia.

A

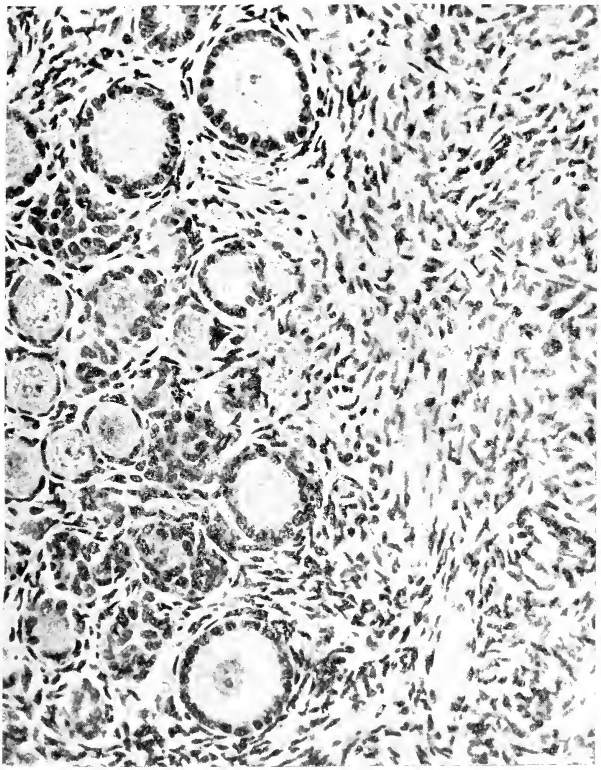


Fig. 99.—*Development of interstitial tissue of the ovary in rabbit..* x 280.

A. 2½ weeks old (Prot. Nr. 54). No epithelioid cells between the oöcytes, the stroma consisting entirely of cells of connective tissue.—Prepar. of Wagner; photo of Kull.

Aschner's suggestion as to the parallelism between fertility and quantity of interstitial tissue does not conform with what *Athias* (1919, 1921) states about the Cheiroptera, in which there is generally only one young produced yearly, and in which there is, nevertheless, an abundant development of interstitial tissue.

According to Winiwarter, the interstitial tissue is present in all mammals, which differ only in regard to the quantity of this tissue. "As far as I know there is no species," he says (quoted from *Athias*, 1921) "where it (this tissue) is wholly absent." The contradictory data, so noticeable in the papers on the subject, and even in recent ones, he explains as due to the researches being very incomplete. Sainmont and Winiwarter consider the interstitial cells as nutritive organs. It may be emphasized again that interstitial cells have been stated by the different authors to be present in the ovary of the

B

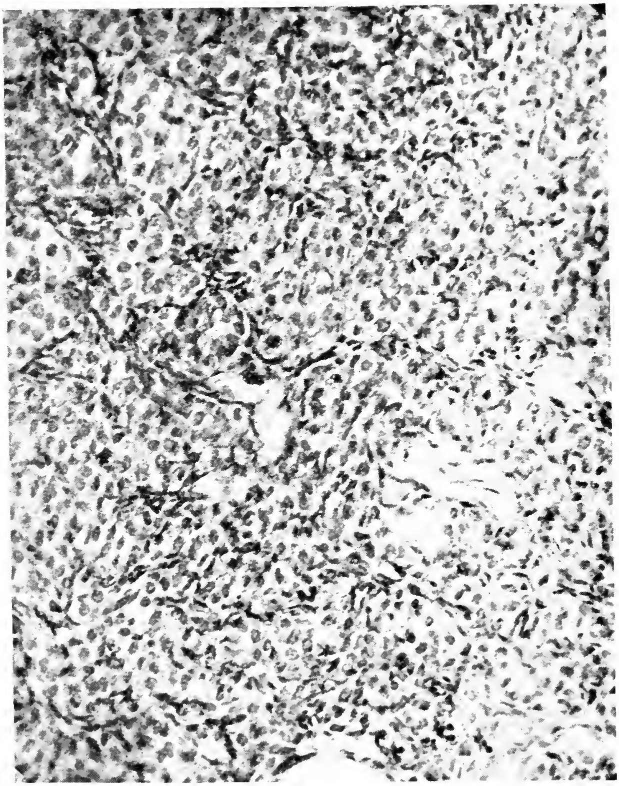


FIG. 99.—*Development of interstitial tissue of the ovary in rabbit.* x 280.

B. 7 months old (Prot. Nr. 118). The stroma consists of small epithelioid cells. Two corpora albicantia are to be seen surrounded by interstitial cells.—Prepar. of Wagner; photo of Kull.

cat, guinea pig, rat, mouse, bat, mole, hedgehog, horse, sheep and goat. Lately, *Athias* (1919) investigated in a very detailed way the question of the interstitial tissue in the ovary of the bat, where this tissue occupies a large space in the ovary. Athias gave also a very thorough description of the cytological character of this tissue, the structure of which he declares to be that of an endocrine gland. The interstitial cells show the attributes of glandular elements. Athias considers the fatty inclusions of the protoplasm as secretory products. But he thinks that the secretion undergoes some chemical change before leaving the cells, since no substance of a lipoid character

C

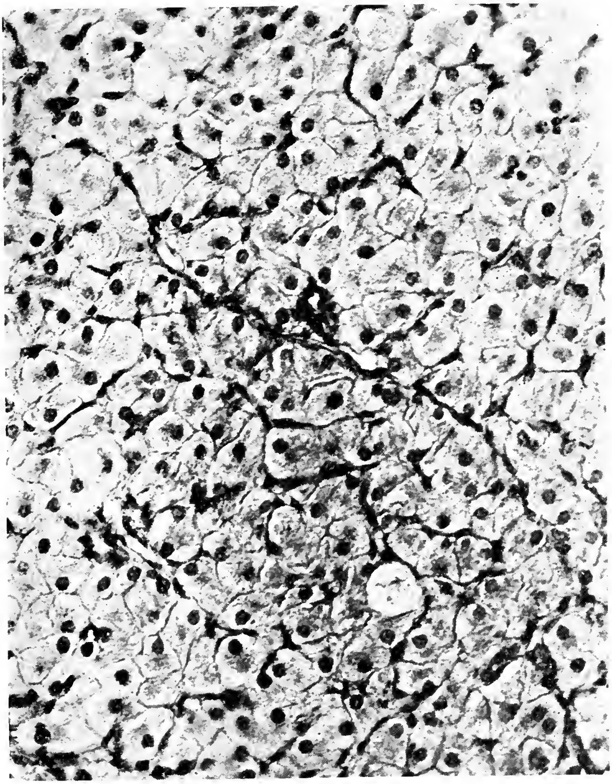


FIG. 99.—*Development of interstitial tissue of the ovary in rabbit.* × 280.

C. 18 months old (Prot. Nr. 44). The epithelioid cells with very rich protoplasm and big spherical nucleus.—Prepar. of Wagner; photo of Kull.

is revealed in the intercellular or lymphatic spaces. *Athias* (1921) also is of the opinion that the interstitial tissue is *always* present in the ovaries of mammals.

There is not as yet unanimity in regard to the interstitial tissue in the ovary of man. According to *Seitz* (1906) and *Wallart* (1907), who examined a great number of human ovaries, beginning with one in a five months old embryo and ending with an ovary of a woman of 91, interstitial cells exist like those described by Limon and others for different mammals as interstitial tissue. They point out that the epithelioid cells with fatty inclusions are already present during embryonic life. Wallart mentions that the number of the cells increases up to puberty. At the time of puberty the interstitial tissue decreases; the greatest development of the interstitial tissue is attained during gravidity. At the climacteric only remains of the interstitial tissue are to be found. Wallart states that the fatty inclusions, always present in the interstitial cells, are often yellow like the fatty granules in the cells of the corpus luteum; they probably contain lutein (*Wallart,* 1907, p. 327). *Winiwarter* (1908) also stated that interstitial cells are to be found in the human ovary. *Fraenkel* (1905, p. 508) and *Schaeffer* (1911, p. 531), on the contrary, claim that not even rudiments of a similar tissue are present in the ovary of the

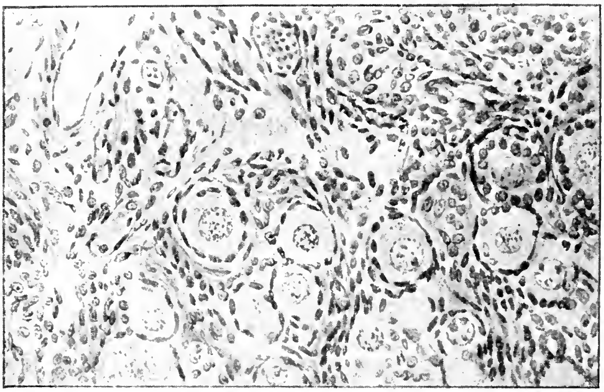


FIG. 100.—*Section through ovary of rabbit 2½ weeks old* (Prot. Nr. 54). Stroma consisting of cells of connective tissue.—Prepar. of Wagner; design of Lehbert.

adult woman. The question has been re-examined by Aschner. He states that the epithelioid interstitial cells are already present in the new-born child. The interstitial tissue is also well developed during early youth, but the quantity of lipoids in the ovary varies very much. Contrary to Wallart, Aschner finds that the interstitial cells in the ovary of man diminish as puberty is approached. The statement of Aschner, that during gravidity the interstitial tissue, after being reduced to its minimum upon the development of the first corpus luteum, increases again, is in accordance with the above-mentioned statement of Wallart. The increase of the interstitial tissue takes place especially in the second half of gravidity. During menstruation no increase in the number of cells could be found by Aschner. Lately the question of the interstitial tissue in the human ovary has been very much discussed by German authors. Most of them deny the presence of such cells in the

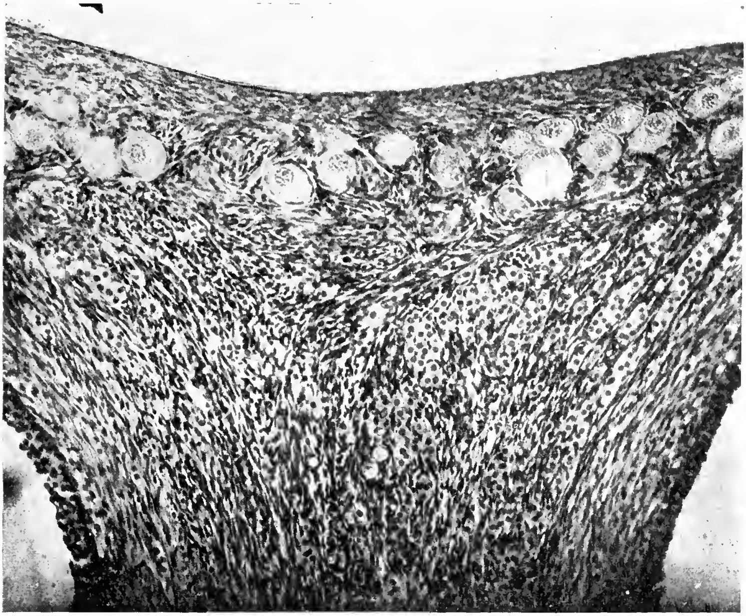


FIG. 101.—*Section through ovary of adult cat* (Prot. Nr. 276). x 150. Epithelioid interstitial cells are visible in the connective tissue of the stroma.—Prepar. of Wagner; photo of Kull.

stroma of the ovary. *Robert Meyer* (1921) declared that there are never nests of interstitial cells in the ovary of the non-pregnant woman independently of the follicular tissue, and that the "interstitial gland" is only a "phantasy" of some authors. On the contrary, *Seitz* (1921) claims that it would be "nonsense" to deny that the gland exists in the guinea pig or in the rabbit, and that the interstitial gland is present also in the woman. This tissue is absent or rudimentary in the woman only after she has attained maturity; it is then replaced by the corpus luteum.

The want of agreement between the statements of various observers may be explained partly by the fact that whereas some restrict the term interstitial "tissue" to cells which exist outside the walls of the follicles, as in the rabbit, others denote the mass of the atretic follicles undergoing degeneration in the ovaries of man and mammals as interstitial tissue, and identify it with the parenchymatous tissue in the ovary of the rabbit. It will be shown in the following section that the interstitial tissue of the ovary, even when really present, as, for instance, in the rabbit, is derived in general *from the follicle*; the interstitial cells originating from the cells of the stroma play quantitatively a very minor rôle. Further, interstitial *tissue* is not necessarily the same as interstitial *gland*. There is no justification for confounding a purely histological question with a physiological one. The confusion which has arisen in regard to this question is unfortunate.

2. The Origin of the Interstitial Cells of the Ovary.

Limon (1901) was the first to undertake a full investigation of this question. He stated in accordance with a suggestion of former authors that the development of interstitial cells is related to follicular obliteration, as seen especially in the rat and in the rabbit (*Figs.* 102, 103). The formation of the interstitial tissue begins in the rat soon after birth, whereas in the rabbit it does not begin until an age of four months, or, as we found, sometimes even later. The whole process begins with the transformation of the irregular or spindle-shaped connective cells of the theca interna, which become spherical and increase in volume. Fat droplets appear in the protoplasm of the cells. At the same time, a degeneration occurs in other cells of the follicle, in the cells of the granulosa and in the ovum itself.

The degenerating cells finally are resorbed. A vascularisation arising from the stroma takes place in the mass of cells which up till now formed the theca interna. Such an atresia goes on in a very great number of follicles (*Fig.* 104). Similar observations were made also by Limon on the guinea pig, on the mouse, and on the bat. We see that the interstitial tissue of the stroma of the ovary is, according to Limon, nothing else than the result of a transformation of atretic follicles. As the epithelioid interstitial cells are derived from the theca interna, it follows, according to Limon, that they are of connective tissue origin.

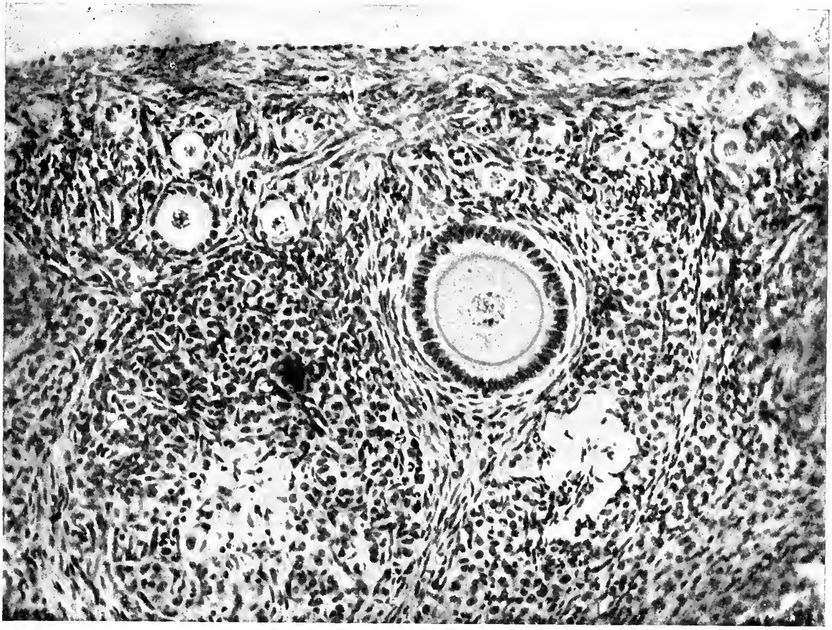


FIG. 102.—*Growing primary follicle with membr. granulosa and theca in rabbit 7 months old* (Prot. Nr. 119). x 200. It can also be seen that threads of interstitial cells arise from atretic follicles; compare the atretic follicle on the left (with corpus albicans) which has still conserved the round shape, with the atretic follicle on the right which has lost its original shape evidently owing to the growth of the primary follicle at its left border.—Prepar. of Wagner; photo of Kull.

Follicular atresia takes place in the ovaries of all mammals. So one would expect also that interstitial cells would be present in the ovaries of all mammals. Since the interstitial tissue in some species is certainly due to follicular atresia, it seems justifiable to identify also as an essentially similar tissue that which is derived from atretic follicles in the ovary of man and other mammals, in which, according to some authors, an interstitial tissue is absent. The only difference is that, in the first, the cells originating from the theca interna of the atretic follicles form a compact parenchymatous tissue, the so-called "interstitial gland" of Bouin and Limon, whereas, in the

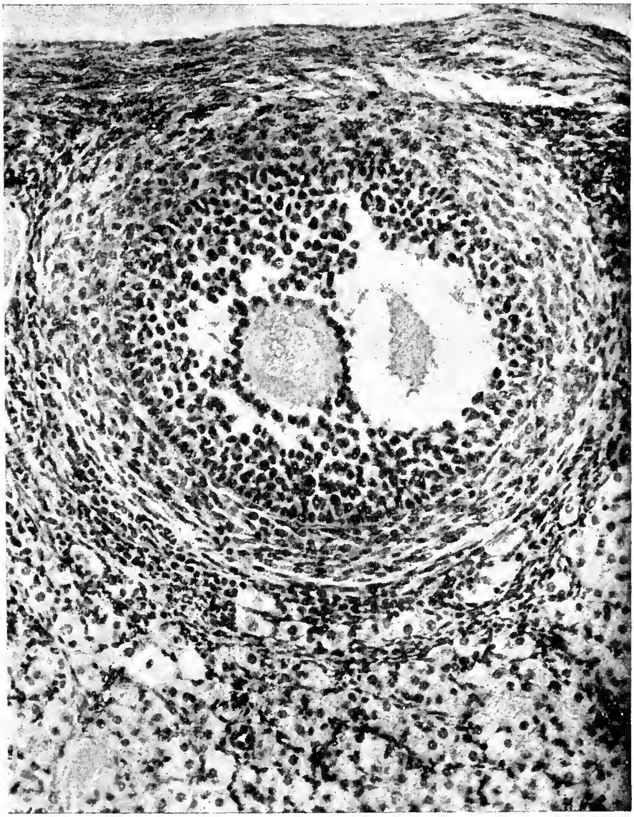


FIG. 103.—*Young Graafian follicle in rabbit* 11½ *months old* (Prot. Nr. 47). x 200. The granulosa, theca interna and theca externa are to be seen. Compare also the size of the interstitial cells in Fig. 102 and Fig. 103.—Prepar. of Wagner; photo of Kull.

second, these cells remain to a great extent as they were originally formed (*Fig.* 96), without tendency to such a confluence as occurs in the rat or rabbit. It is of considerable interest to note that according to *Salazar* (1922) there are even in the ovary of the rabbit some follicles which do not lose their individual existence when becoming atretic, and which do not form directly part of the interstitial tissue. These atretic follicles remain for a certain time surrounded by a connective tissue capsule even thicker than that of a true corpus luteum; afterwards they undergo fatty degeneration and sclerotization.

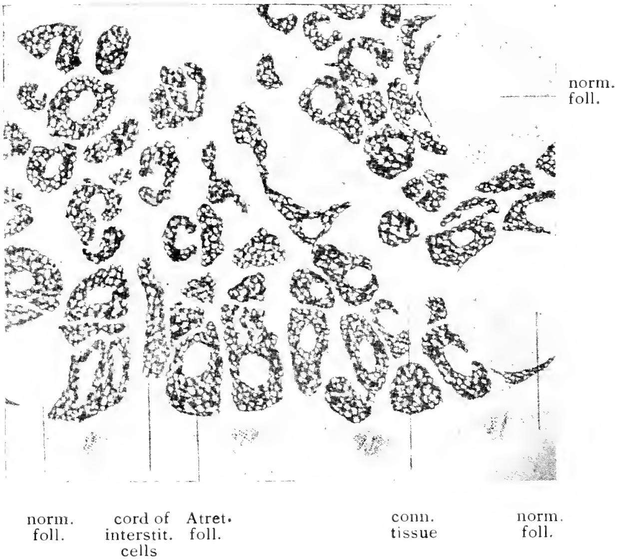


Fig. 104.—*Section through ovary of white rat,* 62 *days old.* x 90. Fix. by Flemming, treated by osmic acid, not stained. Atretic follicles surrounded by connective tissue ; theca cells filled with fat. At different places follicles transformed into cords of interstitial cells.—From Limon.

The state of the ovary in man is different from that in the rat or rabbit, since in the former the greater number of the cells of the theca interna, after having been transformed into epithelioid cells, undergo degeneration and disappear. It may be that some of these cells are transformed again into spindle-shaped connective cells.

The atresia and fatty transformation of the follicles begin in the human ovary in the fifth month of intrauterine life. According to *Winiwarter* (1908), interstitial cells are present in the human ovary long before. But typical interstitial cells are derived also from the connective tissue cells of the stroma. There is no cytological difference between the interstitial cells originating from the stroma and those originating from follicular atresia. Once follicular atresia begins, formation of interstitial cells from cells of the stroma ceases, indeed, to play a quantitatively important rôle.

Observers differ as to the extension of follicular atresia and of the interstitial tissue during childhood, but all agree that an increase of the interstitial cells takes place in man during gravidity. A very great number of follicles undergo atresia in the second half of gravidity. An enormous quantity of interstitial cells is, so to speak, poured out into the ovarian stroma. According to *Seitz* (1906, p. 263), these cells assume the character of lutein cells; they increase in size and become epithelioid, so that their appearance is very like that of the cells of the corpus luteum. Seitz called these cells "theca-lutein-cells." This transformation of cells of the theca interna into theca-lutein-cells becomes all the more intensified, the further gravidity has proceeded. As Seitz points out, all the larger follicles present undergo atresia during gravidity; as the cells of the theca interna increase also in number, a great quantity of new theca-lutein-cells full of fatty and lutein inclusions arise by follicular atresia during the second half of gravidity. Like Seitz, other authors hold that the epithelioid cells of the ovarian stroma containing fat and lutein are derived from the cells of the theca interna. In the fifth section of this chapter we shall learn the physiological bearing of such a transformation of the cells of the theca interna into cells somewhat similar to those of the corpus luteum.

It is, indeed, not impossible that cells of epithelial origin also take part in the formation of the interstitial tissue. The membrana granulosa of the follicle undergoing atresia is possibly such a source of the epithelioid cells of the interstitial tissue. *Rasmussen* (1918) finds it probable that in the woodchuck new interstitial cells can originate from the germinal epithelium. A similar view is held by *Ochoterena and Ramirez* (1920) as a result of observations on the rat and on the rabbit.

According to *Goormaghtigh* (1921), the interstitial cells of the ovary and of the testicle are formed from the mesothelium like the cortical substance of the adrenals. Being of epithelial origin, these cells are transformed into connective tissue cells, to become later, at the time of sexual activity, epithelioid. *Bell* (1920) pp. 27, 28) inclines to the view that interstitial cells can be formed even from corpora lutea.

So we see that the origin of the cells of the interstitial tissue of the ovary may be a very manifold one; the cells of the stroma, the cells of the theca interna, the cells of the granulosa and possibly the cells of the corpus luteum may take part. We are now, indeed, far from the original point of view of *Limon* (1901) and of *Sainmont* (1906), who assumed that the interstitial cells originate exclusively from connective tissue. *When speaking about "interstitial tissue" or "interstitial cells," we always understand cells derived from follicles without presuming whether they originate from connective tissue or from epithelial cells.* In general there seems to be, indeed, great difficulty in stating in terms of histology what the origin of the cells of the atretic follicle or of the interstitial tissue has been, since so many contradictory statements are to be found.

An increase of the interstitial cells in the above-mentioned sense as observed during gravidity can be obtained also experimentally by the application of the X-rays or by transplantation. Now the question arises whether such an hypertrophy of the interstitial tissue in the ovarian stroma causes an increased endocrine activity on the part of the ovary. It seems clear that the answer to this question might furnish important knowledge as to the function of the interstitial cells.

3. The Influence of X-rays on the Ovary.

The statements made by different authors on the reaction of the ovary to X-rays are very contradictory. According to some authors, the follicles and the interstitial cells (or cells of the stroma) are injured by X-rays; according to others, there is only a degeneration of follicles, whereas the interstitial cells may even increase in number. But it seems that in discussing this question it is not always borne in mind that the ovary may react in a different manner according to the mode of irradiation, according to the species, and to the age and condition of the animal. As *Lacassagne* (1913, p. 41) points out, the want of agreement between the statements of the different authors could be explained by the following factors:

(*a*) Differences in the technique of irradiation.

(*b*) Differences in the species, age and size of the animal.

(*c*) Differences in the time between irradiation and histological examination; if the latter is done too early the changes which irradiation induces will not have been completed.

(*d*) Incomplete histological examination.

The third factor is of an especial importance. It is impossible to discuss properly the results of irradiation without taking into consideration what may be called the histological *dynamics* of the ovary. Two fundamental facts must be the starting point in every discussion of this kind; *first,* that the interstitial cells are less sensitive to X-rays than the follicles, i.e., the ova and the cells of the membrana granulosa (see below, p. 230), and *secondly,* that the interstitial tissue, if persisting, has to be provided from time to time with new cells from the follicles undergoing atresia. Realising this one will be able to understand that by decreasing the strength of irradiation the following three separate results will be brought about, without the sensitiveness of the ovary having been different.

First case. Degeneration of both ova and follicles and interstitial tissue, which will be replaced by common connective tissue.

Second case. Degeneration of all ova and follicles, while the interstitial tissue is injured only slightly or not at all; but as the interstitial tissue can persist only when provided with new cells by follicles, degeneration of follicles will result after a certain time in a reduction and disappearance of the interstitial tissue.

Third case. Injury of the follicles without full degeneration of ova but increased atresia; by this a great number of interstitial cells will be provided by the obliterating follicles, and an increase in the interstitial tissue will occur.

As Lacassagne stated, the sensitiveness of the follicle seems to be different according to the degree of its development; in view of this factor the reaction of the ovary to X-rays will become still more manifold. Further, it seems clear that there will be also transitions between the cases mentioned above;

"Case 2" and "Case 3" could end both with atrophy of the interstitial tissue and re-establishment of the normal condition of the ovary. Clinical observations make it probable that by therapeutical irradiation some kind of a transition between "Case 2" and "Case 3" is generally brought about; there is an injury of the follicles, but evidently not so great and not permanent, as in "Case 2." *Paul Werner* (1918), who has

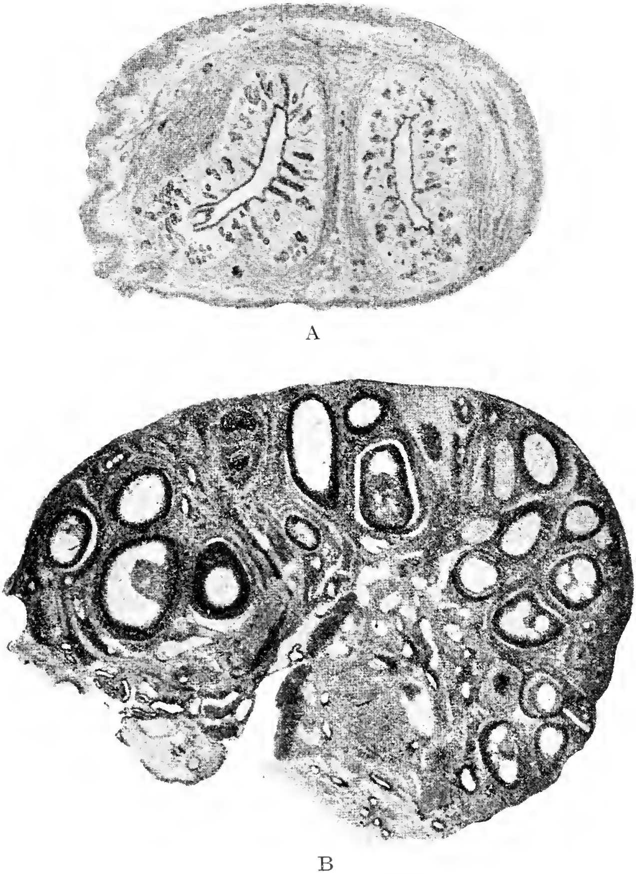


FIG. 105.—*Influence of X-rays on sex characters in virginal female guinea pig.*—From Steinach and Holzknecht. *Normal virginal guinea pig, 4½ months old.*
A. *Uterus* (before bifurcation). x 9.
B. *Ovary.* x 18. Follicles at different stages of development.

examined 376 radiated women, concludes that in young individuals the activity of the ovary is stopped only temporarily, that a complete return to a normal state is possible; this is shown by the fact that, after amenorrhoea, caused by irradiation, menstruation almost always reappears after a certain time; women treated by irradiation can conceive subsequently, and give birth to entirely normal children.

In view of these considerations, it is easy to understand that the reaction of the ovary to irradiation is an extraordinarily manifold one.

The influence of the strength of irradiation on the mode of reaction of the ovary has been investigated by different authors, and most recently by *Steinach and Holzknecht* (1916). They stated that by an unique irradiation of a certain strength (about 12 "Holzknecht-units") an obliteration of the follicles and an increase of interstitial cells can be obtained in guinea pigs (*Figs.* 105 B and 106 B). By an unique irradiation of a greater strength both follicles and interstitial tissue can be destroyed. Even by merely changing the position of the animal, for instance, by irradiating the ventral instead of the dorsal side, the same strength will cause destruction of interstitial tissue instead of hypertrophy. We see that only those experiments can be compared with one another where exact doses of X-rays have been given, and where all the other conditions of the experiment have been the same. As long as quantitative relations are not duly considered, there can be no possibility of any agreement between different authors concerning the influence of X-rays on the ovary; the position is the same here as with any other stimulus known to the physiologist.

Bouin, Ancel and Villemin (1906–1907), working on the rabbit, were the first to show that an obliteration of the follicles can be caused by X-rays, the interstitial cells remaining intact. *Houssy and Wallart* (1915) showed that an increase of the interstitial tissue may take place in the ovary of man when irradiated on account of uterine myoma. Similar observations were made by *Hewer* (1915, p. 444) on white rats, and by *Aschner* (1918, p. 45) on the dog. In view of these observations there can be no doubt that by the employment of regulated doses an atresia of a very large number of follicles and a great increase of interstitial cells can be obtained.

What will be now the condition of the organism in such circumstances? This question was examined by Bouin, Ancel and Villemin. They irradiated rabbits several times; two to four weeks after the last irradiation the animals were killed. They describe a marked atrophy on the part of the uterus and the tubes, the vagina, and the clitoris, as well as the mammary glands. No corpora lutea were present in the ovaries, an almost complete atresia of the follicles took place, whereas the interstitial tissue persisted. The authors concluded from these experiments that an atrophy of the genital organs can be checked only by the corpus luteum, and that there was no participation of the interstitial tissue in the endocrine function of the ovary.[1] [Later on the authors came to another conclusion; see p. 259.]

We shall show in the following sections of this chapter that this conclusion was erroneous, and it may be pointed out here that puberal development of the uterus in the rabbit can take place before any corpus luteum has developed in the ovary. Indeed, Bouin seems to have been one of the first to call attention to the fact that, before sexual intercourse, there is often no development of a corpus luteum in the ovary. In a virgin rabbit of about 18 months old we found no corpus luteum in the ovary; nevertheless, the uterus was normal.

That the conclusion of the French authors in regard to the exclusive dependence of the sexual characters on the corpus luteum is not justified, is shown especially by the experiments of Steinach and Holzknecht. They irradiated guinea pigs two to four weeks old, exposing the back once to about 12 "Holzknecht-units." As already mentioned, by exposing the ventral side to X-rays, a complete destruction of both follicles and interstitial tissue took place; the animals showed signs of castration effects. On the contrary, the animals irradiated on the back showed about eight weeks after the irradiation a marked increase in the nipples. The area surrounding the nipple was rounded and shiny; mammary glands could be felt. Even milk secretion was observed for two or three weeks. The microscopical examination of the mammary gland of such an irradiated virgin animal revealed a condition similar to that

---

[1] An atrophy of the clitoris after castration is not very probable. In castrated rabbits I never could find macroscopically any changes in the region of the clitoris.

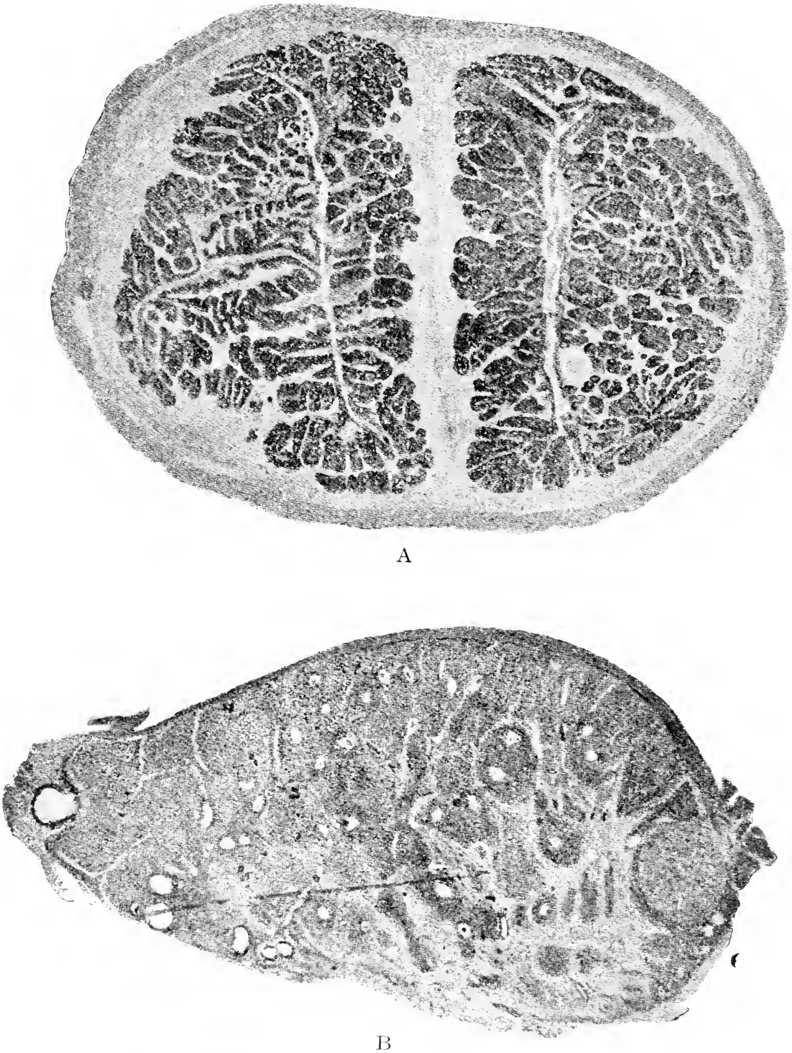


FIG. 106.—*Influence of X-rays on sex characters in virginal female guinea pig.*—From Steinach and Holzknecht. *Virginal guinea pig, $4\frac{1}{2}$ months old, treated at an age of* 3 *weeks with X-rays.*

A. *Uterus.* x 9. Highly developed.

B. *Ovary.* x 25. Atresia of most of the follicles.

of a pregnant female; there was a compact gland, rich in blood vessels; the epithelium was full of fat droplets. Also the uterus was in a condition characteristic of pregnancy (*Figs.* 105 A and 106 A). The ovaries were found about three months after irradiation to be smaller than normally; a great many follicles were atretic, and the number of the interstitial cells was extraordinarily increased. Steinach and Holzknecht mention that the whole stroma of the ovary was transformed into a mass of lutein cells.

It seems justifiable to conclude from these experiments that the marked development of the mammary gland and of the uterus was caused by an increase of the interstitial tissue derived from the follicles. Such a conclusion seems especially true when comparing these results with those observed in animals where irradiation caused destruction and sclerotization of the whole ovary and at the same time signs of castration. A similar observation was made before by *Biedl* (2nd ed., p. 337) on the uterus of the rabbit. He stated that sclerotization of the ovary after irradiation is accompanied by an atrophy of the uterus. There is no room for the objection that the highest degree of development which can be attained by the mammary gland and the uterus after irradiation is caused by a direct action of X-rays on these organs, since Steinach and Holzknecht made another experiment in which the ovaries were removed after a great development of the mammary gland had occurred after irradiation; they then observed an atrophy of the mammary gland.

From all these experiments it is possible to conclude that from the follicles endocrine cells are, so to speak, poured into the stroma in an increased number, and that consequently the influence of the ovary upon the mammary gland and uterus becomes greater. Steinach speaks of such an irradiated ovary as an isolated endocrine gland; there is in reality no isolation, as ova are still to be found in such an ovary. But this objection does not matter; for in order to reach the above conclusion it is not necessary to suppose that all the ova or follicles throughout the whole ovary must have disappeared. The conclusion is justified, as it was shown that greater follicular atresia, and consequently an increased number of interstitial cells, bring about a greater development of the mammary gland and of the uterus, and that this development does not take place if an atrophy of the epithelioid cells of the stroma was also caused by irradiation.

The experiments of Steinach and Holzknecht have not yet been repeated[1], but it is desirable that they should be, in view of the theoretical and practical interest involved in the questions. Above all, it is desirable that we should be in a position to explain the different results in the experiments of the French and Viennese authors. It may be also that in the experiments of the former the possibility of "Case 3" of our scheme was realised, but that the French authors interrupted their experiments before an hypertrophy of the interstitial tissue could take place. Furthermore, it is possible that at the beginning an injury to the interstitial tissue took place (transition from "Case 2" to "Case 3" in our scheme). As Steinach and Holzknecht pointed out, the first external results of the irradiation became visible about three to four weeks later, and the highest degree in the development of the nipples was observed only eight weeks after irradiation. Steinach and Holzknecht possibly would have arrived at a negative result like Bouin, Ancel and Villemin, if they had interrupted their experiments sooner; and possibly the French authors would have attained a positive result if they had continued their experiments longer. Moreover, the technical points we discussed above must be taken into consideration.

New experiments with X-rays were recently made by *Guggisberg* (1922) with the special purpose of elucidating the question as to which part of the ovary performs the endocrine function. Guggisberg's criticism directed against our view is, in reality, in opposition to suggestions which neither Steinach nor myself ever made. He concludes from his experiments that the follicles act as an endocrine organ, a supposition the possibility of which we have never denied. Guggisberg first stated that with rabbits castration leads to an increased sensibility to adrenaline; about a month after

---

[1] Since this was written *Rahel Plaut* (1923) communicated similar experiments. The statements of Steinach and Holzknecht were fully confirmed as to the changes in the uterus and the mammary gland occurring after irradiation. There was no hypertrophy of the uterus and of the mammary gland when castration was previously performed. But according to Plaut the hypertrophy of the mammary gland failed to occur also in the case when only the uterus was previously removed. She assumes that the ovary acts on the mammary glands through the intermediation of the uterine mucosa. But this conclusion is in contradiction to what we know from the feminized male guinea pig. See Chapter VI.

castration he found a transitory glycaemia to take place when quantities of adrenaline, which were too small to cause glycaemia in normal rabbits, were injected. Then Guggisberg examined rabbits treated by X-rays to ascertain their sensibility to adrenaline, and found a similar increase to that after castration. There was also an accumulation of fat, whereas there was no atrophy of the uterus. The histological examination revealed, about two months after irradiation, a pronounced injury to the follicles, but no change in the interstitial tissue. On considering the increased sensibility to adrenaline as a sign of castration caused by a lack of an internal ovarian secretion, Guggisberg concluded that the interstitial tissue does not participate in the endocrine function of the ovary, only the follicles being the true endocrine organ. This conclusion is without justification. The fact that no signs of castration were visible in the uterus, which is so sensitive to the ovarian hormone, makes it highly probable that the irradiated ovaries in the experiments of Guggisberg were still performing their endocrine function. It may be that the quantitative level of the endocrine activity was *lowered*, and by this circumstance the disturbance could be explained. But it is by no means certain that the increased sensibility to adrenaline or the accumulation of fat should be considered as caused by a disturbed production of sexual hormones. On the contrary, it is possible to regard the accumulation of fat as correlated with reduced activity in the generative part of the gonad. (See the statements of *Heymans*, Chapter II.).

4. Transplantation of the Ovary.

Like the testicle, the ovary undergoes profound changes after transplantation. *Ribbert* (1898) was the first to make detailed observations concerning these changes in the ovarian graft. After autotransplantation in the rabbit the greater follicles and the corpora lutea undergo degeneration; "reparation" takes place by follicular development of the smaller follicles which remained hitherto intact. Similar observations were made by many other authors. The experiments of Marshall and Jolly may be especially mentioned. According to them (*Marshall and Jolly*, 1910, p. 324) all the follicles may finally undergo atresia in the ovarian graft in the rat (autotransplantation and homoiotransplantation). In some cases the graft consisted almost entirely of lutein cells. They stated also (1907) that in the rat the transplanted ovary can undergo cyclical changes like the normal ovary. They found in the graft at the commencement of the breeding season large follicles, afterwards also corpora lutea. Evidently ovulation can take place in the transplanted ovary. According to all authors who have made histological observations on the ovarian graft, the difference between a normal ovary and an ovarian graft seems to be merely that there is an accelerated atresia of those follicles which have already attained a certain size at the time when transplantation was performed. There is possibly also an accelerated atresia afterwards. By this a predominance or an hypertrophy of interstitial tissue consisting of epithelioid, or lutein cells, is caused.

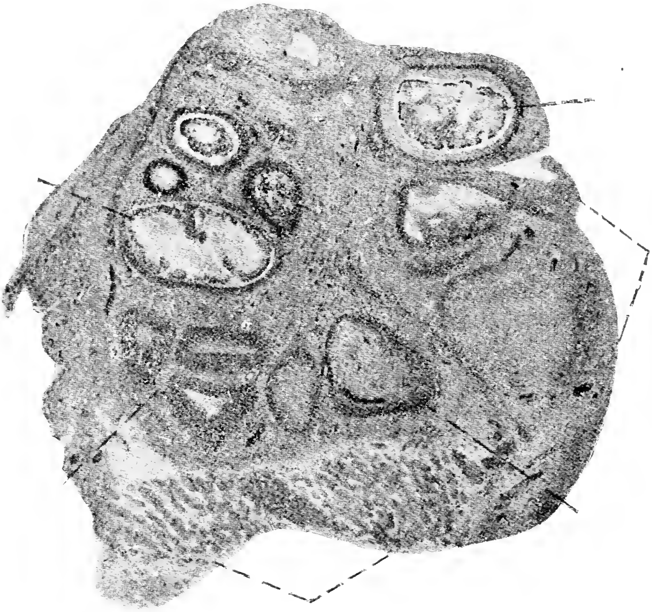


FIG. 107.—*Section through ovary engrafted six months previously into a castrated male.* x 25. Increased follicular atresia.—From Steinach.

Several authors have made histological observations also on the condition of the ovarian graft in a normal or castrated male. *W. Schultz* (1900) was the first to show that an ovarian graft can "take" in a male organism, even when the latter has not been previously castrated. According to him the condition of an ovarian graft in the male is not different from that in the female (1910).

A large number of observations on ovarian grafts have been made with the special purpose of investigating the bearing of the ovary on the production of sexual hormones. *Steinach* (1912) transplanted into young castrated male rats and guinea pigs immature ovaries without ripened follicles, and observed all the changes characteristic of the normal ovary up to formation of corpora lutea. This condition lasted only a few months; the older the graft, the smaller was the number of the follicles attaining ripeness. There is finally, according to Steinach, an atresia of almost all follicles in the ovarian graft (*Figs.* 107, 108.) By this a marked hypertrophy of the interstitial tissue is caused, the cells of the granulosa being transformed into cells from which all transitions to lutein cells are to be seen. Similar experiments were made by *Athias* (1915, 1916 a, 1916 b). He found even eight and a half months after transplantation, besides atretic follicles, a great number of primary follicles. The ovaries transplanted by Athias were taken from adult animals, whereas those of Steinach were from young ones; it may be that the condition of the ovarian graft depends

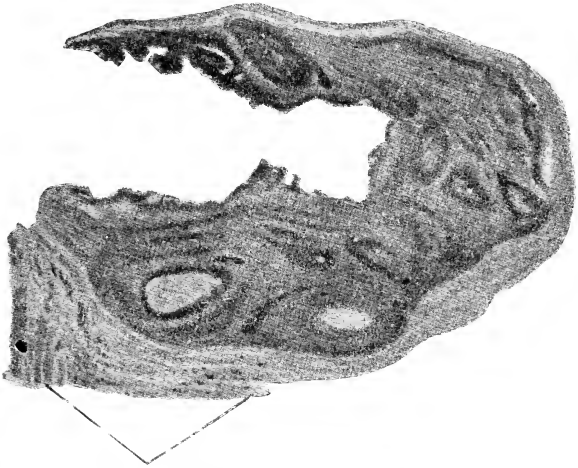


FIG. 108.—*Section through ovary engrafted a year previously on a castrated male.* x 25. Mostly follicles undergoing atresia.—From Steinach.

also upon the age of the ovary at the time of transplantation. In accordance with Steinach, Athias points out that the number of the atretic follicles is very great in the ovarian graft, and that the theca interna is highly hypertrophied. The richly vascularized stroma is full of nests of interstitial cells. Lately *Athias* (1922) has given a full account of his histological work on ovarian grafts; he insists especially on the tendency of the graft to undergo cystic degeneration. According to *Moore* (1921 a) corpora lutea do not develop when the ovary is engrafted into a male which has not been previously castrated.

It seems evident that the time at which the more or less complete transformation of follicles into interstitial tissue will have occurred, must differ from case to case. For instance Marshall and Jolly found once in autotransplantation a normal condition of the ovary fourteen months after the operation; in a case of homoiotransplantation the ovary was still normal six months after the the operation. (In both cases the ovary was implanted into the kidney). If now we compare these statements, which are only instances of what was seen by several other observers after autotransplantation and homoiotransplantation of the ovary, with the statements of Steinach and Athias concerning the condition of the ovary engrafted into the male, it seems that the results are different according to the sex of the animal into which the ovary was engrafted. The difference is indeed mainly a quantitative one. The follicles of an ovarian graft in a castrated male are possibly less able to attain ripeness and to form corpora lutea; follicular atresia is probably augmented in such grafts, and consequently an hypertrophy of the interstitial tissue must finally take place. A detailed study of this special question was made by *Sand* (1918, pp. 121-51) in a very great number of experiments on rats and guinea pigs. On examining the grafts about six months or less after the operation he confirmed the fact that the follicles can ripen in the ovarian graft; in the majority of his experiments Sand also found corpora lutea. In regard to the comparative condition of the graft in castrated females and castrated males, Sand states that there is in the latter a tendency to an intensified follicular atresia, and to an increase of interstitial cells derived from the theca interna; he concludes that the follicles are in the male really less able to ripen and to form corpora lutea. We do not yet understand the precise factors whereby the variation in the ovarian graft according to the sex of the host into which it is transplanted can be explained.

The above statements in regard to the condition of the ovarian graft have an especial bearing upon the question as to the cells involved in the endocrine functions of the ovary. We have already learned that signs of castration are absent if the implanted ovary "takes." Now Marshall and Jolly stated that signs of castration are absent also, if an atresia of all the follicles has taken place. *Bell* (1920, p. 47) implanted in the rabbit only the central part of the ovary, which contains no follicles, and is composed entirely of interstitial cells (as shown in serial sections of the graft); twenty-four days afterwards there was no atrophy of the uterus. From all these observations one must conclude that the epithelial and epithelioid interstitial cells of which such a graft is composed are able to perform the internal secretory functions ascribed to the ovary. But the objection may be made that notwithstanding the highly augmented follicular atresia and notwithstanding the transformation of a very great number of follicles into interstitial cells, ova were still present in the grafts, and that these elements might have produced the internal secretion. This is the same objection that we had to deal with before, when discussing in the preceding section the experiments in which a more or less complete atresia of the follicles was obtained by means of X-rays. Such an objection was made by *Bucura* (1913, p. 1839). But it was shown experimentally that this objection is not justified, although the fact remains true that ova and young follicles may be present in the transplanted ovary. We have referred to the experiments of *Steinach* (1916) where the ovarian grafts were made into castrated males. These grafts were able to *feminize* the male, in which an hypertrophy of the mammary gland and milk secretion were observed. Steinach's statements were confirmed by *Athias* (1915, 1916 a, 1916 b), *Sand* (1918), and *Moore* (1921 b) and by myself and my co-workers. We must conclude that the great development of the mammary gland was caused by the fact that in the ovarian graft an intensified follicular atresia and an intensified formation of interstitial cells took place. The hypertrophied tissue then gave rise to an increase of female sex hormones. In view of these considerations, it seems justifiable to assume that the follicles undergoing atresia, and the cells derived from the latter, represent in the ovary a gland with an internal secretion. One might object that this may be true only for the species on which the above-mentioned experiments were made, and for those species where there is an interstitial tissue in the ovary like that in the rabbit. But we have seen that no essential difference exists between the follicle undergoing atresia and the interstitial tissue like that of the ovary of the rabbit.

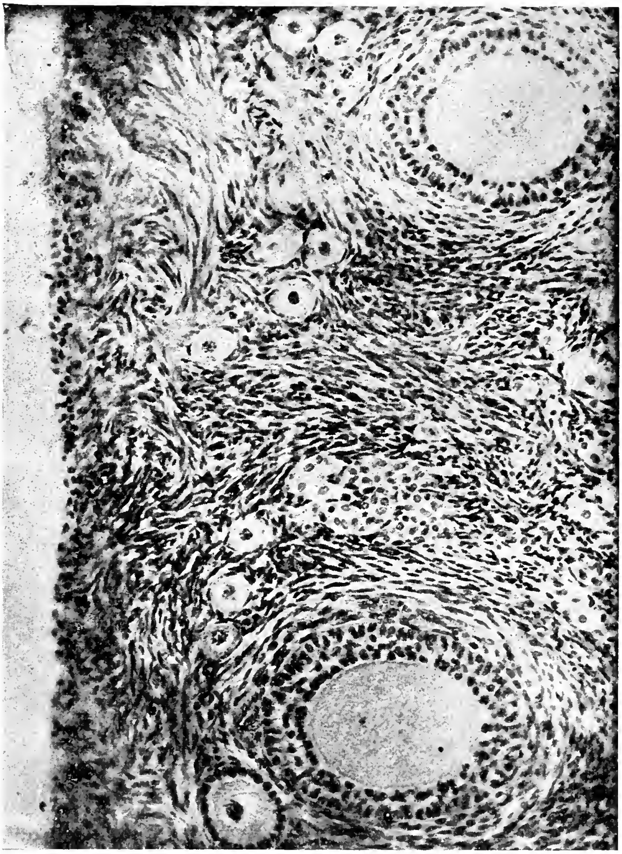


FIG. 109.—*Disappearance of primary ova in highly hypertrophied minute ovarian fragments.* x 200.
A. Normal ovary of rabbit 18 months old (Prot. Nr. 50).

Severe criticism has been directed against the conclusions of Steinach and Holzknecht, and it has been pointed out that in the ovarian graft oöcytes and small normal follicles are present. But as I desire to emphasize again, this does not matter.

FIG. 109.—*Disappearance of primary ova in highly hypertrophied minute ovarian fragments.* x 200.
B. Ovarian fragment of animal of same litter (Prot. Nr. 52). Thick capsule of connective tissue. No primary ova to be seen in the section. For details see the text.

The point is, that there is in the ovarian graft an *acceleratep* follicular development and, as a result of this, an *hypertrophy* of the interstitial tissue; there is at the same time an *intensified* hormonic effect (development of the mammary gland). Then we must assume that the ovarian change referred to, the intensified production of lutein cells or of interstitial cells, is the cause of the greater hormonic effect, or the cause of an intensified production of sexual hormones.

We have seen above that it is very likely that an hypertrophy of the interstitial cells takes place both in auto- and homoiotransplantation. If this is true, one might expect to find evidence of an intensified internal secretion also after engrafting an ovary into a castrated female. In the first edition of this book I pointed out that the microscopical figures published by *Marshall and Jolly* (1907) suggest that the uterus was more developed in the animal with autotransplantation than in the normal animal; the original coloured figures 5 and 7 on Plate II. of their paper may be referred to here; but the black and white reproduction shows this clearly enough (Fig. 49). I observed a rabbit on which involuntarily an autotransplantation was made, and which gave further support to my suggestion (1922 b). I castrated this animal at an age of about two months. When killed sixteen months later the uterus was found to be even more developed than in one of the normal controls of the same litter. On making a thorough examination of the abdominal cavity, we found two pieces attached to the dorsal peritoneum and resembling ovarian tissue although no Graafian follicles were visible. The microscopical examination showed that the pieces were really ovarian fragments which evidently underwent an enormous hypertrophy and very profound alterations. Although the weight of the two pieces together was about that of one normal ovary of the normal control, only a few young ova were present in these fragments (*Fig.* 109 B); their number may be estimated at a small percentage of the normal number of ova (*Fig.* 109 A.) Follicles at different stages of ripeness were present, but hardly any distended Graafian follicles; this indicates that there was an accelerated follicular atresia in the ovarian fragments. The follicles were embedded in the mass of interstitial cells in such a manner that they represented more or less the central part and the interstitial tissue the cortical part of the fragment. The whole fragment was covered by a thick capsule of connective tissue. The lack of young ova in these ovarian fragments is to be explained by the fact that most of them had entered upon follicular development, the hypertrophy of an ovarian fragment being nothing else than the follicular development of a relatively greater but absolutely normal number of ova (*Lipschütz*, 1922 a, b, c). My observation gives strong support to the assumption that the cells derived from the follicle at different stages of development form part of the endocrine apparatus of the ovary whereas the oöcytes themselves are not involved in the endocrine function.

Recently *Haberlandt* (1921, 1922) has performed experiments which give further evidence of the intensified endocrine function of the transplanted ovary. We shall discuss these in another section of this chapter.

We still have to deal with the fact that the endocrine function of the ovary is regulated by quantitative laws very different from those valid for the testicle. Whereas it seemed possible to us to accept in accordance with Pézard the validity of the law of "All or Nothing" for the testicle, we see that, for the ovary, increase of endocrine cells causes increase of endocrine function. The climax of the latter is attained when the corpus luteum graviditatis is formed.

5. THE CONDITION OF THE OVARY IN PARTIAL CASTRATION.

We saw that testicular fragments never hypertrophy in the mammal, but nevertheless are sufficient for performing a normal endocrine function, even when they are extremely small. On the other hand, ovarian fragments hypertrophy to a very considerable extent, as was demonstrated by *Bond and Horsley*, and *Carmichael and Marshall* (1908), and confirmed by ourselves (1922). Very small ovarian fragments can attain the volume of a normal ovary. In this respect there is no difference between ovarian fragments in partial castration and the whole ovary after unilateral castration; various authors, and lately Arai and myself, have demonstrated that the remaining ovary doubles its weight. *Arai* (1920 a, b) has shown that the number of ripening follicles in the remaining ovary is twice as large as in the normal one. This means that the number of ripening follicles present in the body of a given species is constant at a given age. Arai has counted also the total number of ova in the normal and the remaining ovary, and has come to the conclusion that the total number of ova in the latter is the same as in the former. Evidently the hypertrophy of the ovary is to be explained by the fact that a relatively larger number of ova enters upon follicular development.

In our experiments with partial castration of rabbits we were able to demonstrate that this suggestion is justified. In fragments which represented originally a quarter and a half of an ovary (the second ovary having been removed), and which attained the volume of about a normal ovary, we found that the number of young ova was very reduced (*Fig.* 110).

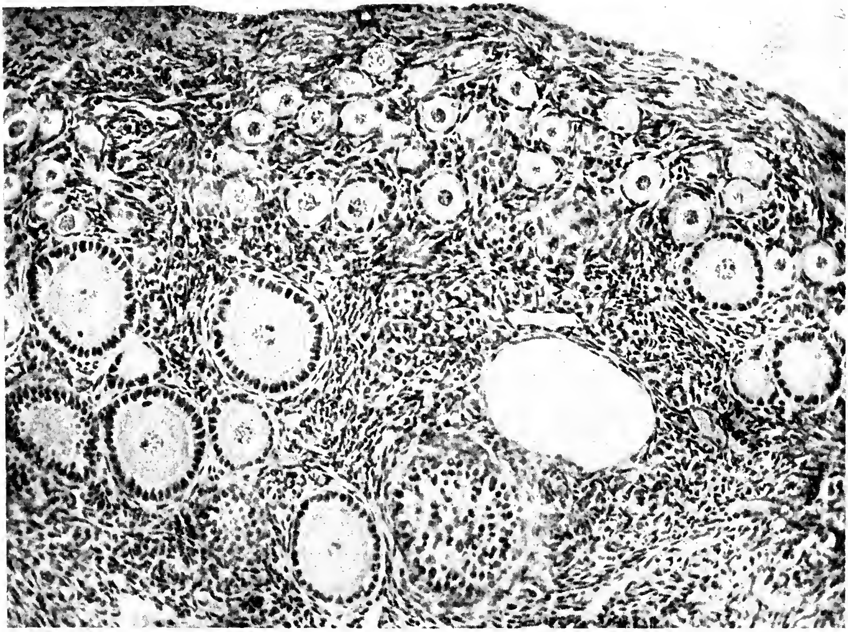


FIG. 110.—*Decrease of number of oöcytes in ovarian fragment.* x 200.
A. Section through ovary of rabbit 7 months old (Prot. Nr. 136).
Prepar. of Wagner; photo of Kull.

In another case which we described in the foregoing section, the number of young ova in the hypertrophied fragments was extraordinarily small, representing only about two or four per cent. of the normal On the contrary, the number of ripening follicles and the quantity of interstitial tissue were as large as in a normal ovary. Evidently the majority of young ova had been used up in follicular development.

In view of all these observations it seems clear that hypertrophy of ovarian tissue implies that a relatively larger number of ova present in the remaining ovary, or in the ovarian fragment, enters into follicular development, and that there is no increase in the number of ova.

New formation of ova in post-natal life may indeed be possible under certain circumstances. *Athias* (1920) relates having observed such a phenomenon in an engrafted ovary in the guinea pig.

FIG. 110.—*Decrease of number of oöcytes in ovarian fragment.* x 200.

B. Section through ovarian fragment of rabbit of same age as A (Prot. Nr. 134). The fragment represented originally about ¼ to ⅓ of an ovary, but six months later it had almost the same weight as a normal ovary at this age. A place extremely "rich" in oöcytes was chosen in B. The number of oöcytes in B is much reduced as compared with A.

Prepar. of Wagner; photo of Kull.

When comparing the condition of a testicular and an ovarian fragment, two questions arise:—first, how the difference between them can be explained, and secondly, whether the hypertrophy of the ovarian fragment is really a compensatory one for endocrine purposes.

The first question can be settled, I think, without special difficulty. Since the number of young ova in readiness, so to speak, for follicular development is very great, there is in an ovarian fragment an almost endless supply available for follicular development or "hypertrophy," unless indeed the fragment is extremely small, as in our last experiment, related above. The case of a testicular fragment seems to be a wholly different one; what takes place in a testicular fragment is only development up to a normal volume corresponding to the given fragment of a testicle, since, after completion of spermatogenesis in all the tubules of a fragment, there seems to be no anatomical substratum for further growth. In other words, every cubic millimetre of testicle has a constant maximal potential mass, which is attained when spermatogenesis is completed. On the contrary, a cubic millimetre of ovary has no constant or limited potential mass, the latter depending upon the relative number of ova which enter upon follicular development. It would appear, therefore, that the dynamics of testicular and ovarian growth provide an explanation for the differences as observed in these respects between an ovarian and a testicular fragment.

The second question is of a more difficult order. There is normally in the female greater variation in the condition of the sex characters, and no doubt exists that this variation is connected with follicular development in the ovary. The relatively larger number of ova entering in an ovarian fragment upon follicular development may be considered as participating in a process of reparation or regeneration. There may be some general factors in the female organism regulating the number of follicles in the ovarian tissue, like the factor regulating in the male organism the speed of testicular growth (*Lipschütz*, 1923 and 1924 a; *Lipschütz and Voss*, 1924 c). We have no knowledge of the special localization of such hypothetical factors.

6. THE INTERNAL SECRETION OF THE CORPUS LUTEUM.[1]

We have seen that genetically the interstitial cells of the ovary belong mostly to the follicular apparatus, and that these cells are, so to speak, discharged from the atretic follicles into the ovarian stroma. Further, we saw it was very probable that these cells represent an endocrine organ, which can hyper-

---

[1] The new papers of *Marshall* (1923) and of *Corner* (1923) and the new edition of *Marshall's* book (1922) may be referred to here.

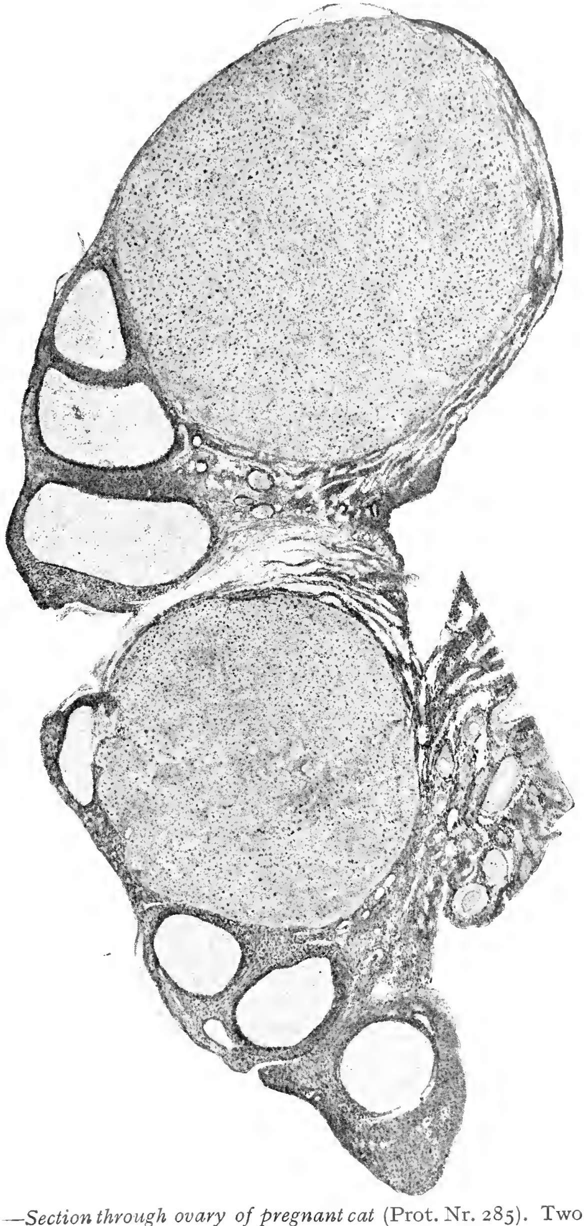


FIG. 111.—*Section through ovary of pregnant cat* (Prot. Nr. 285). Two embryos were found in the left uterus; ovary from the same side. Two corpora lutea and great quantity of Graafian follicles. The corpora lutea occupy almost the whole ovary.—Prepar. of Wagner; design of Lehbert.

trophy under experimental conditions, and cause an hormonic effect, as normally observed only in gravidity. In view of these results two new questions arise: are there, first, *genetical* and, secondly, *physiological* relations between the cells of atretic follicles or the interstitial cells on the one hand, and the corpus luteum, which characterizes the ovary during gravidity, on the other?

(*a*) *Histogenesis of the corpus luteum.*

The origin of the cells of the corpus luteum graviditatis (*Fig.* 111, see also *Fig.* 98) has been a matter of much discussion. According to most authorities these cells are derived only from the membrana granulosa; others are of the opinion that cells of the theca interna also give rise to cells of the corpus luteum. The first theory implies that the cells of the corpus luteum are of epithelial origin only, whereas, according to the second, cells originating from connective tissue can also become luteal cells.

Great importance has been attributed to this question by various authors. If the corpus luteum is formed only from cells of the membrana granulosa, and if the cells of the interstitial tissue (to which atretic follicles belong) originate only from the theca interna or from stroma cells, the two formations are genetically different. But, on the other hand, if the cells of the corpus luteum are of a mixed origin, the whole apparatus of epithelioid cells of the ovary might be regarded as genetically one. It seems clear that this conclusion might supply evidence of a functional similarity between the two parts of the ovary. I myself have no experience of this field of enquiry, and it is for the histologist to settle the question as to the origin of the cells of the corpus luteum. Comparative observations on different species play a great rôle in these discussions. Most observers agree that in lower vertebrates, as in fishes, amphibians and reptiles, the corpus luteum, when present, is built up out of the epithelial cells of the granulosa (*Marshall*, 1905). On the contrary, *Aschner* (1914 a, 1918) pointed out that in some species the ovum is surrounded only by a simple layer of cells belonging to the granulosa, and that cells of the theca take an important part in the building up of the corpus luteum. But this is not true for all lower vertebrates, an hypertrophy of the cells of the granulosa having been observed by

Mingazzini in reptiles, and by Giacomini in birds, amphibians and fishes. The condition also seems to vary in the different species of fishes (Wallace), some presenting hypertrophy of the follicular epithelium and others not. Van der Stricht made observations on the bat and concluded that here the corpus luteum is of a mixed origin. *Bell* (1920) holds that the corpus luteum is formed entirely of cells of the theca interna. On the contrary ***Fraenkel*** (1914, p. 20) defends the view that the corpus luteum is formed only by cells of the membrana granulosa, in accordance with Sobotta for the rabbit and mouse, with Franz Cohn for the rabbit, and with Rob. Meyer and others for man. *Marshall* (1901 and 1903, quoted from *Marshall,* 1905) has demonstrated this for the sheep, and *Zietschmann* (1921) for the cow. As regards birds, amphibians, reptiles and fishes, Fraenkel declares that no corpus luteum exists in these species at all, and that even in the monotremes and marsupials the corpus luteum is only rudimentary. According to Hill and O'Donoghue the corpus luteum is present in the monotremes, and certainly in the marsupials.

The contradictory statements of the above-mentioned authors as to this question are evidently caused by the fact that there is in reality no sharp line of demarcation between the atretic follicle and the corpus luteum, just as there is no sharp distinction to be drawn between the atretic follicle and the interstitial tissue. Aschner insists that there is something approaching an identity between the atretic follicle and the corpus luteum in lower vertebrates. The former is often spoken of as the so-called "corpus luteum atreticum" in some mammals, i.e., in the case of atretic follicles closely resembling real corpora lutea. Even Fraenkel admits that sometimes the atretic follicle is formed by cells both of the membrana granulosa and theca interna intermingled with each other, although in general, according to him, only the cells of the theca interna form the atretic follicle. Various authors (Völker, Winiwarter Sainmont and recently *Gerlinger,* 1923 a) have called attention to the so-called "partial" corpus luteum, being a follicle which has not ruptured, but is undergoing atresia and producing lutein cells derived from the granulosa only in a limited zone of the wall.

Many authors have insisted on the great resemblance between the cells of the atretic follicle (the theca-lutein cells of Seitz) and the lutein cells of the real corpus luteum. On the other hand, some authors, as Winiwarter and Sainmont, hold that the atretic follicle, like the corpus luteum is composed only of cells of the granulosa. But if the assumption of *Lane-Claypon* quoted from *Marshall,* 1905), of *Ochoterena and Ramirez* (1920) and of *Goormaghtigh* (1921) as to the origin of the interstitial cells and of the cells of the follicular wall from the germinal epithelium is true, all these controversies lose their importance.

Speaking generally, the process of formation of a corpus luteum seems to be as follows. The epithelial cells of the membrana granulosa become hypertrophied; there is also probably a proliferation of these cells. The follicular membrane between the membrana granulosa and the theca interna ruptures; both cells intermingle, if the origin of the corpus luteum is a mixed one, as possibly is the case in some species, since the epithelioid cells of the theca interna often resemble the cells of the granulosa to such a degree as to be indistinguishable from one another. Connective tissue with blood vessels grows into the mass of epithelioid cells, and the whole structure becomes vascularized in such a manner that every cell seems now to be in direct communication with a blood vessel. Fatty inclusions appear in the cells; these inclusions are sometimes of a yellow colour—the so-called lutein. In the ovary of man or of the horse the corpus luteum may occupy half of the ovary, in the cow much more. The corpus luteum persists only for a certain time, undergoing afterwards sclerotization or hyaline degeneration; it may be that in some species, as in the rabbit, the corpus luteum becomes converted into interstitial tissue. No essential difference exists between the corpus luteum graviditatis and the corpus luteum menstruationis; the difference is only that in pregnancy the corpus luteum persists for a longer time.

We mentioned that there are in the mammal transitions between the atretic follicle and the corpus luteum. In the preceding sections we pointed out that there are transitions between the interstitial tissue, like that in the ovary of the rabbit, and the masses of epithelioid cells of the theca interna remaining in the wall of an atretic follicle. I think it is clear enough that there is a close histological and genetic relationship between all the epithelioid cells in the ovary, between the interstitial cells, the cells of the atretic follicle and those of the corpus luteum. In view of this close relationship it is easy to understand why there are so many terms for the derivatives of the follicle in the ovary of the mammal and why so many contrary opinions have been held as to the origin of the corpus luteum.

It would seem that the first of the questions put at the beginning of this section may be settled in a positive sense. The second question, dealing with the physiological relationships between the interstitial tissue and the corpus luteum, will be discussed in the following section.

(*b*) *The functional relationship between the corpus luteum and the interstitial tissue.*

Different authors, such as Beard, Prénant, and Born, have emphasized that the corpus luteum is a gland with an internal secretion, that the corpus luteum causes by its hormonic action the cyclical uterine changes of menstruation, and the changes which the uterus undergoes in pregnancy. A glance at a microscopical section of the corpus luteum shows that the closest relations between epithelioid cells and blood vessels are present, just as in the liver. And we can fully agree with *Fraenkel* (1910) that there could, indeed, be no better example to show to the beginner to illustrate the structure of a gland with an internal secretion than the corpus luteum (*Fig.* 112; see also *Fig.* 94 a), where each cell is in direct relation with a blood vessel, and for the most part surrounded by blood vessels on every side. *Fraenkel* (1903) showed that pregnancy can be brought to an end in the rabbit, if the corpora lutea are destroyed by cauterization during the first six days after conception; a result like that obtained by castration. Fraenkel performed 163 of these experiments, and always with the same result. Further, *Fraenkel* (1903, p. 480) demonstrated that the next menstruation can be prevented in man by cauterization of a fresh corpus luteum; Fraenkel made this experiment several times when performing abdominal operations, and he pointed out that such a cauterization is not only without any danger, but may be positively useful, as convalescence is furthered if not interfered with by menstruation too soon. *Fraenkel* concluded (1903, p. 480) from his experiments that the corpus luteum has in all mammals the same glandular functions after whatever intervals it reappears; the function of the corpus luteum is to prevent the return of the uterus to an infantile state or to prevent climacteric atrophy of the uterus, and, further, to render possible the transformations in the uterine mucosa necessary for the fixation and growth of a fertilized ovum. If fertilization has really taken place, the corpus luteum remains functional for a further period, assisting in the uterine transformation and in the development of the ovum. If fertilization does not take place, menstruation sets in, and the corpus luteum enters into regression.

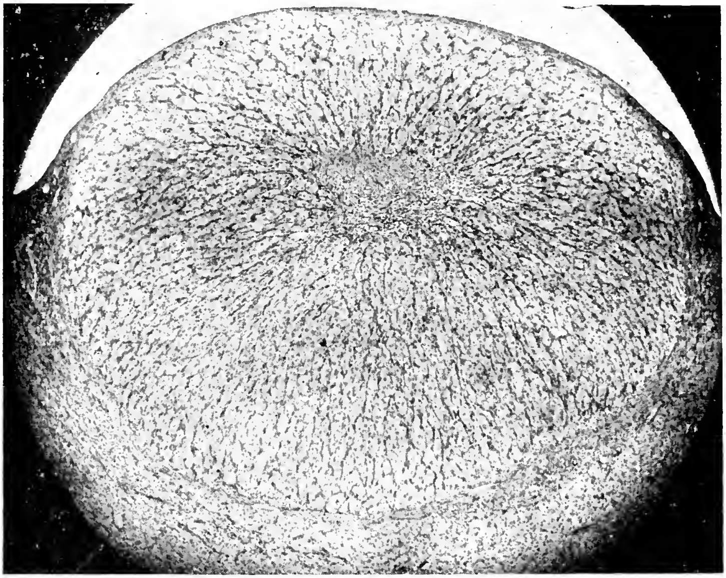


FIG. 112.—*Section through fresh corpus luteum of rabbit* (Prot. Nr. 104). x 40. The c.l. protruding out of the surface of the ovary.—Prepar. of Wagner; photo of Kull.

The experiments of Fraenkel were controlled and confirmed by several authors; the question was studied especially by *L. Loeb* (1910, 1917, 1918) and *Bouin and Ancel* (1910, 1911).

L. Loeb has shown in numerous experiments that the production of a deciduoma or a maternal placenta in the absence of a fertilized ovum can be evoked, if a few days after spontaneous ovulation incisions are made in the uterine mucosa. If the ovaries or the corpora lutea are extirpated, the deciduoma is not produced.

In the rabbit there is generally no spontaneous periodical ovulation such as is observed in various other mammals (according to Bouin and Ancel in the dog, horse, pig and cow, in monkeys, and in man). But ovulation takes place in the rabbit after coition or sexual excitement. Now, Bouin and Ancel caused an artificial rupture of Graafian follicles in virgin rabbits by puncturing the ripe follicles. They also arranged for coition with males in which several months previously the vasa deferentia had been ligatured; in these experiments ovulation took place without pregnancy following. Ancel and Bouin stated that in these animals a growth of the uterus and the mammary glands occurred such as is normally observable at the beginning of pregnancy (*Fig.* 113). The mammary gland remained in this state of hypertrophy for about two weeks; the climax of the uterine development was attained in about ten days. Afterwards both organs began to decrease, and in about 25 days passed back to their original state. There is for a certain time a state of *pseudo-pregnancy*, to use an expression of Hammond and Marshall. The examination of the ovaries showed that after the artificial rupture of two or three ripe follicles, these cease to develop, but other ripe follicles of the same or the second ovary transform themselves into corpora lutea. If all ripe follicles are punctured or destroyed by cauterization, there is no formation of corpora lutea. In the latter case no changes occur in the uterus or in the mammary gland. There is a formation of corpora lutea also after sterile coition with a ligatured male. If the corpora lutea formed are destroyed, the characteristic changes undergo rapid reversal. Niskoubina, a pupil of Bouin, showed that these experimentally produced corpora lutea resemble, in their appearance and in their duration, normal corpora lutea as present in the first half of pregnancy. As Bouin and Ancel point out, there is also a striking time relation between the development of the experimentally produced corpus luteum and the changes which the uterus and the mammary gland undergo; the regression of the corpus luteum begins about two weeks after puncture or sterile coition, i.e., at the same time as regression of the uterus and the mammary gland sets in. From all these experiments Bouin and Ancel concluded that the characteristic changes which take place in the uterus and in the mammary gland in the beginning of pregnancy are caused by the corpus luteum. The

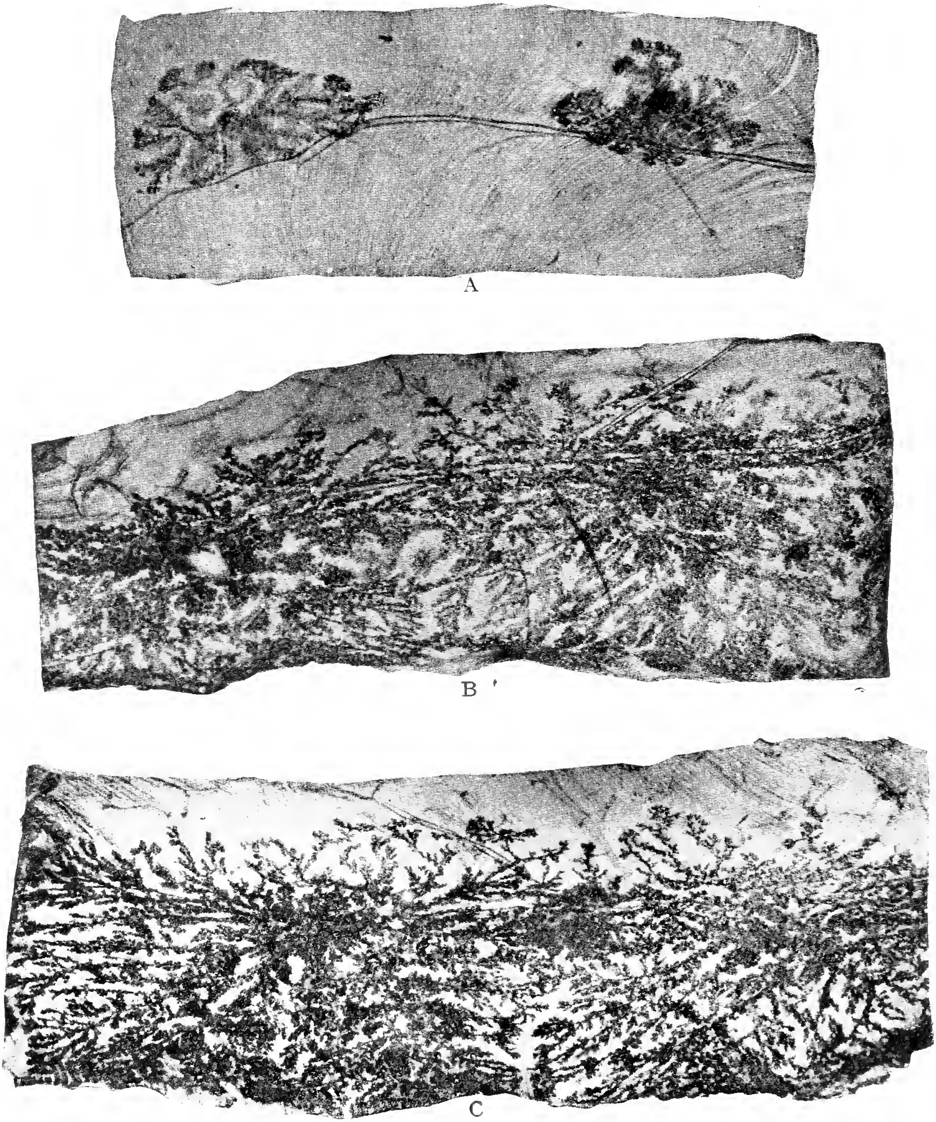


FIG. 113.—*Influence of the corpus luteum on the mammary gland of the rabbit.* —From Ancel and Bouin.

A. Two mammary glands of a normal rabbit during heat.

B. Virginal rabbit 5 days after a sterile coition. Confluence of both highly developed glands.

C. Virginal rabbit about 5 days after punction of ripe follicles.

placenta and the foetus are evidently not necessary for the occurrence of these changes. The conclusions of Bouin and Ancel are in accordance with those of Fraenkel. *Hammond and Marshall* (1914) confirmed Ancel and Bouin's description of the uterine changes occurring under luteal influence in the rabbit.

It is not intended here to give a full account of all the controversies concerning the question as to the endocrine function of the corpus luteum. This organ is, indeed, not the only factor involved in the uterine changes in pregnancy, as is shown by the above-mentioned experiments of L. Loeb, in which deciduomata were experimentally produced at the time of "heat" by mechanical stimulation of the uterine mucosa. On the other hand, Loeb showed it to be probable that the longer persistence of the corpus luteum is due to the presence of the maternal placenta. He stated that after degeneration of the experimentally produced deciduomata ovulation again occurred, i.e., the corpus luteum which hitherto inhibited ovulation now ceased to do this. Possibly the embryo contributes towards the preservation of the decidua, and the decidua to the persistence of the corpus luteum, which in its turn inhibits a new ovulation and assists in the further development of the decidua. The observations of *Biedl, Peters* and *Hofstätter* (1921), who, like Heape, implanted fertilized ova into the uteri of non-pregnant rabbits, give some experimental evidence for such an assumption. These observers stated that the implanted ova can undergo further development for some time in the foster-mother. They state further that they sometimes observed changes in older corpora lutea in the ovary of the uterine foster-mother, and these may be considered as of the nature of a process of reactivation. The question needs more detailed investigation before a complete solution can be reached.

In a preceding section of this chapter we have seen that an intensified follicular atresia, as caused by X-rays or by transplantation into the male, and as augmenting the quantity of the epithelioid interstitial cells in the ovary, is followed by changes in the uterus and the mammary gland such as are characteristic of pregnancy; in these latter experiments the changes were even more pronounced than in those of Bouin and Ancel. An hypertrophy of the mammary gland and milk secretion can evidently take place without real corpora lutea having been formed. After all it seems clear that the hormonic function accomplished by the corpus luteum can be performed also by different kinds of follicles becoming atretic, by epithelioid interstitial cells passing from the latter into the stroma. A similar statement was made by *Sand* (1919, pp. 141 and 175) as a result of experiments upon ovarian transplantation. As to the hormonic effect, there is no essential difference between the cells of follicles undergoing atresia and the cells in process of being changed into those of corpora lutea. The corpus luteum graviditatis seems to represent merely a new and plentiful supply of very active endocrine cells resembling all the other epithelioid interstitial cells of the ovary.

We see that the second question we have set ourselves must be answered also in a positive sense. There is evidently a close functional relationship between the interstitial cells and the corpus luteum. We must assume that, as to the hormonic function, they differ from one another only quantitatively.

There are many other proofs of this contention. It is known that the number of atretic follicles in the human ovary is much increased in pregnancy. All authorities have made similar statements, although they disagree very much as to the interstitial tissue in the ovary; the latter disagreement is evidently due, as already mentioned, rather to a difference in terminology than to conflicting observations. Now it is of great interest to note that, according to Aschner, the increase in follicular atresia in the human ovary takes place in the second half of gravidity, i.e., when the corpus luteum has already undergone degeneration. If this statement of Aschner is true, one might agree with *Biedl* (p. 337) that evidently the interstitial cells derived from the atretic follicles take up the function of the lutein cells of the corpus luteum after degeneration of the latter; possibly lutein cells of the theca interna take up the function of the lutein cells of the granulosa. A further proof of the above thesis seems to be given by the observation of Aschner that the interstitial tissue is more developed in those species where the number of young in the litter is greater. The view taken by Aschner is worth further comparative investigation. (See the statement of Athias on p. 217.)

The observations made by *Athias* (1921) on the motility of the uterus are also a proof that the corpus luteum is not the only organ concerned in hormone-production. Athias stated that the spontaneous movements of the uterus, which, as he showed experimentally, depend on the sexual hormones, appear in the guinea pig at an age of one month, and attain their maximal height at an age of about two months. Now the first ovulation takes place long afterwards. Athias suggests that the chromatolytic processes going on in the granulosa of the follicle during atresia (*Salazar*, 1919), and resembling secretory processes very closely, are a source of sexual hormones. Production of hormones is evidently possible only when a certain degree of development is attained by the follicle and the interstitial cells; this is shown by the following observation of Athias. The ovary of the guinea pig, according to Athias, already contains interstitial cells and normal follicles in the first month; since uterine movements are absent, it seems clear that at this stage follicles and interstitial cells are not capable of furnishing the hormones acting on the uterus.

Interesting experiments on the question of functional relationship between the corpus luteum and the interstitial tissue have been performed lately by *Haberlandt* (1921, 1922). It has long been known that ovulation is inhibited by the corpus luteum. *L. Loeb* (1910, 1918) showed that in the guinea pig extirpation of the corpora lutea in the first week after ovulation hastens the next ovulation. By extirpation of the corpora lutea an ovulation can be experimentally produced even in pregnancy, whereas there is normally, in the guinea pig, an atresia of all but the smallest follicles. These experiments show that the persistence of corpora lutea, not pregnancy itself, is what prevents ovulation. Ovulation can be experimentally inhibited by injection of an extract of corpus luteum, as shown by the experiments of *Pearl and Surface* (1914) on fowls, and *Herrmann and Stein* (1916) on rabbits and rats. Now Haberlandt engrafted subcutaneously into rabbits which previously had given birth to young the ovaries from pregnant animals; the normal ovaries remained untouched. One to four weeks after the operation the animals were put with males. Whereas normally fertilization takes place after two or three coitions, the experimental animals remained sterile for one and a half to three months, or after 14 to 21 coitions. Similar results were obtained with guinea pigs. The histological examination of the grafts revealed that no corpora lutea were present, but there was a small number of atretic follicles and a highly developed typical interstitial tissue. Since ovulation in the normal ovary was inhibited without corpora lutea being present in the graft, one must assume that the atretic follicles or the interstitial tissue produced hormones similar to those of the corpus luteum, and thus suppressed ovulation.

We have hitherto compared the interstitial tissue with the corpus luteum of pregnancy only. But the experiments of Fraenkel show that menstruation also depends upon the corpus luteum. Is there a similar functional relationship between the interstitial cells and the corpus luteum menstruationis? As already mentioned, the number of atretic follicles which constitute, in the human ovary, an organ homologous with the interstitial tissue of other animals, according to Aschner decreases in man gradually until puberty, when the first corpus luteum menstruationis appears. So one might suppose that the first corpus luteum menstruationis takes over the function of the atretic follicles in the same manner as the latter take over the functions of the degenerating corpus luteum graviditatis in the second half of pregnancy. But the statements of the different observers as to the quantity of interstitial cells, in the broader sense of the term, in the human ovary at different times are very conflicting. Aschner thinks that just as the corpus luteum menstruationis replaces functionally the interstitial tissue of the human ovary, so the corpus luteum appearing at the time of heat in the ovary of the lower mammals also replaces interstitial cells to a certain degree in respect of hormonic function.

Bouin and Ancel (1909) have discussed fully the question of functional relationship between the interstitial tissue and the corpus luteum menstruationis, or, to be more accurate, the periodic corpora lutea. They assumed that in those species where there is a spontaneous ovulation, as in man, monkeys, dog, horse, pig and cow, and where there is no interstitial tissue, in the sense of a parenchyma of epithelioid cells, but only nests of epithelioid cells in the form of atretic follicles, the periodic corpora lutea represent a physiological equivalent of the interstitial tissue. On the contrary, the interstitial tissue is well developed in those species where, according to Bouin and Ancel, no spontaneous ovulation occurs, as in the rabbit, guinea pig and cat. Here no periodical formation of new epithelioid cells takes place, and here the function of the latter is performed by the interstitial tissue in the restricted sense of the term. The authors pointed out that the interstitial tissue and the periodic corpus luteum are both derived from follicles, and both consist of similar cells, and that in species with spontaneous ovulation the first periodic corpus luteum appears at the time of puberty, at which time in species without spontaneous ovulation the interstitial tissue just attains full development. Bouin and Ancel hold the opinion that the interstitial tissue and the periodic corpus luteum are responsible for the development of the female sexual characters in the same kind of way as is effected in the male by the interstitial cells of the testicle; but they think that the corpus luteum graviditatis is functionally different from the interstitial tissue or the periodic corpora lutea.

Objections may be made to some of the details in the classification of Bouin and Ancel. A spontaneous ovulation may occur in the rabbit and in the guinea pig. This was already known to Bouin and Ancel. I have convinced myself that real corpora lutea may occur also in virgin rabbits even at an age of about seven months;[1] but in other cases, indeed, I could not detect real corpora lutea in the ovaries of virgin rabbits even 12 to 20 months old. Corpora lutea in virgin guinea pigs are described by *Aschner* (1914 b, p. 459). Corpora lutea have been found several times by various observers also in engrafted ovaries of guinea pigs and rats. There is also no sharp distinction between the real corpus luteum and the atretic follicle. It must be borne in mind further that in those species where a compact interstitial tissue is absent, atretic follicles are present in the ovary, and that there is no essential difference between these two formations (see also p. 227). This is why I proposed in the first edition of this book to alter the classification of Bouin and Ancel in the following manner: first, species in which periodic corpora lutea are not always formed and there is a well developed interstitial tissue, and, secondly, those with periodic corpora lutea and less developed interstitial tissue. In species where the periodic corpora lutea play a smaller rôle, the compact interstitial tissue acts as a compensatory organ. Notwithstanding the objections which have been

---

[1] Dr. Hammond has drawn my attention to the possibility of this being caused by the sexual intercourse between females as often observed. Then the corpus luteum of the virgin rabbit is to be explained on similar lines to those in the experiments of Bouin and Ancel.

raised to some details, it must be acknowledged that the classification of Bouin and Ancel marked an extremely important step in the development of the theory of the hormonic action of the ovary, as this classification implies that there is no essential functional difference between the follicles undergoing atresia or the interstitial tissue on the one hand, and the periodic corpus luteum on the other. Both furnish endocrine cells, and they can functionally replace one another.

The objections which may be made against the assumption of Bouin and Ancel that the corpus luteum graviditatis is functionally wholly different from the interstitial tissue or from the periodic corpus luteum, are of more importance. We have already discussed the functional relationship between the interstitial tissue and the corpus luteum graviditatis; the experiments of Steinach and Holzknecht provide definite proof of this. But the physiological relationship between the corpus luteum menstruationis and the corpus luteum graviditatis can also be proved. *Hitschmann and Adler* (1913) have shown that about ten days before menstruation the uterus undergoes changes characteristic of the beginning of pregnancy. The mucosa may resemble a decidua of early pregnancy to such a degree that there is no microscopical difference between the two; the cells are polygonal, the glands are long and curved, the blood vessels are enlarged. Evidently the essential part of the process is not the menstrual bleeding, but the early transformation of the mucosa into a decidua. The menstrual bleeding is only a sign of the beginning of involution, which takes place if there is no fertilization. Now we know from the observations of Fraenkel on the ovaries of women in abdominal operations undertaken for other reasons, that the new corpus luteum is already present about ten days before menstrual bleeding occurs, just at the time when, according to Hitschman and Adler, the premenstrual changes set in. There is also a swelling of the breasts, occasionally followed by secretion. Similar observations concerning the corpus luteum and the premenstrual uterine changes have been made also by other workers such as *Robert Meyer* (1913) and *Carl Ruge II* (1913). These time relations between the corpus luteum menstruationis and the cyclic changes in the uterus and in the breasts, which are characteristic of the beginning of pregnancy, are a sufficient proof that a functional relationship exists between the corpus luteum menstruationis and the corpus luteum graviditatis. The menstrual bleeding is only one of two alternative processes which the uterus undergoes after the premenstrual changes have set in; these premenstrual changes are followed by pregnancy when an egg has been fertilized and has entered into the uterus, or else they end by an expulsion of the hyperæmic mucosa if fertilization has not taken place. There is not, however, complete unanimity among the different authors in regard to the dependence on the corpus luteum of the cyclic uterine changes in man. This question we shall return to in the next section.

The statements of *Marshall and Halnan* (1917) on the correlation existing between ovarian changes and those in the uterus and in the mammary glands of non-pregnant dogs after the period of heat, are of interest here. The authors kept under observation bitches for about 30 to 40 days after the beginning of bleeding from the vaginal opening. Histological examination of the ovaries revealed the persistence of corpora lutea, which were in different stages of development. The uterus and the mammary glands were found to undergo changes of a similar kind to those which take place during pregnancy, but not to reach the same degree of development. Retrogression of these organs set in about 30 days after ovulation, but the mammary gland remained for a longer period in a state of activity. Marshall and Halnan conclude that in the case of the non-pregnant dog after "heat," a series of changes homologous with the changes occurring in the pseudo-pregnant rabbit takes place; in both cases the changes are correlated with luteal development in the ovary. The persistence of corpora lutea in the ovary of the non-pregnant dog, "which is possibly greater in some individuals than in others, elucidates the not uncommon phenomenon of bitches which had not been impregnated secreting milk at or near the end of the pseudo-pregnant period." An investigation on the correlation existing between ovarian and uterine changes was made also by *Gerlinger* (1923 b) in the laboratory of Bouin. There is no doubt that the phenomena of heat are correlated with follicular processes in the ovary.

It is a question of a different order as to why after fertilization further changes take place in the uterine wall, and especially in the mammary glands, which are a long distance off from the foetus. We must assume that an influence is exerted by the placenta and the foetus by means of hormones. This influence might be either a direct or an indirect one. In the first instance substances from the placenta would be carried by the blood to the mammary glands, and so act on them. In the second, which is very probable, these substances would act also on the ovary; that such an action really takes place is rendered likely by the fact that the corpus luteum of pregnancy persists longer than the corpus luteum of menstruation or the periodic corpus luteum. The above-mentioned observations of L. Loeb on the relation existing between an experimentally produced placenta and the ovarian changes may be again referred to in this connection. One may assume that the influence the placenta has on the mammary glands may here be indirect, the development of the mammary gland being caused by an increased formation of endocrine cells in the ovary, depending upon the placenta. Weighty evidence for such an assumption is given by the above-mentioned experiments of Steinach and Holzknecht on guinea pigs treated with X-rays, where growth of the mammary glands and milk secretion were observed without a placenta having been formed. A further proof is given by the numerous experiments of Steinach, Athias, Sand, Moore, Lipschütz and his co-workers, who observed milk secretion in male animals after implantation of ovaries. But, on the other hand, it seems clear that besides the influences exerted on the mammary gland by the ovary, there must be still other factors at work, since we know that the growth of the mammary glands does not cease if castration is performed in the second half of pregnancy. It may be that the changes produced during pregnancy in the ovary are followed by changes in other ductless glands, and there are many indications that this actually happens, All these manifold factors must be taken into consideration in dealing with the question as to the factors responsible for the hypertrophy of the mammary glands in pregnancy and for milk secretion after birth.

(c) *Objections to the theory of the internal secretion of the corpus luteum.*

Objections have been made to the assumption that the corpus luteum causes menstrual changes or the characteristic cyclical changes of heat. These objections have been discussed especially by *Aschner* (1918, pp. 46–57) for menstruation, by *Marshall* (1910, pp. 336–345), and by *Marshall and Runciman* (1914) for the oestrous cycle.

It has been pointed out by different authors that the time relations between the formation of the corpus luteum and the appearance of the menstrual changes in the uterine mucosa cannot be taken as a proof that a connection exists between the two. It has been claimed that the uterine changes begin before the follicle is ruptured, i.e., at a time when the ripe Graafian follicle is still present. More recently *Schickelé* (1921) has insisted on the fact that the premenstrual uterine changes may occur when no corpus luteum is to be detected in the ovary, and that there may be a corpus luteum in the ovary without premenstrual changes taking place in the uterus. A similar standpoint is taken by *Henry* (1922). It has been also found that after removal of an ovary with a corpus luteum menstruation occurred two or four days after the operation. The authors concluded from the latter observation that the corpus luteum inhibits menstruation. A further proof of this assumption, according to Aschner, exists in the fact that several days after removal of one or both ovaries a bleeding from the uterus may often occur, and that women with a unilateral cyst of the corpus luteum show amenorrhoea. We shall show below that these clinical observations are by no means contrary to the conception of the endocrine function of the corpus luteum.

Menstruation occurs also in monkeys without ripe follicles or fresh corpora lutea being present at the time of menstruation (*Heape*). The same is true for "heat" in the lower mammals. In various species of bats heat and copulation occur in the autumn, whereas ovulation takes place only in the following spring; the spermatozoa are kept during the whole hibernation in the uterus It seems clear that in this case the heat cannot be caused by a corpus luteum or by a ripe Graafian follicle. In most animals ovulation is preceded by the so-called "pro-oestrum," which is the first stage of heat; this is further evidence that there are no corpora lutea at the beginning of heat. In those cases where an ovulation takes place sometimes only after coition (see above), heat cannot be caused by a real corpus luteum. Marshall and Runciman performed experiments on the question of time relations between ovarian changes and heat. They concluded tentatively that in the dog the commencement of heat does not necessarily depend upon ripe Graafian follicles or corpora lutea.

In subsequent experiments by *Marshall and Wood* (1923), however, it is shown that the occurrence of heat is normally correlated with the presence of follicles in what is called the "pre-inseminal stage." Marshall and Wood destroyed in dogs the ripe Graafian follicles by cauterisation a short time before a heat period was due; the period was missed; on the contrary, heat was not postponed, or only slightly so, if the follicles were cut into without being destroyed. The results were the same as in the former experiments of Marshall and Runciman, the Graafian follicles having been only pricked and ruptured.

According to Aschner, one must assume that the follicle, and especially the *ovum* itself, produces the internal secretion of the ovary. As to the ovum, this conception is absolutely unfounded and unacceptable; only a few of those who are consistently antagonistic to the conception of the endocrine function of the interstitial cells, have adopted this standpoint. There is, indeed, no evidence whatever that the ovum itself acts in the mammal as a gland with an internal secretion. In one of our experiments already mentioned only a small percentage of the normal quantity of ova was present in the hypertrophied ovarian fragments, and nevertheless this animal had a uterus better developed than that of a control animal of the same litter. The *ripening* of the ovum seems to be an essential influence, since the transformation of hitherto inactive cells into active endocrine cells evidently depends on some process going on in the ovum and connected with its ripening. The view that the follicles in general can cause menstrual changes by an internal secretion is not contrary to the assumption that the corpus luteum has this function. From what we have learnt in the preceding paragraphs of this section it seems clear enough that there is no definite histological or functional distinction between the different formations which are derived from the follicle. I think that *at all the stages of follicular development, beginning with a very early one up to a ripe Graafian follicle and to a corpus luteum, the follicle can produce an internal secretion, but its activity varies according to the respective stages.* A similar view is held by *Bucura* (1913), by *Sand* (1918, 1921), and by *Athias* (1923); but I cannot agree with Bucura that the interstitial cells of the ovary act only as a store for the hormones produced in the cells of the follicle. There is no evidence for such an assumption. This conception of Bucura follows from his belief that there is a sharp histological distinction between the "follicle" and the "interstitial tissue," the first consisting of epithelial cells of granulosa, the second of connective cells in the theca interna. But we have seen that such a distinction has no real existence.

When we have realised that, in regard to function, only quantitative differences exist between the different stages of follicular development, we can understand why cyclical uterine changes, as in the premenstrual phase, can begin before a ripe Graafian follicle or a corpus luteum is present. The ruptured and vascularized follicle on the one hand, and the premenstrual changes in the mucosa on the other, represent only stages in the chain of causation. Evidently the follicles at different stages of development differ from one another as to this endocrine activity only quantitatively; this explains why after irradiation by X-rays, when an increased follicular atresia is caused, and when an increased number of interstitial cells is activated, the same hormonic effect can be obtained as by means of a corpus luteum. By assuming that only quantitative differences exist in endocrine activity at different stages of follicular development, we can also understand why menstruation may occur in some animals (as with monkeys) in the absence of either a ripe Graafian follicle or a corpus luteum.

The same is no doubt true also for the heat periods of the lower mammals. It does not seem to me justifiable to centre the whole problem around the question as to whether a ripe Graafian follicle or a corpus luteum is present at the time of the prooestrum or not. It is necessary to determine rather whether at the prooestrum those changes take place in the ovary, which could be considered as signs of increased activity on the part of the endocrine cells. And it must be remembered that probably *different sorts of endocrine cells come into play,* and that the cells of the theca interna of atretic follicles, the cells of the granulosa of ripening follicles, and lutein cells of the corpus luteum may all participate. It follows that it is absolutely necessary to examine the whole follicular apparatus together with the stroma, regarding them as a unity, if we wish to investigate the question as to the dependence of menstruation, heat, and the changes of pregnancy upon the ovary.

Marshall and Wood (1923) hold that the interstitial cells, the ripening follicles and the corpus luteum produce qualitatively different hormones; the secretion of the interstitial cells may be responsible for maintaining the normal nutrition of the uterus, the secretion of the ripening follicles may account for the phenomena of heat, and the secretion of the corpus luteum may cause the uterine and the mammary hypertrophy during pregnancy. I do not think that there is as yet sufficient experimental evidence for such a definite delimitation between the different endocrine elements of the ovary.

The objections Aschner made as a result of clinical observations to the view that menstruation is caused by the corpus luteum are without foundation. Menstrual bleeding is evidently caused by the fact that the premenstrual uterine changes suddenly cease instead of continuing till pregnancy; this, we assume, is due to the corpus luteum entering upon regression. Now we can understand how it is that a corpus luteum which persists longer than usually can retard menstrual bleeding; a persisting corpus luteum is evidently correlated with a persisting premenstrual stage, and that means that menstrual bleeding will be retarded. Menstrual bleeding is nothing else than a pregnancy which has failed to come about, or a very early abortion. As *Labhardt* (1920) has rightly pointed out, it is gravidity, not menstruation, which is monthly prepared for in the uterus. The amenorrhoea observed in cases of unilateral cysts of the corpus luteum can be explained as a prolonged premenstrual stage, or a prolonged persistence of pregravid uterine changes. To decide this question it would be necessary to examine the uterine mucosa in such clinical cases. Aschner says that the menstrual bleeding is "inhibited" by the corpus luteum, this "inhibition" being one of the functions of the corpus luteum. This view to my mind is absolutely unacceptable. *The dynamics of the corpus luteum and of the uterine mucosa must be taken into account, if one is to understand the manifold clinical cases of amenorrhoea.* These dynamics will also explain why under certain conditions a premature disappearance or destruction of the corpus luteum can accelerate menstrual bleeding. It is clear that a premature menstrual bleeding may occur if the corpus luteum disappears at a time when the premenstrual changes have already attained a certain degree. And there will be no bleeding at all when the destruction of a fresh corpus luteum is brought about very early, when the developmental uterine changes have not yet taken place, as in the clinical cases of Fraenkel. (See p. 251.)

7. The Phases of Puberty in the Female.

Usually a marked distinction is drawn between the changes which take place in the genital organs and the mammary glands at the time of sexual maturation, and those which take place in these organs in pregnancy. There is evidently a tacit assumption that the attachment of the ovum and the placenta and foetus produce the changes characteristic of pregnancy which are indeed in many ways different from those occurring during sexual maturation. There can be no doubt that the placenta and the foetus are responsible to a certain degree for the changes of pregnancy. But, as already remarked, we have as yet no certain knowledge concerning the mechanism of this interaction. On the other hand it has been demonstrated that changes characteristic of pregnancy can be caused experimentally in virgin females by provoking certain changes in the ovary (X-rays, transplantation). So it seems impossible to separate rigorously the changes of pregnancy from those of sexual maturation, and we agree with Steinach that it depends upon the endocrine apparatus of the ovary whether the genital organs and the mammary glands shall attain the stage characteristic of the normal sexually mature virgin female, or whether these organs shall attain, after fertilization, the stage of development characteristic of pregnancy. It can scarcely be denied that other parts of the organism also and other ductless glands besides the ovary contribute to the changes of pregnancy. But nevertheless it seems more than probable that this interaction of the other internally secreting glands does not take place until the ovary has initiated the whole chain of changes.

We have seen also that there is no reason for assuming any essential differences between the corpora lutea graviditatis and those corpora lutea which are periodically formed after ovulation. There is in both cases a formation of luteal cells, the number of which is merely greater in the first case. As already remarked, the attachment of the ovum evidently produces a longer persistence and a greater development of the corpus luteum than is possible in connection merely with menstruation.

We have seen further that the premenstrual changes in the uterine mucosa resemble those of early pregnancy.

In view of these considerations it seems justifiable to regard the changes which occur in the organism during pregnancy as a further link in the chain of changes which begin in the organism at the time of sexual maturation. Every menstruation and every pregnancy are really of the nature of a repeated and highly intensified sexual maturation. If the first corpus luteum menstruationis can be called a "puberty gland" in a narrower sense of the term as causing sexual maturation or puberty, all the subsequent corpora lutea menstruationis and all the corpora lutea graviditatis are nothing else than parts of this puberty gland.

Just as we have compared all the changes occurring in menstruation, heat and pregnancy with those which take place at the time of sexual maturation or puberty in the narrow sense, so in the same way we may compare with the latter the different stages of development preceding sexual maturation. There is indeed at the time of puberty no process which is essentially new to the organism. There is in reality only an extraordinary acceleration of processes which were going on up to this time at a slow rate. This would be true even for an animal like the male rabbit, where there is possibly no internal secretion produced by the gonad between birth and early puberty. Furthermore, the formation of the first corpus luteum is not an essentially new process, since we have seen that there is no real difference as to function between atretic follicles and interstitial tissue arising from them on the one hand, and corpora lutea on the other. The first and all the following corpora lutea menstruationis and all the corpora lutea graviditatis are to be understood as parts of the female endocrine sex gland, originating together with all the other endocrine cells from the follicular apparatus from soon after birth till sexual maturity.

All the various endocrine cells which are to be found in the ovary represent an essential unity, the endocrine gland of the ovary. The manifold changes and rhythms undergone by the female, both somatically and psychically, in sexual life may be regarded as phases of puberty in a broader sense of the word, caused by developmental changes in the endocrine gland of the ovary. These quantitative changes evidently play in the female a much greater rôle than in the male.

We have supposed that there are for man two great phases of puberty corresponding to two climaxes in the development of the sexual gland. In a similar way we may suppose that there are two great phases of puberty for woman. The second great phase is the time when the first corpus luteum menstruationis develops, and this leads to the climax of puberty in woman, that is to say, to pregnancy. As to the hypothetical first great phase, we have at present little knowledge concerning the endocrine gland or, in other words, concerning the ovarian changes during embryonic life. Unanimity does not yet exist as to follicular atresia during extrauterine life, and there is still less knowledge of the follicular apparatus during embryonic life. According to some authors (see *Aschner,* 1914 b, p. 479) follicular atresia already occurs in the fifth month of embryonic development. Would it be possible to attribute to this follicular atresia the production of endocrine cells and hormones necessary for the development of the somatic sexual aharacters? It is conceivable also that the endocrine cells originate during embryonic life from other parts of the ovary. *Lacassagne* (1913, p. 201) is of the opinion that in the rabbit the epithelioid cells of the interstitial tissue may originate from ordinary stroma cells. According to *Athias* (1919) interstitial tissue is considerably developed in the bat during foetal life, the cells originating from the ovarian stroma. Evidently in the early embryonic development epithelioid endocrine cells arising from stroma cells predominate, the follicle becoming later the most important or even the sole seat of origin for these cells. But, as Athias states, the interstitial cells also of the young female bat all take origin from the ovarian stroma, and there is even in the adult bat a transformation of connective cells of the stroma into interstitial cells. The condition of the ovary during embryonic development may indeed be different in individual species. As far as I can understand from an extensive Dutch paper published by *Van Beek* (1921), a pupil of Krediet, follicular atresia begins in the cow at a very early period. But many authors state that no such process occurs before birth (see *Zietschmann*, 1921, pp. 242–43).

What we know concerning the parallelism between the differentiation of endocrine elements in the ovary and the differentiation of sex characters during embryonic development is still very vague.

It is possible that there is in women no embryonic climax in the endocrine gland. We have mentioned in Chapter II. that the bodily proportions of women resemble infantile ones more than those of men do; possibly transformation of an asexual or a bisexual soma into the female requires less hormonic activity than transformation into the male. In Chapter IX. we shall learn that with twin calves the female partner may be influenced by the sex gland of the male and even, as shown by Lillie and his co-workers, the female sexual organs be partly transformed into male ones; but the male partner is never affected by the female. I know very well that I am treading on uncertain ground in discussing these very hypothetical matters. But what I wish to emphasize is that all these questions concerning the endocrine sex glands during embryonic life must be investigated, not only by histological methods, but also by experimental ones. This has recently been done for the first time by Lillie's pupil Minoura.

CONCLUSIONS.

It is highly probable that the internal secretion of the ovary of the mammal is elaborated, partly by cells of the membrana granulosa, and partly by cells of the theca interna, and that these cells originate from follicles undergoing atresia or from ripe follicles rupturing and transforming themselves into corpora lutea.

It is difficult to decide whether the increased internal secretion of the ovary is caused by a proliferation or only by an activation of the endocrine cells. As with the interstitial cells of the testicle, which increase before or at the time of heat, mitosis seems to be rare in the epithelial and epithelioid cells of the ovary.

It is very probable that in man and in many other species the endocrine cells of the ovary become transformed, when they are not undergoing degeneration, into common connective tissue cells or into fibrous connective tissue. In these species there is, from a certain age onwards, a periodic new growth of endocrine cells (corpus luteum periodicum *or* menstruationis); also, these new endocrine cells persist only for a certain time.

The new growth of the endocrine cells is especially pronounced when ovulation is followed by implantation of a fertilized ovum, i.e., when gravidity takes place (corpus luteum graviditatis).

The endocrine cells of the corpus luteum graviditatis do not remain in functional activity for the whole duration of gravidity, and the organ finally undergoes sclerotization. Now, in the second half of gravidity other endocrine cells replace the degenerating corpus luteum; these cells originate from the theca interna, and possibly also from the granulosa of the follicles, which at that time undergo atresia in an increased number.

After gravidity is over new ova ripen and new endocrine cells are produced; a new menstruation or a new heat begins.

The cyclical uterine changes and the cyclical increase in sexual activity as observable in menstruation and heat, evidently depend upon an activation or a functional increase of the endocrine cells in the ovary.

From what we have seen above it seems clear that the endocrine function of the ovary is intimately connected with processes taking place in the follicle. Possibly these processes depend upon the ripening of the ovum, though it is not necessary that the ovum should attain maturity. Moreover, it is not even necessary that the ovum should remain alive. There seems to be a far-reaching analogy between the endocrine mechanism of the ovary and that of the testicle in the mammal. In both sexes the post-embryonic transformation of inactive cells of mesodermic or mesenchymatic origin may depend upon impulses coming from the generative tissue without full maturation or without even the further presence of ripening generative cells being necessary ("follicular theory"). Another possibility must also be taken into consideration. It is conceivable that the processes which take place in the cells of the granulosa or the theca interna are *primary* processes, both causing the development of the ovum, and at the same time being connected with hormone-production in the cells of the follicular wall itself.

B. OTHER VERTEBRATES.

It would be of great interest to know whether endocrine cells of a nature similar to those in the mammal occur also in the ovaries of other vertebrates. But we have already mentioned (Part A, Sect. 6, *a*) how conflicting the statements of different authors are concerning follicular development and the existence of the corpus luteum among lower vertebrates.

It was claimed that in amphibians the hormonic action which the ovary has on the soma, must be due to the ova, since there are no epithelioid interstitial cells present. We related in Chapter IV. the experiments of *Harms* (1914, p. 117) on *Bufo vulgaris*. He removed the testicle while leaving untouched the Bidder's organ. Harms relates that he observed in the operated animals the cyclical hypertrophy of the pads; the animals showed also the clasp reflex. If both the testicles and the Bidder's organ were removed, signs of castration showed themselves. But the cyclical changes took place in those animals into which after removal of the testicle and of the Bidder's organ, the latter was engrafted into the dorsal lymphatic sac. Harms considers the Bidder's organ as a rudimentary ovary in which interstitial cells are not to be found. So he concludes from his experiments that the germinative cells of this organ are capable of producing sexual hormones.

The experiments of Harms were repeated, and by no means confirmed, by *Guyénot and Ponse* (1922, 1923). These authors stated that removal of the Bidder's organ alone does not interfere with the normal cyclic changes of the pads or with the sexual behaviour. And contrary to the results obtained by Harms those animals whose testicles were removed (the Bidder's organ remaining untouched), showed no development of the pads when operated upon in June; those animals which were operated upon in October at a time when the pads of the next year's cycle are already partly formed, showed an anticipated regression of the pads. There was also a total lack of the clasp reflex, and the animals were not capable of copulation. The authors conclude from their experiments that the sex characters of the toad do not depend upon the Bidder's organ. They go so far as to suggest that this organ, being a rudimentary one, has no function at all; they consider it as some kind of progonad which stops functioning early, and is to the functional gonad somewhat as the pronephros is to the definite mesonephros in Batrachia.

The experiments of *Lauche* (1915) upon partial castration of frogs may also be mentioned here. He removed the greater part of the ovaries in two frogs, and stated that the number of young ova which entered upon development was greatly increased. There was, as he says, an acceleration in the development of ova. He concludes from his experiments that this is caused by an increased demand on the endocrine function of the generative tissue of the ovarian fragment. I do not find that this conclusion is justified. The experiments with partial castration in mammals, which we related above, show that the question is probably a much more complicated one.

What we know about the seat of hormone-production in the ovary of birds is also very incomplete, although several authors have contributed much to this question in the last five years. *Goodale* (1916) observed that castrated hens which had assumed the male plumage reassumed the female one, and afterwards again assumed the male one; Goodale observed six similar hens. One might suppose at first that there was in these cases a regeneration of ovarian tissue left unwittingly in the body; for some this may, indeed, have been so. But on the other hand Goodale states that in certain of his cases there was no trace of ovarian tissue. In these birds he found a new organ which developed in the place of the removed ovary. The histological examination, which was, however, incomplete, revealed that this organ resembled that which is to be found sometimes in normal hens and ducks on the right side in the place corresponding to the left ovary.[1] It is impossible to say whether there was any relation between the body on the

---

[1] It may be remembered that in birds the sexual organs develop only on the left side, whereas they degenerate on the right side.

right side and the organ which developed in the castrated hens on the left side; according to Goodale there may have been one. In castrated ducks, which showed a similar change from male to female plumage, Goodale found this organ only once.

The observations of Goodale make it highly probable that there was in his experiments a periodic change in hormone-production. "It is evident that if the organs are concerned with the changes, there must be some change in the activity of the organs either preceding the changes in plumage or accompanying them" (*Goodale,* 1916, p. 292).

Goodale mentions that these organs are very likely identical with the bodies described by various observers in cock-feathered females. We shall return to this important question in Chapter IX., when discussing some experiments by Pézard and Zawadowsky. The observations of Goodale leave no doubt that production of sexual hormones or production of hormones identical with the latter is possible without any ovum being present in the body.

A thorough investigation into the follicular development and the seat of production of sex hormones in birds has been made by certain American authors, especially by *Pearl* and *Boring* (1917, 1918 a, 1918 b). According to these observers there is during follicular development a complete degeneration of the granulosa, whereas the theca interna undergoes hypertrophy. The interstitial cells are derived from the theca interna. In the theca interna are located also groups or nests of epithelial cells, which are very different from the usual glandular interstitial cells. These cells, which they call "lutear cells," are about three times as large as the interstitial cells; their nucleus is bigger, the cytoplasm is usually clear and vacuolated in appearance; a few acidophile granules are occasionally present, while the real interstitial cells are crowded with granules. When follicular atresia is completed the big clear cells contain a yellow pigment, and this is why the authors call these cells lutear cells. There is, according to Boring and Pearl, no difference between an atretic follicle and a corpus luteum; "they are practically identical in the hen" (*Pearl and Boring,* 1918 a, p. 15). The lutear cells of the corpus luteum also are formed from the cells of the theca interna.

The interstitial cells in the ovary of birds are homologous with those in the ovary of mammals; according to Boring and

Pearl there cannot be the slightest doubt as to this. The interstitial cells of the ovary are identical, as to their structure, with the interstitial cells of the testis. Since the interstitial cells, according to Boring and Pearl, are not a constant element in the anatomy of the testis of the domestic fowl, the authors find it very difficult to suppose that these cells have any causal influence upon the sex characters. They consider the lutear cells only to be the seat of hormone-production in the ovary. This assumption is based mainly on a thorough study of several cases of hermaphrodite birds which revealed certain male characters. They examined the question as to how far the intermingling of male and female sex characters in any individual case could be explained by an abnormality in the structure of the respective gonads. From this detailed examination, Boring and Pearl concluded that the "amount of lutear cells or pigment is in precise correlation with the degree of external somatic femaleness exhibited by the individual." We shall return to this paper of Boring and Pearl in the chapter on "Intersexuality."

It may be insisted here that the conception of Boring and Pearl does not agree with the statements of *Goodale* (1919), and especially with those of *Nonidez* (1920, 1922). They consider the granule-containing interstitial cells of the ovary, like those of the testis, to be modified lymphoid elements. But besides these cells there is, according to Nonidez, in the ovary and in the testis of the fowl still another type of interstitial cells originating from degenerating sexual cords. These are the lutear cells of Boring and Pearl.

In 'Part A' of this chapter we learned the very interesting fact that ovarian fragments in the mammal undergo hypertrophy, this being caused by a relatively greater number of ova entering upon follicular development, and the absolute number of developed follicles after partial castration approaching the total number present in two normal ovaries. Similar statements were made by *Pearl and Schoppe* (1921), on exact quantitative lines, on the fowl long before the experiments of Arai and those of myself on the mammal. These authors found that in the ovary which regenerated from an ovarian fragment, originally of about $\frac{1}{3}$ to $\frac{1}{2}$ of a normal ovary, almost the normal quantity of visible oöcytes was present. As there is in the fowl no new formation of oöcytes, the "regeneration" of an ovarian fragment can here be explained only by the assumption that a relatively increased number of primary oöcytes proceed to develop till the normal number of follicles is attained. Since a similar conclusion can be drawn from the experiments of Lauche on the frog (see above), it seems very likely that the same quantitative law holds for all vertebrates.

We have already pointed out the fact that testicular hypertrophy is by no means a compensatory one caused by an increased demand for sex hormones after partial castration. There is likewise no reason to explain by such an assumption the increased follicular development in an ovarian fragment.

BIBLIOGRAPHY FOR CHAPTER V.

[* *Not seen in the original.*]

Ancel *et* Bouin. 1909. Sur les homologies et la signification des glandes à sécrétion interne de l'ovaire. *C. R. de la Soc. de Biol.*, 67, p. 464 et 497.

—— 1910. Recherches sur les fonctions du corps jaune gestatif. I. Sur le déterminisme de la préparation de l'utérus à la fixation de l'oeuf. *Jl. de Physiol. et Pathol. Génér.*, 12.

—— 1911. Sur les fonctions du corps jaune gestatif. II. Sur le déterminisme du développement de la glande mammaire aux cours de la gestation. *Jl. de Physiol. et Pathol. Génér.*, 13, p. 31.

Arai. 1920a. On the postnatal development of the ovary (albino rat), with special reference to the number of ova. *Amer. Jl. of Anat.*, 27, p. 405.

—— 1920b. On the cause of the hypertrophy of the surviving ovary after semispaying (albino rat) and on the number of ova in it. *Amer. Jl. of Anat.*, 28, p. 59.

Aschner. 1914 a. Über den Kampf der Teile im Ovarium. *Arch. f. Entw.-Mech.*, 40, p. 565.

—— 1914 b. Über Morphologie und Funktion des Ovariums unter normalen und pathologischen Verhältnissen. *Arch. f. Gynäkologie*, 102, p. 446.

—— 1918. *Die Blutdrüsenerkrankungen des Weibes und ihre Beziehungen zur Gynäkologie und Geburtshülfe.* Wiesbaden.

ATHIAS. 1915. L'activité sécrétoire de la glande mammaire hyperplasée, chez le cobaye mâle châtré, consécutivement à la greffe de l'ovaire. *C. R. de la Soc. de Biol.*, 78, p. 410.

—— 1916a. Etude histologique d'ovaires greffés sur des cobayes mâles châtrés et enlevés au moment de l'établissement de la sécrétion lactée. *C. R. de la Soc. de Biol.*, 79, p. 553.

—— 1916b. Sur le déterminisme de l'hyperplasie de la glande mammaire et de la sécrétion lactée. *C. R. de la Soc. de Biol.*, 79, p. 557.

—— 1919. Recherches sur les cellules interstitielles de l'ovaire des Cheiroptères. *Arch. de Biologie*, 30, p. 89.

—— 1920. Invagination de l'épithélium superficiel et néoformation ovulaire dans l'ovaire transplanté chez le cobaye. *C. R. de la Soc. de Biol.*, 83, p. 1647.

—— 1921. Sur la sécrétion interne de l'ovaire. *Arch. internat. de Physiol.*, 18, p. 296.

—— 1922. Etudes histologiques sur la greffe ovarienne. *Libro en honor de D. Santiago Ramón y Cajal.* Madrid.

—— 1923. Sur la signification physiologique des phénomènes d'atrésie folliculaire et des cellules interstitielles de l'ovaire. *C. R. de la Soc. de Biol.*, 88, p. 1315.

VAN BEEK. 1921. Microskopisch- en macroscopisch anatomisch onderzoek naar de ontwikkeling van het ovarium bij het rund. *Diss. med. vet.* Utrecht.

BELL (W. Blair). 1920. *The Sex-Complex.* 2nd ed. London.

BIEDL. 1913. *Innere Sekretion.* 2 Aufl. Berlin-Wien. Vol. II., p. 320 ff.

—— PETERS *und* HOFSTÄTTER. 1921. Experimentelle Studien über die Einnistung und Weiterentwicklung des Eies im Uterus. *Zeitschr. f. Geburtsh. u. Gynäkolog.*, 84, p. 59.

BORING *and* PEARL. 1917. Sex Studies IX.: Interstitial cells in the reproductive organs of the chicken. *Anatomical Record*, 13, p. 253.

—— *and* PEARL. 1918b. Sex Studies XI.: Hermaphrodite birds. *Jl. of Experim. Zool.*, 25, p. 1.

BOUIN, ANCEL *et* VILLEMIN. 1906. Sur la physiologie du corps jaune de l'ovaire. Recherches faites à l'aide des rayons X. *C. R. de la Soc. de Biol.*, 61, p. 417.

—— 1907. Glande interstitielle de l'ovaire et rayons X. *C. R. de la Soc. de Biol.*, 62, p. 337.

BUCURA. 1913. Zur Theorie der inneren Sekretion des Eierstocks. *Zentralbl. f. Gynäkol.*, 37, p. 1839.

CARMICHAEL *and* MARSHALL. 1908. On the occurrence of compensatory hypertrophy in the ovary. *Jl. of Physiol.*, 36, p. 431.

CORNER. 1923. Oestrus, ovulation and menstruation. *Physiolog. Reviews*, 3, p. 457.

FRAENCKEL (L.) 1903. Die Funktion des Corpus luteum. *Arch. f. Gynäcol*, 68.

—— 1905. Vergleichende histologische Untersuchungen über das Vorkommen drüsiger Formationen im interstitiellen Eierstockgewebe (glande interstitielle de l'ovaire). *Arch. f. Gynäkol.*, 75.

—— 1910. Neue Experimente zur Funktion des Corpus luteum. *Arch. f. Gynakol.*, 91.

—— 1914. Normale und pathologische Sexualphysiologie des Weibes. In Liepmann, *Handbuch der gesamten Frauenheilkunde*, III. Leipzig.

GERLINGER. 1923 a. Corps jaunes partiels de l'ovaire de Chienne. *Bull. de la Soc. Anatomique*, Mai.

—— 1923 b. Le cycle oestrien de l'utérus chez la Chienne et ses rapports chronologiques avec le cycle oestrien de l'ovaire. *C. R. de la Soc. de Biol.*, 89, p. 193.

GOODALE. 1916. Further developments in ovariotomized fowl. *Biolog. Bulletin*, 30, p. 286.

—— 1919. Interstitial cells in the gonads of domestic fowl. *Anatom. Record*, 16, p. 247.

*GOORMAGTIGH. 1921. Organogenèse et histogenèse de la capsule surrénale et du plexus coeliaque. *Arch. de Biol.*, 31, p. 83 (quoted from *Ber. üb. d. ges. Physiol.*, 8, p. 228).

GUGGISBERG. 1922. Die Arbeitsteilung im Eierstock. *Zentralbl. f. Gynäkol.*, 46, p. 402.

GUYÉNOT *et* PONSE. 1922. L'organe de Bidder et les caractères sexuels secondaires du Crapaud (Bufo vulgaris). *C. R. de la Soc. de Biol.*, 86, p. 751.

—— —— 1923 a. L'organe de Bidder du crapaud est il indispensable à la vie ? *C. R. de la Soc. de Biol.*, 89, p. 63.

—— —— 1923 b. Nouveaux résultats concernant le déterminisme des caractères sexuels secondaires du crapaud (*Bufo vulgaris*). *C. R. de la Soc. de Biol.*, 89, p. 129.

HABERLANDT. 1921. Über hormonale Sterilisierung des weiblichen Tierkörpers. *Münch. Mediz. Wochenschr.*, p. 1577.

—— 1922. Über hormonale Sterilisierung weiblicher Tiere durch subkutane Transplantation von Ovarien trächtiger Tiere. *Pflügers Archiv*, 194, p. 235.

*HAMMOND *and* MARSHALL. 1914. The functional correlation between the ovaries, uterus and mammary glands in the rabbit. *Roy. Soc. Proc.* B., 87.

HARMS. 1914. *Experimentelle Untersuchungen über die innere Sekretion der Keimdrüsen.* Jena.

HENRY. 1922. Recherches anatomo-cliniques sur les rapports entre l'évolution du corps jaune et l'apparitions des règles (23 observations). *C. R. de la Soc. de Biol.*, 86, p. 1162.

HERRMANN *und* STEIN. 1916. Über die Wirkung eines Hormones des Corpus luteum auf männliche und weibliche Keimdrüsen. *Wien. klin. Wochenschr.*, 29, No. 25.

HEWER. 1915. The direct and indirect effects of X-Rays on the thymus gland and reproductive organs of white rats. *Jl. of Physiol.*, 50.

HITSCHMANN *und* ADLER. 1913. Ein weiterer Beitrag zur Kenntnis der normalen und entzündeten Uterusmucosa. *Archiv f. Gynäkol.*, 100.

HONORÉ. 1900. Recherches sur l'ovaire du lapin. II. Recherches sur la formation des Corps jaunes. *Arch. de Biol.*, 16, p. 563.

HUSSY *und* WALLART. 1915. Interstitielle Drüse und Röntgenkastration. *Zschr. f. Geburtsh. u. Gynäkol.*, 77.

KOHN (Alfred). 1914. Morphologische Grundlagen der Organotherapie. In Jauregg und Bayer, *Lehrbuch der Organotherapie.* Leipzig.

LABHARDT. 1920. Über das Verhalten des Corpus luteum zur Menstruation. *Zentralbl. f. Gynäkol.*, 44, No. 8.

LACASSAGNE. 1913. *Etude histologique et physiologique des effets produits sur l'ovaire par les rayons* X. Thèse méd. Lyon.

LAUCHE. 1915. Experiment. Untersuch. an den Hoden, Eierstöcken und Brunstorganen erwachsener und jugendlicher Grasfrösche (Rana fusca Rös.). *Arch. f. mikroskop. Anat.*, 86, Abt. II., p. 51.

LIMON. 1901. *Etude histologique et histogénique de la glande interstitielle de l'ovaire.* Thèse de Nancy.

*—— 1904. Observations sur l'état de la glande interstitielle dans les ovaires transplantés. *Journ. de Physiol. et Pathol. Génér.*, 6 (quoted from Marshall, 1910).

LIPSCHÜTZ, WAGNER *et* TAMM. 1922a. Sur l'hypertrophie des fragments ovariens dans la castration partielle. *C. R. de la Soc. de Biol.*, 86, p. 240.

—— *et* WAGNER. 1922b. Nouvelles observations sur l'hypertrophie des fragments ovariens. *C. R. de la Soc. de Biol.*, 86, p. 1122.

—— (*in collaboration with* WAGNER, TAMM *and* BORMANN). 1922c. Further experimental investigations on the hypertrophy of the sexual glands. *Proceed. of the Roy. Soc.*, 94, p. 83.

—— 1923. Über die kompensatorischen Reaktionen der Geschlechtsdrüsen. *Skand. Arch. f. Physiol.*, 43, p. 75.

—— 1924 a. Condition de l'utérus après la castration partielle. *C. R. de la Soc. de Biol.*, 90, p. 197.

—— *et* VOSS. 1924 b. Dynamique de l'hypertrophie ovarienne. Expériences sur des chattes. *C. R. de la Soc. de Biol.*, 90, p. 199.

LOEB (L.) 1910a. Über die Bedeutung des Corpus luteum. *Zentralbl. f. Physiol.*, 23, p. 73.

—— 1910b. Weitere Untersuchungen über die künstliche Erzeugung der mütterlichen Plazenta und über die Mechanik des sexuellen Zyklus des weiblichen Säugetierorganismus. *Zentralbl. f. Physiol.*, 24, p. 203.

—— 1917. The relation of the ovary to the uterus and mammary gland from the experimental aspect. *Surgery, Gynecol. and Obstetrics.*

—— 1918. Corpus luteum and the periodicity in the sexual cycle. *Science*, 48, p. 273.

MARSHALL. 1905. The development of the Corpus luteum. A review. *Quart. Jl. of Microscop. Sc.*, 49, p. 189.

—— *and* JOLLY. 1907. Results of removal and transplantation of ovaries. *Transact. Roy. Soc., Edinburgh*, 45, Part III., No. 21.

—— 1910. *The physiology of reproduction.* London, 1910. 2nd edition, 1922.

—— *and* RUNCIMAN. 1914. On the ovarian factor concerned in the occurrence of the oestrous cycle. *Jl. of Physiol.*, 49, p. 17.

—— *and* HALNAN. 1917. On the post-oestrous changes occurring in the generative organs and mammary glands of the non-pregnant dog. *Proceed. Roy. Soc.*, 89, p. 546.

—— 1923. The internal secretions of the reproductive organs. *Physiolog. Reviews*, 3, p. 335.

—— *and* WOOD. On the ovarian factor concerned in the occurrence of oestrus. *Jl. of Physiol.*, 58, p. 74. See also Carmichael and Marshall.

MEYER (Robert). 1913. Über die Beziehung der Eizelle und des befruchteten Eies zum Follikelapparat, sowie des Corpus luteum zur Menstruation. *Archiv. f. Gynäkol.*, 100.

—— 1921 a. Ein Mahnwort zum Kapitel "Interstitielle Drüse.' *Zentralbl. f. Gynäkol.*, No. 17.

—— 1921 b. Beiträge zur Lehre von der normalen und krankhaften Ovulation und den mit ihr in Beziehung gebrachten Vorgängen am Uterus. *Arch. f. Gynäkol.*, 113, p. 1.

MOORE. 1921a. On the physiological properties of the gonads as controllers of somatic and psychical characteristics. III. Artificial hermaphroditism in rats. *Jl. of Experim. Zool.*, 33, p. 129.

—— 1921b. IV. Gonad transplantation in the guinea-pig. *Jl. of Experim. Zool.*, 33, p. 365.

NONIDEZ. 1920. Studies on the gonads of the fowl. I. Hematopoietic processes in the gonads of embryos and mature birds. *Amer. Jl. of Anatomy*, 28, p. 81.

—— 1922. Estudios sobre las gónadas de la gallina. II. El tejido intersticial del ovario. *Libro en honor de D. Santiago Ramón y Cajal.* Madrid.

OCHOTERENA *and* RAMIREZ. 1920. The origin and evolution of the interstitial cells and of the ovary, and the significance of the different internal secretions of the ovary. *Endocrinology*, 4, p. 541.

*PEARL *and* SURFACE. 1914. Studies on the physiology of reproduction in the domestic fowl. IX. On the effect of Corpus luteum substance upon ovulation in the fowl. *Jl. of Biol. Chem.*, 19, p. 263 (quoted from Loeb, 1918 and Haberlandt, 1922).

—— *and* BORING. 1918a. Sex Studies X. The Corpus luteum in the ovary of the domestic fowl. *American Jl. of Anatomy*, 23, p. 1.

See also BORING AND PEARL.

—— *and* SCHOPPE. 1921. Studies on the Physiology of reproduction in the domestic fowl. XVIII.: Further observations on the anatomical basis of fecundity. *Jl. of Experim. Zool.*, 34, p. 101.

PLAUT. 1923. Demonstration von Präparaten von Mamma, Uterus und Ovarien. *Klin. Wochenschr.*, 2, p. 953.

RASMUSSEN. 1918. Cyclic changes in the interstitial cells of the ovary and testis in the woodchuck (marmota monax). *Endocrinology*, 2, p. 353.

REIFFERSCHEID, 1911. Experimentelle Untersuchungen über Regeneration durch Röntgenstrahlen geschädigter Ovarien. *Zeitschr. f. Röntgenkunde*, 13, p. 285.

—— 1914. Die Einwirkung der Röntgenstrahlen auf tierische und menschliche Eierstöcke. *Stahlentherapie*, 5, p. 407.

—— 1922. Zur Frage der biologischen Wirkung der Röntgenstrahlen auf die Ovarien. *Strahlentherapie*, 14, p. 628.

RIBBERT. 1898. Über Transplantation von Hoden, Ovarien und Mamma. *Arch. f. Entw.-Mech.*, 7, p. 688.

RUGE II (Carl). 1913. Über Ovulation, Corpus luteum und Menstruation. *Arch. f. Gynäkol.*, 100.

SAINMONT. 1906. Recherches relatives à l'organogenèse du testicule et de l'ovaire chez le chat. *Arch. de Biol.*, 22, p. 71.

SALAZAR. 1919. *Sur la période chromatolytique de la granulosa atrésique de la lapine.* Mém. publ. par la Soc. Portug. d. Sc. Natur., Sér. biolog., No. 2.

—— 1922. Sur l'existence de faux corps jaunes autonomes dans la glande interstitielle de la lapine. *Anatom. Rec.*, 23, p. 189.

SAND. 1919. *Experimentelle Studier over Kφnskarakterer hos Pattedyr.* Copenhagen.

—— 1921. Etudes expérimentales sur les glandes sexuelles chez les mammifères. *Jl. de Physiol. et Pathol. Génér.*, 19, p. 305.

SCHAEFFER. 1911. Vergleichende histologische Untersuchungen über die interstitielle Eierstockdrüse. *Arch. f. Gynäkologie*, 94.

*SCHICKELÉ. 1921. Etudes sur la fonction des ovaires (ovulation, corps jaune et menstruation). *Gynécol. et obstétr.*, 3, p. 170.

*SCHULTZ (W.) 1900. Transplantation der Ovarien auf männliche Tiere. *Zentralbl. f. allgem. Pathol. u. pathol. Anat.* (quoted from Schultz, 1910).

—— 1910. Verpflanzungen der Eierstöcke auf fremde Spezies, Varietäten und Männchen. *Arch. f. Entw.-Mech.*, 29, p. 79.

SEITZ. 1906. Die Follikelatresie während der Schwangerschaft, insbesondere die Hypertrophie und Hyperplasie der Theca-interna-Zellen (Theca-Lutein-Zellen) und ihre Beziehungen zur Corpus luteum-Bildung. *Arch. f. Gynäkol.*, 77.

—— 1921. Primat der Eizelle, Corpus luteum, Menstruationszyklus und Genese der Myome. *Arch. f. Gynäkol*, 115, p. 1.

SOBOTTA. 1895. Über die Bildung des Corpus luteum bei der Maus. *Anatom. Anz.*, 10, p. 482.

—— 1896. Über die Bildung des Corpus luteum bei der Maus. *Arch. f. mikroskop. Anat.*, 47, p. 261.

—— 1898. Über die Entstehung des Corpus luteum der Säugetiere. *Ergebn. d. Anat. u. Entw.-Gesch.*, 8, p. 923.

—— 1901. Über die Entstehung des Corpus luteum der Säugetiere. *Ergebn. d. Anat. u. Entw.-Gesch.*, 11, p. 946.

—— 1906. Über die Bildung des Corpus luteum beim Meerschweinchen. *Anatom. Hefte*, 32, p. 91.

STEINACH. 1912. Willkürliche Umwandlung von Säugetier-Männchen. *Pflügers Archiv*, 144.

—— 1916. Pubertätsdrüsen und Zwitterbildung. *Arch. f. Entw.-Mech.*, 42, p. 307.

—— *und* HOLZKNECHT. 1916. Erhöhte Wirkungen der inneren Sekretion bei Hypertrophie der Pubertätsdrüsen. *Arch. f. Entw.-Mech.*, 42, p. 490.

TANDLER *und* GROSS. 1913. *Die biologischen Grundlagen der sekundären Geschlechtscharaktere*, p. 91–97.

WALLART. 1907. Untersuchungen über die interstitielle Eierstockdrüse beim Menschen. *Arch. f. Gynäkolog.*, 81.

WERNER (Paul). 1918. Beitrag zur Kenntnis des Verhaltens der Eierstockfunktion nach der Röntgentiefentherapie. *Arch. f. Gynäkol.*, 110.

WINIWARTER. 1908. Das interstitielle Gewebe der menschlichen Ovarien. *Anat. Anz.*, 23, p. 1.

—— *et* SAINMONT. 1909. Nouvelles recherches sur l'ovogenèse et l'organogenèse de l'ovaire des mammifères (chat). *Arch. de Biol.*, 24, p. 97.

*—— 1920. Quelques remarques sur la sécrétion interne (A propos d'un ouvrage récent). *Liège Méd.*, No. 34 (quoted from Athias, 1921).

ZIETZSCHMANN. 1921. Über Funktionen des weiblichen Genitale bei Säugetier und Mensch. Vergleichendes über die zyklischen Prozesse der Brunst und Menstruation. *Arch. f. Gynäkol.*, 115, p. 201.

Chapter VI.

The Sex Specific Action of the Testicular and Ovarian Hormones.

HITHERTO in the present work we have refrained from discussing the important question as to the sex specific action of the testicular and ovarian hormones. Yet we have tacitly assumed that the hormones have a sex specific action, since we concluded from the castration experiments that the soma is asexual during embryonic life, and that it does not develop sex characters before the gonad is differentiated. But we have not yet presented any incontestable argument in support of the view that there is a sex specifity for the respective hormones.

This question has been investigated by various authors, and in this chapter we shall deal with their experiments.

A. EXPERIMENTS ON AMPHIBIANS.

Steinach (1910) injected into castrated male frogs triturated ovaries of females on heat. He stated that the clasp reflex is evoked by this stimulus in just the same way as it is by injecting testes. However, by injecting ovary the reflex is not so fully evocable, and the experiment is not so regularly successful as when testicular substance is employed. *Harms* (1910) and *Meisenheimer* (1912) also found that the clasp reflex in castrated male frogs may return after injection of ovary. Relying on these experiments, we may suppose that hormones are formed also in the ovary, which may thus condition the oestral phenomena in the male.

Meisenheimer has studied carefully the behaviour of the thumb pad in male frogs after introduction of ovarian substance, the ovaries having been put into the dorsal lymphatic sac. By so doing the growth of the pad was induced, and an hypertrophy of the epithelium and the glands was brought about. The pad of the castrated male injected with ovary is easily distinguished from that of an ordinary "castrate." But there is a striking difference between a castrated male injected with ovary and one injected with testicle, as shown particularly by histological examination. The epidermis is not so thick, the epithelial tuberosities are much smaller in numbers and the surface of the pad remains generally smooth. As to the behaviour of the epidermis, the castrated male injected with ovary is somewhat intermediate between an ordinary "castrate" and a "castrate" injected with testicle. The influence of the ovary was particularly evident upon the glands; their number was considerably enlarged in comparison with that found in the "castrate."

We see that the oestral changes of the pad can be effected by the testicle and by the ovary alike, although the action of the ovary is less pronounced than that of the testicle. The experiment on frogs cannot, indeed, be considered as a proof of a sex specific endocrine action of the sexual glands in amphibians, though, on the other hand, they cannot be used as a proof against such an assumption. Meisenheimer has drawn from these experiments the general conclusion that the sexual glands in mammals also do not act in a sex specific manner. That this conclusion, however, is not justified follows from what is said below.

Heterosexual transplantation in tritons was attempted by *Herlitzka* (1900, quoted from *Kammerer*, 1919); the grafts underwent degeneration in the course of a few months. But *Bresca* (1910) succeeded in transplanting the tissue of the yellow dorsal line of a female *Molge cristata* on to the back of a male, where normally at time of "heat" a comb develops. He stated that the graft became transformed at the time of heat into a typical indented male comb. This was due not to a regeneration of the removed normal male comb, since such a one did not develop in control animals from which the male comb was also removed but on to which no female graft was placed.

Harms (1921) made experiments on toads, dealing with the question as to the sex specifity of the hormones. He stated that in about 10 per cent. of the males examined oöcytes were present in the Bidder's organ. He removed the testicles from these animals, and then kept them under observation for three years. He found that the Bidder's organ showed an increased tendency to form ovarian tissue. Harms concludes, therefore, that normally the testicle inhibits development of ovarian tissue in the Bidder's organ. Notwithstanding the presence of ovarian tissue the toads remained typical males in somatic appearance and sexual behaviour. Harms concluded that no transformation of sex can be produced in adult animals. But two years later *Harms* (1923) stated that all the animals operated on in the above manner became transformed about 4 to 5 years after the operation, somatically and psychically into females. The *uteri masculini* changed into female uteri and oviducts; the form of the head became female-like.

Ponse (1923) by testicular transplantation has provoked development of pads on both thumbs in a young castrated female toad. The pads appeared about seven months after the operation.

Wagner (1922), on my incentive, made experiments on tadpoles, which were fed with frog ovaries and testicles, but no sex specific influence was observed.

B. FEMINIZATION AND MASCULINIZATION IN MAMMALS AND BIRDS.

Experiments undertaken to influence the organism of the mammal and bird by implanting a gland of the other sex have been made by different authors, as by Hunter as early as 1780, and in later times by Foges, Meisenheimer, and Bucura. Numerous authors have grafted testicles and ovaries upon the castrated or normal organism of the other sex in order to study the behaviour of the transplanted sexual gland itself. The successful experiments of *W. Schultz* (1910) may be mentioned here.

But Steinach was the first to attempt to clear up the question of the *specific hormonic action* of the male and female sexual glands by experiments systematically performed by means of "*crossed transplantation*."[1]

In his experiments, *Steinach* (1912) started with the following considerations. If the action of the male and female sexual hormones is the same, then it should be possible to cause complete development of young castrated males to full sexual

---

[1] The term "*crossed transplantation*" was first used by *Caullery* (1913, p. 113). The term "*sex specific*" was introduced by myself (*Lipschütz*, 1914, p. 408).

maturity by implanting into them ovaries instead of testicles. But, if male and female sexual hormones differ from one another, a successful implantation of an ovary into a young castrated male should cause it to develop not into a mature male, but into a mature female, and the converse result should occur by implantation of a testicle into the body of a castrated female. If the action of the sexual hormones is a sex specific one, it ought to be possible to produce arbitrarily, to a certain degree at any rate, the respective sexual characters by implanting an ovary or a testicle into a castrated animal. Or, in other words, it should be possible to "feminize" a castrated male by an implantation of ovaries and to "masculinize" a castrated female by an implantation of testicles. As we shall see, this supposition proved correct. Steinach has demonstrated the feminizing action of the ovary and the masculinizing action of the testicle in rats and guinea pigs. All the investigators who have repeated the experiments of Steinach have verified his results, including Brandes on the fallow-buck, Sand and Moore on the rat and the guinea pig, Athias and Lipschütz and his co-workers on the guinea pig, Goodale on the cock and the drake, and Pézard and Zawadowsky on the cock and the hen.

1. EXPERIMENTS ON MAMMALS.[1]

(*a*) *Feminization.*

Implantation of ovaries has been carried out by Steinach on rats at the age of three or four weeks, and on guinea pigs at the age of two or three weeks. In a series of experiments on rats the ovaries were transplanted on to the peritoneal surface of the abdominal wall; in another series of experiments on rats and guinea pigs on to the external surface of the abdominal wall. According to Steinach, the graft "takes" only if the animal has been castrated beforehand. The graft was put on a wounded place, produced by scraping the peritoneal covering or the muscle. According to Steinach this method, involving probably an hyperæmia and a good vascularization for the graft, is very satisfactory. In order to secure a better vascularization, *Sand* (1918 a) "punctured" the graft by piercing the surface in many spots with the point of a very fine needle.

---

[1] With the experiments on man we shall deal in Chapter IX.

In such a way, perhaps, as Sand believes, the resistance is overcome which the albuginea offers to the ingrowing of blood vessels. But in spite of all these measures, the grafts did not always "take," either in the experiments of Steinach or in those of Sand.[1] The number of the unsuccessful experiments was greater than that of the successful ones. One might suppose that the ovaries were in some way influenced and injured by male hormones still active in the host. Sand, who performed a great number of experiments, deferred transplantation for one to five weeks after castration with a view to getting the male animals as far as possible into an "indifferent" or neutral condition. The chances of success, however, were not improved thereby, as may be seen from his experimental results. The subcutaneous transplantation on to the external surface of the abdominal muscles is to be preferred to the peritoneal graft, since in the first case the progress and fate of the transplanted organs may be followed by external inspection and palpation. We have given particulars concerning the histological changes in the graft in a previous chapter.

In a rat four weeks old the penis is still very undeveloped. The prostate is just visible with the naked eye, and the seminal vesicles are much smaller than in the adult animal. In the prepuberally castrated animal these conditions do not change much; the organs remain in an infantile stage of development, although the penis may continue to grow to a certain degree. Now we learned that these organs fully develop if testicular implantation is made after castration. On the contrary, the development of the penis, prostate and vesicles is not promoted if ovaries are implanted. Steinach relates that the development of these organs is even inhibited by the ovarian graft, the penis of the feminized rat being shorter than that of the ordinary castrated animal. The question as to whether the ovary has an inhibitory action is of the greatest theoretical importance, as we have already seen when discussing the results of castration in birds, in which such an inhibitory action is beyond any doubt. But this question has not yet been studied sufficiently in mammals. I examined the penis of two fully grown feminized guinea pigs, operated on by Steinach some years ago; I found that the penis was

---

[1] We shall deal in detail in Chapter IX. with the supposed antagonism of the sex glands.

shorter and narrower than that of an ordinary "castrate." But having examined in the last three years a great many castrated guinea pigs, I now see that the proportions of the penis after castration depend on the age at which castration was performed (*Bormann*, 1922); there is also great individual variation. So I am now rather inclined to the view that the question of an inhibitory action of the ovary in the mammal is not yet definitely settled, although such an action is more than probable.

FIG. 114.—*Influence of ovarian transplantation on the teats of the castrated male guinea pig.*—Photo of Steinach.
A. Normal male.

Steinach implanted in one case into a castrated male, together with the ovaries, the uterus and the tubes; the latter developed. Rudimentary organs of the male, such as the teats and the mammary glands, develop in the male organism under the influence of the implanted ovary, and become finally like those of a normal female (*Fig.* 114 A, B). In the first weeks after birth there is no difference between the teat of the male and that of a female guinea pig. The teats and the mammary glands begin to grow in the female at about the age of two months and become transformed into the organ characteristic of the virgin female. A further growth of the teats and the glands takes place during gravidity and lactation. In the same manner the teats develop in the feminized male. The teats are long, thick, and red, and the area around them is shiny and protruding, as in a normal female during gravidity. As shown by microscopical examination the mammary glands themselves really develop as in the normal female during gravidity and lactation. There is sometimes even a secretion of milk which can be pressed out from the gland. Such animals are sought out by young ones which attempt to suck. Sometimes the feminized male takes care of the young and suckles (*Fig.* 115). The milk secretion persisted in certain cases for quite a prolonged period, but there were intervals without milk secretion.

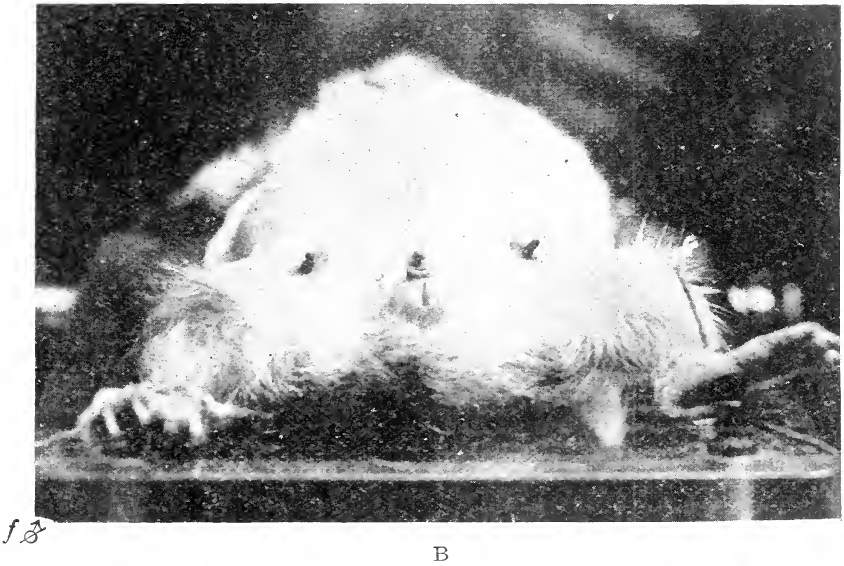


FIG. 114.—*Influence of ovarian transplantation on the teats of the castrated male guinea pig.*—Photo of Steinach.
B. Feminized male (during period of lactation).

Steinach's discovery has been fully confirmed by *Athias* (1915), by *Sand* (1918, 1919), by *Moore* (1919 a, 1921) and by *Harms* (1922), by *Lipschütz* and *Krause* (1923 b and c) and by *Lipschütz* and *Voss* (unpublished experiments); the statements of these authors differ from those of Steinach only in details. In the experiments of Athias the teats in the feminized male attained a length of 7·5 mm.; they were enlarged at their base; there was a protruding area around them; after a short interval an abundant milk secretion set in. Sand observed a considerable hypertrophy of the teats and glands, but no milk secretion, but, as Sand points out, this was

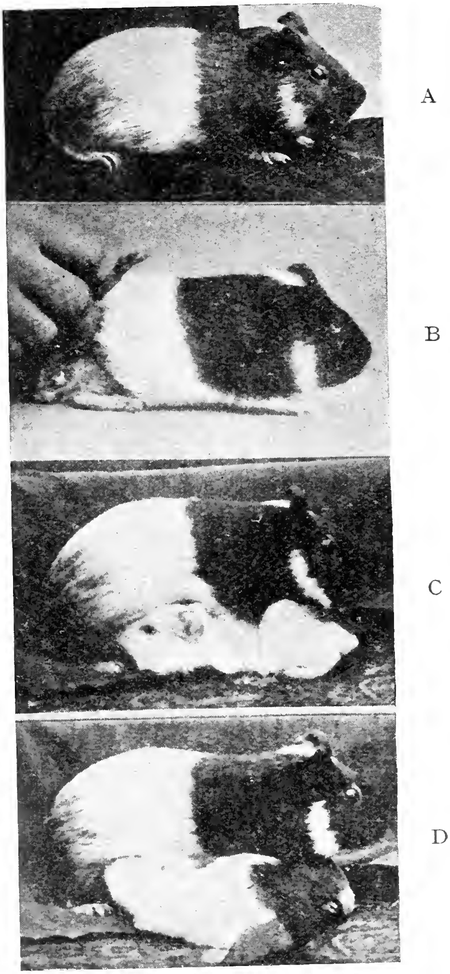


FIG. 115.—*Feminized male guinea pig suckling young.*—From Steinach.
A. Feminized male.
B. Demonstration of penis.
C. Suckling one young.
D. Suckling two young.

probably due to the fact that he removed one of the two implanted ovaries, and that soon afterwards the second graft underwent degeneration. Moore observed development of teats and glands to an extent similar to that of pregnant females. But his animals showed no feminine inclination towards young ones and repelled any attempts on their part to suck. In our own experiments on guinea pigs the teats and the mammary glands were like those of a pregnant female, and there was milk secretion. Sometimes only *colostrum* could be pressed out.

Steinach's results were confirmed also by *Brandes* (1914) in an experiment on a stag on to which ovaries were engrafted after castration. The mammary glands hypertrophied. There were no horns in the feminized stag, and the *pomum adami* was not visible at all. Unfortunately Brandes made no detailed communication on his results; only a short account was given by him in a daily paper, and in letters published in the scientific press. It is noteworthy that the committee of the Zoological Garden of Dresden, of which Brandes is the director, prohibited him from continuing his experiments, on the ground that they were opposed to morality and to the good reputation of the Garden.

In view of these experiments there can be no doubt that male and female sexual hormones act differently. They act in a sex specific manner, i.e., they transform the organism so as to accord with the characteristics of one or the other sex.

The microscopical examination of the ovarian graft in the male "castrate" reveals that the cellular elements to which we ascribe the endocrine function of the ovary are more numerous than in a normal organ, as with an ovary exposed to X-rays. There is an increased follicular development and atresia. This explains the fact that specific sexual characters may develop in the feminized male in a more pronounced manner than in the normal virgin female. There is, as Steinach points out, not only a feminization, but really an *hyperfeminization*. If, on the contrary, the graft undergoes degeneration and transformation into fibrous connective tissue, the teats of the feminized animal revert to the rudimentary structures characteristic of the normal male or the castrated female. One of Moore's experiments confirming those of Steinach's is very significant in this respect (*Moore*, 1921, p. 371).

Athias performed the following experiment. Three days after the beginning of milk secretion he removed the ovarian grafts. The milk secretion persisted for nine days; then the mammary glands began to regress, and in about a week the regression was already very pronounced.

It may be mentioned that the sex specific influence of the ovary on the teats and the mammary glands cannot be studied on the rat, as no teats are macroscopically visible in the male rat (*Myers*, 1917).

Steinach describes also the changes which the feminized animal undergoes in body weight and body proportions. According to King and Donaldson (see *Donaldson*, 1915) a striking difference in body weight between the male and female Norway rat may be observed at an age of about three months. 150 days after birth the male has body weight about 60 gr. greater than that of the female; at an age of 365 days this difference is about 85 gr. In adult guinea pigs the difference between male and female may be as much as about 200 gr. to the advantage of the male. According to Steinach the feminized male rat has a much lower weight than that of a normal male or a "castrate" (*Figs.* 116 *and* 117), and he concludes that the weight of the castrated male is inhibited by the ovarian graft, the growth capacity becoming like that of a female. Similar observations were made by Steinach on the guinea pig. One might object that this inhibition of growth is caused not by the ovarian graft, but rather by the operation itself when performed on such young animals; but Steinach has pointed out that there was no inhibition of growth in those cases in which the ovarian graft did not "take." There is, according to Steinach, an even greater difference in body weight between a normal male and a

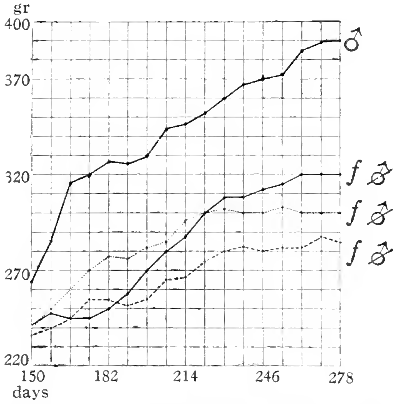


FIG. 116.—*Body weight of normal and feminized male rats.* At an age of 9 months the feminized animals weighed about 100 gr. less than normal males.—Drawn from figures of Steinach (1912, table 1, p. 94).

feminized one, than between a normal male and a normal female; Steinach speaks here also of an hyperfeminization due to an increased hormonic action of the proliferated endocrine cells of the ovary during the period of body growth. It must be pointed out, however, that normal animals show great individual variation in regard to body weight. Definite conclusions in this field can be drawn only from very extensive data.

We have already mentioned that after the disappearance or degeneration of an ovarian graft which had a feminizing effect, the teats and the mammary glands ceased to develop. Steinach observed in these cases also an increase of body weight, the animals attaining in a few weeks the weight of normal males.

Sand has not directed his attention to the question of the body weight; he had his experimental animals under observation no longer than a few months, whereas a striking difference in body weight betwen normal and feminized male was observed by Steinach at an age of about six months. The question as to the influence of the sex gland on body weight is discussed more fully by *Moore* (1919). We shall deal with his criticisms in the section on "Masculinization."

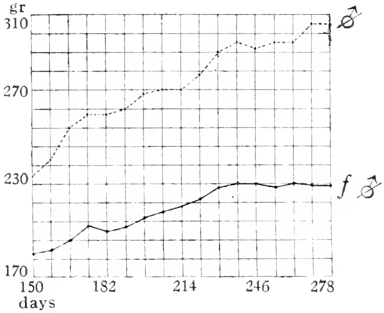


FIG. 117.—*Body weight of castrated and feminized male rats.*—Drawn from figures of Steinach (1912, table 2, p. 95).

There are, according to Steinach, striking differences also in the body proportions between the normal and the feminized male (*Figs.* 118 *and* 119). Steinach made for this purpose several direct measurements and examined X-ray plates of normal and experimental animals. Further, Steinach describes differences in the coat of the rat, the long, coarse and rough hair of the male becoming transformed in the feminized animal into the short fine and soft hair of the normal female. Steinach claims also to have observed an accumulation of fat in the pelvic region of the feminized male in a manner characteristic of the female; he believes further that this accumulation of fat is absent in those castrated males in which the engrafted ovary did not "take," and in which no other signs of feminization were present. I think Steinach was mistaken as to this detail; the accumulation of fat in the abdomen of the castrated male animal being in my experience sometimes absolutely enormous.

FIG. 118.—*Litter of normal guinea pigs, about 7 months old.* Female between two males.

This accumulation of fat after castration was indeed only absent in cases of chronic disease.

Notwithstanding all the objections which have been made in regard to details, there can be no doubt that the experiments

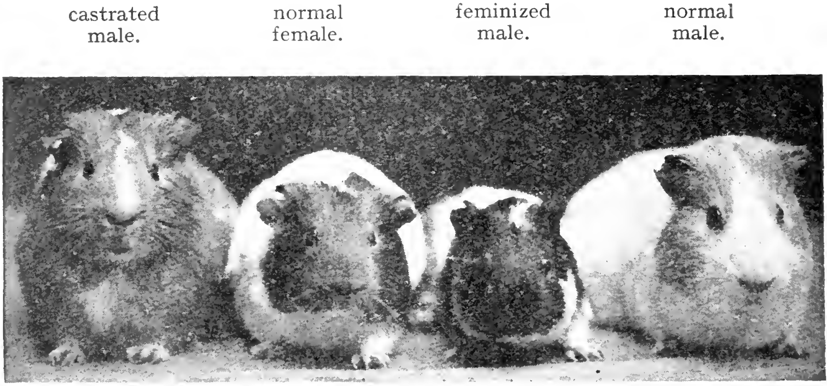


FIG. 119.—*Influence of ovarian transplantation on size of male guinea pig.* —From Steinach.

of Steinach and of those who have repeated them show that the development of female sex characters in the male animal is induced by the ovary, and it is very probable that the development of male sex characters is inhibited by this organ.

The ovary turns the development of the whole organism on to female lines. There can be no doubt that the soma is influenced by the ovary in a sex specific manner.

Harms (1922, p. 242) draws attention to the fact that the "uterus masculinus" of the guinea pig does not become transformed into a female organ, but remains in the same infantile stage as at the time of the operatiom. Harms is mistaken in thinking that what he calls "uterus masculinus," i.e., the vesiculae seminales of the guinea pig, is an organ homologous with the female uterus. This is not the case, the vesiculae seminales being in genetic relation to the vas deferens and not to the ducts of Müller.

It can be further demonstrated that not only the somatic sex characters, but also the psycho-sexual behaviour is influenced by the ovary. We learned from experiments with castration, injection and transplantation that the sexual hormones have an erotizing effect. Experiments performed on the frog have shown, that the clasp reflex can be evoked to a certain degree also by injection of ovarian substance; evidently the ovary produces some erotizing hormone which is identical with or similar to that of the testicle. But this observation on the frog is not sufficient for drawing the general conclusion that there is no sex specifity in the erotizing action of the ovary. That this conclusion is erroneous follows from the fact that the psycho-sexual behaviour of the somatically feminized male resembles that of a female. Evidently the hormones of the ovary do not erotize in a male direction, but in a female one. The indications of a female erotization are, according to Steinach, the following:—

1. The feminized male rat exhibits the "tail-reflex" characteristic of the female and consisting in the raising of the tail when followed by the male. Some kind of tail-reflex can be observed also in the normal male and in the castrated male; but according to Steinach this is not the true tail-reflex characteristic of the female.

2. The feminized male rat is treated by the normal male as though it were a female. The feminized male is followed by the normal male, which makes repeated attempts at coitus.

3. The feminized male, like the normal female of the rat and guinea pig, shows the "averting-reflex," consisting in the

raising of one of the hind legs and moving it for averting the leaping of the male.

It must be said that it is very difficult to draw conclusions concerning the psycho-sexual behaviour of the rat and guinea pig. Sand was uncertain as to whether female erotization of his somatically feminized rats really occurred, although there were some indications of this happening; there was no tail-reflex and no averting-reflex. On the contrary, Moore relates that in his experiments some of the male rats with successful ovarian grafts exhibited unmistakable maternal behaviour towards young ones. In the experiments with guinea pigs into which ovaries were successfully engrafted, and which showed a marked hypertrophy of the mammary gland, the same author was uncertain about the occurrence of female erotization; the behaviour of his four feminized male guinea pigs was masculine in every respect. They showed no feminine instincts towards young animals, and even frightened them away when the young made attempts to suck. We see, therefore, considerable discrepancy in the results of different investigations. We shall meet with similar disagreement when dealing with the experiments upon masculinization. But notwithstanding all these contradictory details, the experiments of Steinach and of his successors leave no doubt that the sexual hormones in the mammal erotize the central nervous system in a sex specific manner.

It has been claimed by different authors that the female has a higher body temperature than that of the male (*cf. Tigerstedt*, 1910; *Przibram*, 1923). Similar results were obtained by *Hans Przibram* (1915, 1923) and his pupils (*Bierens de Haan*, 1922) on the rat, and by *Steinach* and myself on the guinea pig (1916 a, 1917 c). Our figures seemed to show also that the body temperature of the castrated female is lower than that of the normal female, whereas the temperature of the castrated male remains unaltered. Steinach stated that the body temperature of the feminized male is as high as that of the normal female. In view of these considerations it seemed justifiable to conclude that there is a feminization of the castrated male by the ovary in regard to body temperature. One might suppose that the sexual hormones act in a specific manner on those parts of the central nervous system upon which the regulation of the body temperature depends; it would be an action similar to that on the sexual reflexes. I should state, however, that I lost confidence in my own measurements on the guinea pig after *Bormann, Brunnow* and *Savary* (1923, see also *Lipschütz,* 1923 a) in our Institute repeated these experiments on the rabbit. In their experiments, performed with great care, there was no difference between the normal male and female; there was also no difference between the castrated and the normal female; Bormann and Brunnow examined rabbits of different ages, as I thought that possibly the sex difference in body temperature would become more pronounced after full sexual maturity was attained. But they found subsequently no difference between male and female in animals of full sexual maturity. The animals were as far as possible of the same litter. Recently *Ocaranza* (1922) stated that there is no difference in the body temperature of male and female guinea pigs. Steinach's and my conclusions derived from records on the guinea pig are erroneous. Evidently the number of our records was not sufficient, and the individual variation was too great. As Brunnow and Bormann showed, the result of the reading depends largely on technical details, especially on the position of the animal at the time of measurements, and on the depth to which the thermometer is introduced into the rectum.

(*b*) *Masculinization.*

Steinach (1913) performed experiments with implantation also of testicle into castrated female rats and guinea pigs. The number of successful experiments was very small, but wholly sufficient for demonstrating the sex specific action of the testicle in the body of a female. In one experiment the testicular graft remained in a female guinea pig for more than three years, i.e., as long as some ovarian grafts in the male organism (*Steinach,* 1916). Similar experiments were afterwards recorded by *Sand* (1918, pp. 89–91); in guinea pigs the grafts underwent resorption, whereas a number of experiments with rats were successful. Successful experiments on the rat and the guinea pig have been recorded also by *Moore* (1919 a, 1921).

We have seen in the preceding section that the development of the teats and mammary glands of the male is induced by the ovarian graft. On the contrary the teats remain undeveloped rudimentary organs if a testicle is engrafted in a castrated female. The uterus undergoes atrophy, as in the ordinary "castrate"; some years ago *Bucura* (1907, 1913, p. 145) observed that a successful testicular graft was not able to prevent the atrophy of the uterus in a castrated female hare. It would be of great interest to determine whether there is also an inhibitory action on the part of the male hormones towards the teat, the mammary glands and the uterus.

The influence of the testicular graft on the corpora cavernosa of the clitoris is of an especial interest, the clitoris being transformed into a penis-like organ (*Fig.* 120). This I showed (1916 b, 1917 a, 1918) when examining guinea pigs in Steinach's laboratory, and operated on by him a long time ago. The external examination of a female with a successful testicular graft revealed that the urogenital region underwent masculinization (*Fig.* 120 C). In the place of the little female urethric tubercle, as the prominence in the aperture of the urethra of the female may be termed, there is a long fold of skin. It differs only from a normal male preputium in having a split on the under side. The preputium can be easily drawn back when an extraordinary picture reveals itself (*Fig.* 120 D). Two red excrescences are seen, which in their mutual position, their colour and their dimensions, are just like normal corpora cavernosa penis, only their length is much less than in the normal male. Between these excrescences lies the aperture of the urethra, evidently at the normal place for a female. There can be no doubt that it was owing to the action of the male sexual hormones that the corpora cavernosa of the clitoris grew and changed into corpora cavernosa penis, and that the preputium of the clitoris changed into a preputium of a penis. It is remarkable, however, that the corpus cavernosum urethrae was absent; the developed organ gave the impression of a totally hypospadic penis. A frontal section through the penis-like organ of the masculinized female would present the appearance of one through the *glans* of a normal penis. The absence of a corpus cavernosum urethrae might be explained in the following manner. Castration, feminization or masculinization is performed on an animal in which the sex characters are already "fixed" to a certain degree. Profound changes take place in the genital region of the male and female animal during the second half of embryonic development. These transformations result in producing the long urethra in the

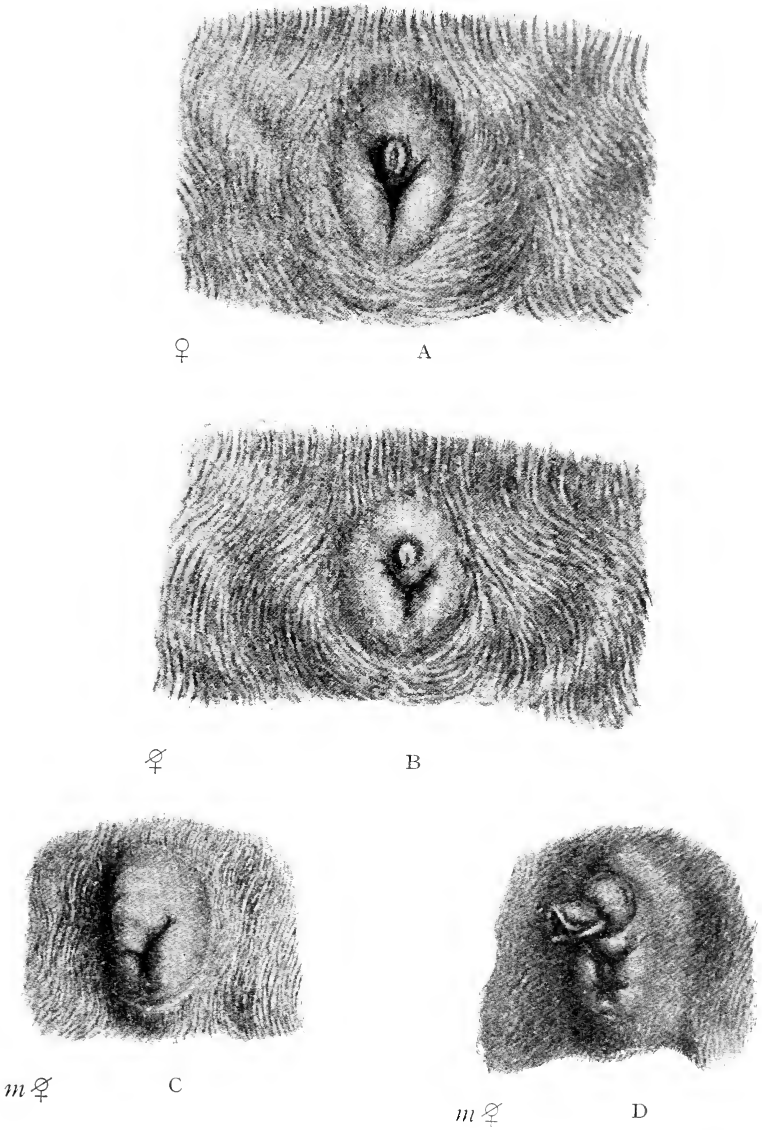


FIG. 120.—*Influence of testicular transplantation on the clitoris of the guinea pig.*

A. Normal female guinea pig.
B. Castrated female guinea pig. No change.
C. Masculinized female guinea pig.
D. Masculinized female guinea pig. Praeputium drawn back. A penis-like organ is formed. For details see text. Nat. size.

male; in the female the vagina between the perineum and the opening of the bladder is formed. We may suppose that these sex characters, already fixed under the influence of the sexual gland, will not be changed in experimental feminization or masculinization in the same manner as during intra-uterine life. This question will be discussed more fully in Chapter XI.

Next to the hypertrophied corpora cavernosa of the clitoris in the masculinized female there are two spikes to be found, which are very similar to the horny styles in the cavity of the intromittent sac of the corpora of the normal male. The styles of the masculinized female differ from the normal ones in colour, size and position. The last-mentioned difference may be explained by the absence of the corpus cav. ur. and of the intromittent sac. We have seen in a preceding chapter that the horny styles are to be seen in the prepuberally castrated male as very small spots, or else they are absent altogether; they are much reduced after postpuberal castration. Now we see the reverse of this phenomenon: the engrafted testicle causes formation of horny styles, which are, however, somewhat different from the normal ones. It may be remarked that all these transformations are absent in the ordinary castrated female, and it is clear that they are produced by a sex specific action on the part of the engrafted testicle.

When the preputium of the masculinized female is drawn back, one finds the red excrescences covered with a whitish-yellow secretion, evidently a preputial secretion like that present in great quantity especially on the short penis of the prepuberal "castrate" (*cf.* p. 21). The same factors which cause an accumulation of preputial secretion in the "castrate" are obviously at work also in the masculinized animal.

The process of transformation of the clitoris into a penis-like organ under the influence of the testicular graft is different from the process of transformation of the teats and the mammary glands in the feminized male, in that the penis-like organ does not attain the normal size and the normal shape of the penis. This question will be discussed more fully in Chapter XI.

The observations on the penis-like organ of the masculinized female are of interest also in relation to the theory of intersexuality.[1] (See Chapter IX.)

Sand has described (1918, 1919) some observations made by him on a penis-like organ in the masculinized rat. In the normal female rat the clitoris is a very rudimentary organ. In masculinized rats, the psycho-sexual behaviour of which was male, Sand found a pronounced hypertrophy of the clitoris, which was transformed into an organ 4 to 5 mm. long, turgescent and full of blood. It may be added, that Sand's observations were entirely independent of mine. *Moore* (1921) also observed the formation of a penis-like organ in two masculinized guinea pigs (out of 18 animals operated). He relates that the genital region resembled that of the male considerably more than that of the female, and he adds that the condition differed in no material respects from that which I described. On the contrary, *Harms* (1922, p. 242) states that in his experiments no change took place in the copulatory organ. In view of the observations of Sand and Moore and myself the negative result obtained by Harms can only be explained as due to a degeneration of the testicular graft. He supplies no details.

As we have seen in the preceding section, there is, according to Steinach, an inhibition of body growth brought about under the influence of the ovary. On the contrary, the testicle seems to favour body growth (*Fig.* 121). The masculinized guinea pig of Steinach, which I myself also observed, was much bigger than a normal female or an ordinary female "castrate"; its proportions were more those of a normal male. According to Steinach there may be even an hypermasculinization in the growth of the skeleton and body generally. But the same objections may be made to this conclusion as to the similar conclusions about the feminized male (see p. 295). *Moore* (1919) claims that there was little evidence that the engrafted testicle affected the weight of rats; on the other hand, *Stotsenburg* (quoted from *Moore*, 1919, 1922) showed that removal of the testicle does not influence the body growth of the rat,

---

[1] Recently we stated that an hypertrophied clitoris and horny styles sometimes are present also in otherwise normal female guinea pigs. I saw four animals of this kind. The hypertrophy was however mostly not so pronounced as in the masculinized animal. The internal organs were quite normal. The phenomenon is an hereditary one. An offspring of one of the above animals showed the same phenomenon. We have not yet made a detailed investigation of the problem which is indeed of a very great interest.

whereas removal of the ovary causes an increase of 17 to 30 per cent. above that of the normal females. So *Moore* (1919) considered the possibility that the greater weight of the masculinized guinea pig was caused rather by removing the ovary than by engrafting the testicle. But new experiments of *Moore* (1922) showed that his criticism was by no means justified, as castrated female guinea pigs attained only the same weight as normal ones.

Steinach describes also differences in the coat of the normal and masculinized females, claiming to have observed a transformation of the fine and soft hair of the female into the coarse and rough hair of the male.

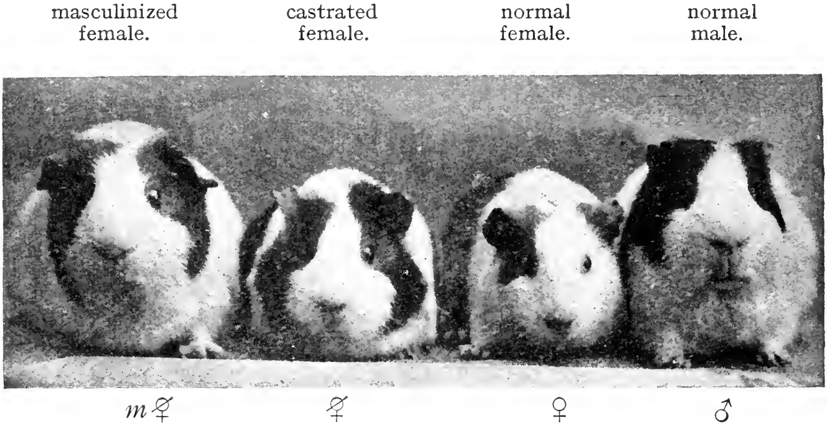


FIG. 121.—*Influence of testicular transplantation on size of female guinea pig.* —From Steinach.

The psycho-sexual behaviour of the masculinized female guinea pig of Steinach was decidedly male. I had the opportunity of observing this animal under different conditions. When a female on heat was put into its cage it behaved towards the female like a normal male, and followed her about. The characteristic call of the male was emitted. Moreover, towards an ordinary male the masculinized female behaved like a rival male and vigorously fought it. The psycho-sexual behaviour of masculinized rats has been systematically studied by Sand who attributed their behaviour to the engrafted testicle. Moore also has described the psycho-sexual behaviour of masculinized guinea pigs, and his observations fully corroborate those described above. In view of all this it is clear that the testicular graft may cause a masculinization, not only of the somatic sex characters, but also of the psycho-sexual behaviour.

The masculinization of a female stag was brought about by Brandes. The female showed the "Adam's apple," which is characteristic of the male, and jumped like a male. There were signs of a beginning of horn growth on the forehead.

Microscopical examination has shown that the testicular graft in females often undergoes a degeneration in the seminiferous part. There is frequently a more or less complete degeneration of the tubules, and an increase of the interstitial cells, as in auto- and homoiotransplantation. In the foregoing section of this chapter we saw that there may be certain indications of an hyperfeminization, as seen in the great development of the mammary glands. We have explained this hyperfeminization as due to the histological changes which the ovarian graft undergoes; an increased number of endocrine cells caused by intense folicular atresia is the factor involved. Now the question arises as to whether there is a correspondence between the histological changes in the graft and the hormonic effect produced in the masculinized female. According to *Steinach* (1916) the vigorous psycho-sexual behaviour of the masculinized female and its greater size and weight are to be considered as signs of an hypermasculinization caused by an increased activity of the interstitial cells, which are now present in an augmented number. On comparing the histological results of eight experiments on rats, Sand came to the conclusion that the degree of masculinization of the female (psycho-sexual behaviour and hypertrophy of the clitoris) is the more intense the greater the number of the interstitial cells in the testicular graft. But against all these quantitative conclusions may be set the same objections as were considered in Chapter IV., in describing other experiments with transplantation as well as observations on cryptorchid animals. The question has been lately discussed by *Moore* (1921) who describes microscopical sections of testicular grafts in two cases of masculinization in guinea pigs. There was little or no hypertrophy of the interstitial cells in one case, the germinal epithelium being not so greatly degenerated as usually in testicular grafts. There was a considerable degeneration of the seminiferous tubules in the second case, the entire mass of germinal epithelium having disappeared, and only a single layer of cells being present. There was a wide separation of the degenerated tubules by large threads of interstitial tissue, consisting of well-stained cells of Leydig. As to the degree of masculinization, the second animal showed a slightly less pronounced transformation in regard to the psycho-sexual behaviour and the external genital organs. Since the interstitial cells were present in greater abundance, Moore concludes that his observations do not support the theory of these cells being the seat of the endocrine function of the testicle. But as we have seen in Chapter IV., the reaction of the soma to the male sexual hormones seems to be governed by other quantitative laws than those postulated formerly; and in view of these considerations Moore's conclusions can hardly be accepted.

* * *

All the experiments recorded above, in which a gonad of one sex was engrafted into the castrated organism of another sex, leave no doubt, that in mammals one and the same organ or tissue reacts in a different manner to the hormones of the gonad according to the sex of the latter. This means that the sexual hormones of the testicle act differently from those of the ovary, or that the sexual hormones act in a *sex specific* manner.

The same conclusion can be also demonstrated by engrafting the gonad of one sex into the uncastrated organism of the other sex. We shall deal with this matter in Chapter IX.

Experiments on castration have shown that after removal of the sex gland the male and female organisms converge to a type common to both sexes; the experiments recorded in this chapter show that the "castrate," which approaches the asexual or neutral type, becomes more or less transformed somatically into the sex to which the engrafted gonad belongs. All these experiments support the theory that there is in mammals during embryonic development an asexual soma identical for all individuals, and that this becomes transformed into the male or female type after a differentiation of the endocrine apparatus of the gonad has taken place, and after the sexual hormones have begun their action of stimulating or inhibiting the growth of the different tissues.

Objections have been raised to this hypothesis on the ground that there is never a complete reversal of one sex into the other after heterosexual implantation. These objections will be dealt with in Chapter XI.

2. Experiments on Fowls.

Castration of the fowl leads to the conclusion that there is an asexual or a neutral form common to both sexes, which is transformed by the action of the hormones of the ovary, or of the testicle into the female or the male type. We learned from the experiments that the plumage and the spurs are hardly influenced by the hormones of the testicle, whereas they are much changed by the hormones of the ovary. This conclusion has been confirmed as a result of numerous experiments by Goodale, performed on the cock and the drake. Similar experiments have been performed by Pézard and Zawadowsky.

Goodale (1914, 1916) castrated a Brown Leghorn cockerel twenty-four days old and engrafted into this bird the ovaries from two pullets of the same strain; the ovaries were cut in several pieces and dropped into the abdominal cavity without any attempt to suture the pieces in position. The immature plumage of the male Brown Leghorn resembles that of the female; later on the characteristic male plumage appears. We saw in Chapter II. that this is true also for the ordinary "castrate," which acquires the brilliant male plumage. On the contrary, a castrated cockerel with an ovarian graft had the plumage of a hen (*Fig.* 122). "The bird was shown to several experienced poultrymen without knowledge of the history of the case, and they all pronounced it a female." The spurs, which remain unchanged in the capon, were in Goodale's operated cockerel undeveloped for a long time. There was no doubt that a feminization of the castrated cockerel had taken place under the influence of the ovarian graft. During the next spring some changes took place, showing that the influence of the ovarian graft was an incomplete one, or else that this influence began to decline; there was possibly also an effect due to small regenerating pieces of testicle. The comb and wattles began to grow and became very red. The bird was observed to crow and to tread the hens. The spurs attained a length of one inch. The weight approached that of a hen. The plumage remained a female one; there were, however, some deviations from the normal female plumage, but "no trace of any of the male feather characters" was seen. The bird was killed a year after the operation; ovarian tissue was found in the abdominal cavity in different positions. No oviduct and no vasa deferentia were detected.

Later on *Goodale* (1918) described further experiments with successfully feminized cocks. The results were similar to those described above. There were, however, differences in the condition of the various individuals. Goodale points out that in the second series of experiments the spurs were well developed, whereas the bird mentioned above showed an inhibition, though not a complete one, of the growth of the spurs. The body-size resembled that of the male. The psycho-sexual behaviour was in some of the experimental birds more or less like that of a normal cock, whereas in others no sexual instincts were to be observed. On the contrary, the comb, wattles and plumage became indistinguishable from that of a female.

FIG. 122.—*Feminized cockerel.* Female plumage.—From a photo kindly lent by Goodale.

In discussing the results of these experiments Goodale deals with three different possibilities: (1) that the portion of the ovary which survived the implantation was not sufficient to control the sex characters entirely; (2) that there was a different genetic basis in each bird, so that each individual reacted differently to similar hormones; (3) that a portion of the testicle remained in the feminized animal. The latter conclusion is, I think, the most probable. Experiments performed by Pézard support this assumption.

In an experiment in which ovaries were implanted in a castrated cockerel, *Pézard* (1918, pp. 147–52) described a slower growth of the spurs, whereas the comb and the plumage remained male. The sexual instincts, which disappeared after the operation, reappeared later. The autopsy showed that the castration of the cockerel was an incomplete one. It is possible, however, that the slower growth of the spurs was caused by the engrafted ovary exerting a feminizing action for a certain time. Pézard performed also experiments upon the transplantation of testes into castrated hens; but here too castration was not completely effectual. Both hens with engrafted testicles exhibited a female plumage; no spurs were present. But in one case the comb was much bigger than in a normal or castrated hen, and the curve of growth of the comb resembled that of a normal cock. Evidently there was an endocrine action on the part of the engrafted testicle in the incompletely castrated hen, a condition of hermaphroditism or intersexuality such as possibly existed also in some of the above-mentioned experiments by Goodale. Such a condition of hermaphroditism was apparently present also in older experiments of *Foges* (1903, pp. 53–54; 1914, p. 383; 1920). Having engrafted testes into a hen (most likely a normal or an incompletely castrated one) Foges observed a growth of the comb and wattles similar to that in a cock. Owing to the insufficient knowledge of endocrinology at that time Foges' results could not be explained as due to the simultaneous presence of both the male and the female gonad.

Feminization experiments have been carried out by *Goodale* (1918) on five drakes, of which three were definitely feminized. The plumage resembled that of the normal female, excepting that some feathers preserved the male characters. The feminization of the plumage was especially pronounced on the head and on the neck. The curl in the tail which characterizes the normal or the castrated drake was absent in the feminized animals as in the normal duck, although the feathers concerned were present; further, in the feminized bird these feathers were not black as in the normal drake, but brown or yellowish brown. In two feminized birds the sexual instincts were changed by the ovarian graft. Whereas the castrated drake preserves the male voice, that of the feminized birds was not a male one, but was something between the male and female voice, or a sort of broken "quack."

Feminization and masculinization experiments on the fowl were performed about four or five years later by *Zawadowsky* (1922, 1923). Abdominal implantation of ovary into the castrated cock was successful in two cases out of six. There was a complete feminization in regard to plumage, shape of body, and voice; the growth of the spurs was inhibited to a certain degree; certain sexual instincts remained unchanged. There were three successful masculinization experiments. The engrafted testicles (subcutaneous transplantation) developed in one case so well as to increase in length four to five times in a month and a half. Histologically the graft represented a fully developed testicle with spermatozoa. The comb began to grow as soon as ten days after the operation. The general behaviour was that of a male. The masculinized hen spreads out the tail and wings, and follows the hens with rapidity and great persistence, offers them food with a truly masculine gallantry, and crows with a clear, well developed male voice.

In view of these experiments the existence of a sex specific endocrine action on the part of the ovary and of the testicle in birds is beyond any doubt. The differences in details in the various experiments are of small moment. We must bear in mind that the result of each experiment may depend on the time at which the heterosexual implantation is made, and possibly also on the quantity of the hormone. We shall deal with this question more fully in Chapter XI.

Very important experiments on the sex specific action of the gonad in fowls have been performed by *Minoura* (1921) in the laboratory of Lillie. Minoura engrafted testicles and ovaries on the surface of the chorio-allantoic membrane of hens' eggs cutting out a small piece of the shell and replacing that piece and sealing it with paraffin after effecting the graft. In a great many cases the graft "took" and became well vascularized; there was a growth of the seminiferous tubules or a development of the follicles consisting of oöcytes surrounded by granulosa cells. The best results were obtained when the graft was made in the second week of incubation.

The embryos were dissected at about two weeks after implantation. "Whenever the grafts exhibited a good growth the embryos were affected, but when the grafts grew slightly or not at all the resulting embryos were nearly normal or apparently not affected." By affected embryos Minoura means those in which male and female characters were present simultaneously. Whereas both Müllerian ducts completely disappear in the normal male embryos in the third week of incubation, there were in the experiments of Minoura embryos with testicular grafts, having gonads *in situ* of the male type and at the same time Müllerian ducts; or there were embryos with testicular grafts, having gonads of the female type, but with a deviation from the normal, in as much as the right gonad also developed, and at the same time the Müllerian ducts were not differentiated to the normal extent; in many cases where testicular grafts were made Wolffian ducts more or less of the male type were present simultaneously with Müllerian ducts. On the other hand embryos with ovarian grafts revealed gonads of the male type with Müllerian ducts partially differentiated as in the female, or gonads of the female type with Wolffian ducts more of the male type. Where the engrafted gonad was a testis, the Müllerian ducts were undifferentiated and showed signs of degeneration. Where the grafted gonad was an ovary, the Müllerian ducts were retained, degenerative changes in the ducts were absent, and the left duct was better developed and more differentiated than the right one. It is naturally impossible to say to which sex the individual egg originally belonged. But there are some indications as to this. The presence and degree of differentiation of the Müllerian ducts in embryos with testicular grafts and gonads of the male type can be only explained by the assumption that these embryos originally developed and differentiated to a certain extent in the direction of femaleness but that *their original ovaries became transformed under the influence of the testicular graft into gonads of the male type.* Minoura rightly concludes from his experiments "that the sexual characters are reversible and that these characters after having differentiated to a certain extent in the direction of one sex may be altered and modified in the direction of the opposite sex . . . the development and differentiation of one sex is stimulated by the secretion of the gonads of the same sex and inhibited by the secretion of the gonad of the opposite sex."

It is of great interest to note that the castrated hen or duck can acquire some male characters which depend normally upon the internal secretion of the testicle. Such observations were made by Goodale (hens and ducks), by Pézard (hens) and by Zawadowsky (hens). In the experiments of Goodale the comb developed in castrated hens in varying degrees, becoming very large and male-like in some of them, but remaining comparatively small in others; there is according to Goodale no clear evidence as to the cause of this difference. The transformation of female characters into male ones seems to be related to a transformation of the rudiment of the sex gland on the right side in the female bird. Now *Zawadowsky* (1922, p. 82) observed a development of male sex characters (comb, wattles, and, to a certain degree also, sexual activity) in castrated hens in which there was no transformation of the right rudiment. One of his castrated hens showed a growth of the comb as in the male. In this bird a regeneration of the left ovary occurred, but no ova were present. After removal of this regenerated gland a regression of the comb took place as in the ordinary "castrate." Zawadowsky concludes from these observations that the ovary may in certain circumstances elaborate male sexual hormones.

The question arises as to whether the specific hormonic effect characteristic of the testicle or the ovary can be exhibited also by other endocrine glands. It cannot be denied that in every specific hormonic effect produced by the gonads other endocrine glands are actively involved; but there is no experimental evidence that a sex specific action similar to that of the gonad is exhibited by other glands, with the one possible exception of the adrenals. We shall deal with these questions below in the chapter on "Intersexuality."

C. EXPERIMENTS ON ARTHROPODA.

Experiments on moths have been performed by *Meisenheimer* (1909) and *Kopeć* (1912). Meisenheimer castrated the male *Lymantria dispar* at the caterpillar stage and implanted ovaries. The latter developed quite normally, but the animals never showed any transformation of the sex characters. The vasa deferentia, the vesicles, the accessory glands and the ductus ejaculatorius were always normal. Kopeć made similar feminization and masculinization experiments using younger caterpillars than those employed by Meisenheimer (caterpillars immediately after the first moulting); he also made repeated transplantation experiments. The grafts "took" and the testicles even showed an hypertrophy; histologically they were like the normal organ. But no influence of the engrafted testicle or ovary on the host of the other sex was ever seen. Injections of blood or of a pulp from the gonad of the other sex into castrated caterpillars made by Kopeć also had no influence even though great quantities were injected.

Experiments on the fiddler crab have been performed by *Morgan* (1920). Boring a hole in the carapace of the male crab he inserted pieces of the ovary taken from a female fiddler; he also did the converse experiment. The small pieces engrafted often got lost, and it could not be determined subsequently how far the graft degenerated and how far it grew, but no effect was ever produced on the claws.

The state of things in the Arthropoda seems to be wholly different from that in mammals. It is of course conceivable that in the Arthropoda the endocrine cells which produce the sexual hormones are widely separated from the gonad or the generative cells.

BIBLIOGRAPHY FOR CHAPTER VI.

[* *Not seen in the original.*]

ATHIAS. 1915. L'activité sécrétoire de la glande mammaire hyperplasée, chez le cobaye mâle châtré, consécutivement à la greffe de l'ovaire. *C. R. de la Soc. de Biol.*, 78, p. 410.

—— 1916. Sur le déterminisme de l'hyperplasie de la glande mammaire et de la sécrétion lactée. *C. R. de la Soc. de Biol.*, 79, p. 557.

BIERENS DE HAAN. 1922. Die Körpertemperatur junger Wanderratten (Mus decumanus) und ihre Beeinflussung durch die Temperatur der Aussenwelt. *Arch. f. Entw.-Mech.*, 50, p. 1.

BORMANN. 1922. Über die Folgen der Kastration in ihren zeitlichen Beziehungen. *Skandinav. Arch. f. Physiol.*, 42, p. 240.

—— BRUNNOW *und* SAVARY. 1923. Über den Unterschied in der Körpertemperatur beim männlichen und weiblichen Kaninchen und über die Abhängigkeit der Körpertemperatur von den Geschlechtsdrüsen. *Skandin. Arch. f. Physiol.*, 44, *p.* 248.

BRANDES. 1914. See *Berliner Tageblatt*, 7th June, 1914 (No. 283, 2 Beiblatt); Kammerer, *Geschlechtsbestimmung und Geschlechtsverwandlung.* Wien, 1918, p. 77; Hirschfeld, *Sexualpathologie*, II., Bonn, 1918, p. 100.

BRESCA. 1910. Experim. Untersuchungen über die sekund. Sexualcharaktere der Tritonen. *Arch. f. Entw.-Mech.*, 29, p. 403.

*BUCURA. 1907. Beiträge zur inneren Funktion des weiblichen Genitales. *Zeitschr. f. Heilkunde*, 28.

—— 1913. *Geschlechtsunterschiede beim Menschen.* Wien–Leipzig.

CAULLERY. 1913. *Les problèmes de la sexualité.* Paris, p. 113.

DONALDSON. 1915. *The rat.* Philadelphia.

FOGES. 1903. Zur Lehre von den sekundären Geschlechtscharakteren. *Pflügers Archiv*, 93 (see espec. p. 53a, 54).

—— 1914. Keimdrüsen. In Jauregg und Bayer, *Lehrbuch der Organotherapie*, Leipzig, 1914, p. 383 u. 384.

—— 1920. Historischer Beitrag zum experimentellen Hermaphroditismus. *Zentralbl. f. Gynäkol.*, 44, p. 87.

GERHARDT. 1909. Der gegenwärtige Stand der Kenntnisse von den Kopulationsorganen der Wirbeltiere, insbesondere der Amnioten. *Ergebnisse u. Fortschritte d. Zoologie.*

GOODALE. 1914. A feminized Cockerel. *Science*, 41, p. 594.

—— 1916. A feminized cockerel. *Jl. of Exper. Zoology*, 20, p. 421.

—— 1918. Feminized male birds. *Genetics*, 3.

GRUBER. 1907. Bau und Entwicklung der äusseren Genitalien bei Cavia coboya. *Morphol. Jahrbuch*, 36.

HARMS. 1910. Hoden- und Ovarialinjektionen bei Rana-fusca-Kastraten. *Pflügers Archiv*, 133.

*—— 1921. Verwandlung des Bidder'schen Organs in ein Ovarium beim Männchen von Bufo vulgaris Laur. *Zool. Anz.*, 53, p. 253.

—— 1922. Keimdrüsen und Alterszustand. Berlin–Wien. (*Fortschr. d. naturwissensch. Forschung*, 11, p. 189.)

—— 1923 a. Die physiologische Geschlechtsumstimmung (Demonstration). *Verhandl. d. Deutschen Zool. Gesellsch.*, 28, p. 37.

—— 1923 b. Untersuch. über d. Bidder'sche Organ der männl. u. weibl. Kröten. II. Mitt. Die Physiol. des Bidder'schen Organs u. d. experimentellphysiolog. Umdifferenzierung vom Männchen in Weibchen. *Zeitschr. f. Anat. u. Entw.-Gesch.*, 69, p. 598.

KAMMERER. 1919. Steinachs Forschungen über Entwicklung, Beherrschung und Wandlung der Pubertät. *Ergebn. d. Inneren Medizin u. Kinderheilk*, 17, p. 295.

KOPEĆ. 1912. Untersuchungen über Kastration und Transplantation bei Schmetterlingen. *Arch. f. Entw.-Mech.*, 33, p. 1.

LIPSCHUTZ. 1914. Steinachs Forschungen über Feminierung und Maskulierung. *Umschau.*

—— 1916a. Körpertemperatur als Geschlechtsmerkmal. *Anzeiger d. Akad. d. Wissensch.*, Wien, No. 22.

—— 1916b. Entwicklung eines penisartigen Organs beim maskulierten Weibchen. *Anzeiger d. Akad. d. Wissensch.*, Wien, No. 27.

—— 1917a. On the internal secretion of the sexual glands. *Jl. of Physiology*, 51.

—— 1917b. Über die Abhängigkeit der Körpertemperatur von der Pubertätsdrüse. *Pflügers Archiv*, 168.

—— 1918. Umwandlung der Clitoris in ein penisartiges Organ durch experimentelle Maskulierung. *Arch. f. Entw.-Mech.*, 44.

—— BORMANN, BRUNNOW *et* SAVARY. 1923 a. Sur la question des différences de température entre les deux sexes. *C. R. de la Soc. de Biol.*, 88, p. 1261.

—— *et* KRAUSE. 1923 b. Recherches quantitatives sur l'hermaphrodisme expérimental. *C. R. de la Soc. de Biol.*, 89, p. 220.

—— —— 1923 c. Temps de latence dans l'hermaphrodisme expérimental. *C. R. de la Soc. de Biol.*, 89, p. 1135.

MEISENHEIMER. 1909. *Experimentelle Studien zur Soma- und Geschlechtsdifferenzierung*, I. Jena.

—— 1912. *Experimentelle Studien zur Soma- und Geschlechtsdifferenzierung*, II. Jena.

MINOURA. 1921. A study of testis and ovary grafts on the hen's egg and their effects on the embryo. *Journ. of Experim. Zool.*, 33, p.1.

MOORE. 1919a. On the physiological properties of the gonads as controllers of somatic and psychical characters. I. The rat. *Journ. of Experim. Zool.*, 28, p. 137.

—— 1919b. II. Growth of gonadectomized male and female rats. *Journ. of Experim. Zool.*, 28, p. 459.

—— 1921. IV. Gonad transplantation in the guinea-pig. *Journ. of Experim. Zool.*, 33, p. 365.

—— 1922. V. The effects of gonadectomy in the guinea-pig, on growth, bone lengths, and weight of organs of internal secretion. *Biol. Bulletin*, 43, p. 285.

MORGAN. 1920. Variations in the secondary sexual characters of the fiddler crab. *American Naturalist*, p. 220.

MYERS. 1917. Studies on the mammary gland. III. A comparison of the developing mammary glands in male and female albino rats from the late fetal stages to ten weeks of age. *Anatomical Record*, 13.

OCARANZA. 1922. La temperatura normal del cuy de nuestros laboratorios. *Revista Mexicana de Biologia*, 3, p. 53.

PÉZARD. 1918. *Le conditionnement physiologique des caractères sexuels chez les oiseaux.* Thèse, Paris. Edition du Bull. Biol. de la France et de la Belgique. (See esp. p. 147–152).

—— SAND *et* CARIDROIT. 1923. Féminisation d'un coq adulte de race Leghorn doré. *C. R. de la Soc. de Biol.*, 89, p. 947.

PONSE. 1923. Masculinisation d'une femelle de crapaud. *C. R. de la Soc. de phys. et d'hist. nat. de Genève*, 40, Nr. 3.

PRZIBRAM (Hans). 1915. Die Umwelt des Keimplasmas. VI. Direkte Temperaturabhängigkeit der Körperwärme bei Ratten. *Anzeiger d. Akad. d. Wissensch*, Wien, No. 25.

—— 1923. *Temperatur und Temperatoren im Tierreiche.* Leipzig–Wien.

SAND. 1918a. *Experimentelle Studier over Kønskarakterer hos Pattedyr.* Copenhagen.

—— 1918b. Experimenteller Hermaphroditismus. *Pflügers Archiv*, 173.

—— 1919. Experiments on the internal secretion of the sexual glands, especially on experimental hermaphroditism. *Journ. of Physiology*, 53, p. 267.

—— See also Bibliography of Ch. IX.

SCHULTZ. 1910. Verpflanzungen der Eierstöcke auf fremde Spezies, Varietäten u. Männchen. *Arch. f. Entw.-Mech.*, 29, p. 79.

STEINACH. 1910. Geschlechtstrieb und echt sekundäre Geschlechtsmerkmale als Folge der innersekretorischen Funktion der Keimdrüsen. *Zentralbl. f. Physiologie*, 24.

—— 1912. Willkürliche Umwandlung von Säugetier-Männchen in Tiere mit ausgeprägt weiblichen Geschlechtscharakteren und weiblicher Psyche. *Pflügers Archiv*, 144.

—— 1913. Feminierung von Männchen und Maskulierung von Weibchen. *Zentralbl. f. Physiologie*, 27.

—— 1916a. Pubertätsdrüsen und Zwitterbildung. *Arch. f. Entw.-Mech.*, 42, p. 307.

—— *und* HOLZKNECHT. 1916b. Erhöhte Wirkungen der inneren Sekretion bei Hypertrophie der Pubertätsdrüsen. *Arch. f. Entw.-Mech.*, 42, p. 490.

TIGERSTEDT. 1910. Die Produktion von Wärme und der Wärmehaushalt. *Handbuch der vergleich. Physiol.*, III. 2. Jena.

WAGNER. 1922. Experimentelle Untersuchungen über die Umwandlung des Geschlechts beim Frosch. *Arch. f. Entw.-Mech.*, 52, p. 386.

ZAWADOWSKY. 1922. *Das Geschlecht und die Entwicklung der Geschlechtsmerkmale.* (Russian with Summary in German.) Moscow, State edition.

—— 1923. *The sex of animals and its transformation.* (Russian.) Moscow–Petrograd, State edition.

Chapter VII.

The Question as to the Isolation of the Sexual Hormones.

A. EXTRACTS OF THE WHOLE SEX GLAND.

In Chapter III. we considered the experiments which have been made upon the injection of the sexual glands and their extracts to show how greatly our knowledge of internal secretion has been influenced thereby. We must never forget that it was through the experiments of Brown-Séquard[1] with subcutaneous injection of testicular extracts that our knowledge not only of the internal secretion of the sexual glands, but of internal secretion in general began. It is well known that the experiments of Brown-Séquard have been much disputed; we have already discussed this question at some length in the third chapter. But notwithstanding all the objections which have been made, the fact remains that here, as so often in the history of science, new scientific principles and new knowledge were established on disputed, or even really erroneous, data.

After Brown-Séquard, repeated attempts were made to obtain from the gonads the chemical substances corresponding to the sexual hormones. The determination of the characters of these substances by an elementary chemical analysis, or the establishment of their chemical constitution was not attempted until later. Several investigators, however, tried to isolate the hypothetical hormones from the gonad. The great therapeutical successes with preparations of the thyroid, and the new exact knowledge of adrenaline gave a powerful incentive to similar attempts to isolate the internal secretions of the gonads. But so far the results of all recorded experiments with injecting these extracts have been disappointing. It is true that many effects have been described—effects on the nervous system, on the circulation, on the metabolism, and

---

[1] On the rôle played by Brown-Séquard in the establishment of endocrinology see *Gley's* book (1914), especially p. 22.

on the sex characters. But the observations of the different investigators disagree very considerably. This is easy to understand if one takes into consideration the fact that the chemical nature of the various extracts must differ greatly according to the special technical methods of preparation. The disagreement is so great that we find one authority attributing to the extract of the gland the capacity for raising the blood pressure, and another describing precisely the opposite effect. *Biedl* (1913, p. 292 of Vol. II.) has strongly criticised all these experiments, pointing out that very probably the effects obtained by these extracts, which are considered as specific of sexual hormones, are often nothing else than effects which can be obtained with extracts of any organ. Possibly profound chemical alterations take place when an extract is made, and we must suppose that the extract contains different products derived from the common proteins of the respective organ. It is known that these derivatives of proteins may have toxic effects on the organism. These products are characteristic not of certain proteins, but of proteins in general. The severe verdict of *Gley* (1914, p. 43) on the experiments concerning the effects of organic extracts in general seems to be justified for the experiments made with extracts from the sex glands: "presque tous les travaux faits depuis quinze ans sur cette question l'ont été avec une méthode, non pas absolument défectueuse, mais incomplète, donc insuffisante."[1]

It cannot be denied that it is possible to produce with extracts from the sex glands some specific effects characteristic of these glands *in situ*, as was shown in Chapter III., especially for the frog. Similar specific effects of sexual hormones have sometimes been obtained also by injection of these extracts into birds and mammals. The reappearance of the turgor of the comb and of the sexual instincts after injection, as in the experiments of *Pézard* (1911), may be mentioned here. We have noted also the successful experiments of *Bouin* and *Ancel* (1906) on injected guinea pigs, and we shall describe in this chapter similar experiments by Fellner and Herrmann on rabbits. But on the other hand one must never forget that the effect of an extract, as already remarked, varies much according to the methods used for its preparation, and this is

---

[1] See also the new edition of *Biedl's* "Internal Secretion" (1922); the book of *Marañon* (1922, ch. XI.) may also be consulted here.

why we must be very careful in drawing conclusions about such experiments. The impression one gets when reading of the contradictory results obtained by different authors with extracts of testes, ovaries, placenta and foetus is not a favourable one (see especially *Gley*, 1914, p. 42). Further, such experiments are of a scientific value only when simultaneously controlled by experiments made with extracts from other organs prepared in just the same manner without any technical deviation. But even in this case the value of injection experiments must remain a very limited one, because these experiments are liable to give a very erroneous idea of the effects of the sexual hormones produced by the gonads in the organism. It is most likely that the extract contains only *some* of the substances which normally are secreted by the sex glands; most probably the manifold effects produced are due to different hormones being secreted. There is little justification for supposing that there is *one* male and *one* female sexual hormone; as little justification as there would be in supposing that adrenaline is the only hormone secreted by the adrenals. Further, we have already mentioned the possibility that by introducing extracts into the body, substances are introduced which normally are never secreted by the sex glands. It must also be taken into consideration that it is not possible to imitate by injection the real quantitative and time relations of the normal glandular function, to imitate, so to speak, the *rhythm* of the normal function. There can be no doubt that the normal functional rhythm of an endocrine gland is of the greatest importance to the organism, and we must suppose that the effects of the substances by which one organ acts on another are subject to the general laws of stimulation. Quantitative and time relations in internal secretion have so far been very insufficiently studied on an experimental basis. But we have seen in the foregoing chapters to how great an extent quantitative problems are involved in investigating the internal secretion of the sex glands. The experiments of Pézard, as well as our own, made on more or less quantitative lines, showed from the beginning that we are here on an almost wholly unexplored terrain, where many special problems await to be investigated.

B. EXTRACTS OF DIFFERENT PARTS OF THE SEX GLAND.

The question as to the effects of extracts of the sex gland becomes still more complicated if we take into consideration the probability that different parts of the testicle and of the ovary are involved in the endocrine functions of these organs in different ways, as we have seen already in Chapters IV. and V. Many experiments have been made dealing with this problem. In Chapter III. we have discussed similar experiments by Bouin and Ancel on the guinea pig, and by Pézard on the cock. In these experiments cryptorchid testicles have been employed for the preparation of extracts. Since all the higher stages of spermatic cells were absent in these testicles, as shown by histological examination, the experiments give further support to the assumption that the production of sexual hormones is possible without maturation of the generative part taking place. The negative results obtained by Barnabo (quoted from *Harms,* 1922), who, in experiments similar to those of Bouin and Ancel, used extracts prepared from testicles after resection of the vas deferens, do not nullify this conclusion, since they may quite easily have been due to the mode of preparation of the extract.

The experiments of Pézard are of especial interest also in another respect. Since the growth of the comb and of the wattles in the capon can be promoted by injecting an extract prepared from the retained testicle of the pig, it is shown by these experients that *the sexual hormones are not specific for each kind of animal.* There is a "sex specifity," but not a specifity for the particular species.

The question as to the effects of extracts prepared from different parts of the ovary has attracted much more interest on account of the great practical significance of these problems in gynæcology. As far as I know the first experiments with injection of corpus luteum were those performed by *Fraenkel* (1903, p. 491; 1910, p. 753). This investigator introduced these extracts into medical practice in the form of tablets prepared from the corpus luteum of the cow. Similar experiments have been made by several others. We need not discuss here the many details concerning the use and the results of this treatment in gynæcological practice, but the papers of *Fraenkel* (1914, p. 692), *Foges* (1914, pp. 401, 407), and *Blair Bell* (1920) may be referred to. Most authorities claim to have observed specific effects from extracts of corpus luteum, but the results seem to be contradictory. This we can easily understand, since the effects, as explained above, must vary according to the mode of preparation.

As to the chemical isolation and definition of the specific sexual hormones the experiments of Fellner and of Herrmann are of an especial interest. These experiments will be dealt with below.

Iscovesco (quoted from *Herrmann and Stein*, 1916) first drew attention to the action of lipoid-containing extracts of endocrine organs. He succeeded in producing a very marked increase of the volume of the uterus by injecting an extract prepared from the ovary by treating it with alcohol and then desiccating the alcoholic extract and treating with acetone, ether and chloroform. This was the method followed by Fellner and Herrmann.

Fellner (1913) worked with extracts of placenta, of ovaries of pregnant animals containing corpora lutea, and of ovaries of non-pregnant animals. He used for extraction a solution of sodium chloride, alcohol and ether. He stated that injection of extracts from pregnant animals caused in rabbits an hyperaemia and a thickening of the muscle layer of the uterus. The epithelium thickened and the number of uterine glands increased. There was an increased growth of the mammary glands and of the nipples; this phenomenon could be observed even in injected male animals. On the contrary, extracts of ovaries of non-pregnant animals had no effect. But extracts of testicle and of thymus had an effect similar to that of organs of pregnant animals. Extracts of the brain were without any effect. Fellner thinks that the specific substance which causes the above-mentioned effects is possibly a lipoid present in the corpus luteum in greater quantity than in other organs. In recent papers *Fellner* (1917, 1920) puts forward the view that the lipoid which he isolated from the corpus luteum is really the specific sexual hormone or possibly one of the sexual hormones secreted by this organ.

Of great interest are the later experiments of Fellner, in which he investigated the question as to whether the same substance is present also in the interstitial cells of the ovary. He prepared an extract from that ovary of the pregnant cow which contains no corpus luteum, but in which the interstitial tissue is highly developed during pregnancy. The extract showed a very marked effect on the uterus. Since such an ovary differs from the ovary of a non-pregnant cow only in the fact that the interstitial tissue is hypertrophied, Fellner is inclined to adopt the view that the interstitial cells of the ovary of the pregnant animal secrete the same substance as the corpus luteum. Fellner even suggests that the action of the interstitial cells of the ovary during pregnancy is *quantitatively* similar to that of the corpus luteum. When comparing the intensity of the effect of an extract prepared from the corpus luteum excised from the ovary with that of an extract prepared from the whole lutein-containing ovary of the pregnant animal, Fellner found that the intensity in the second case was greater than in the first. He explains this result by assuming that in the second case the effect was produced by the combined action of the lipoids extracted from the corpus luteum together with the lipoids of the interstitial cells, whereas in the first case only the lipoids of the corpus luteum were present in the extract. Finally Fellner states that an extract of a corpus luteum of a non-pregnant animal has quantitatively the same effect as that of a corpus luteum of a pregnant animal. The result of these experiments of Fellner may be explained also by the fact that there is in the ovary during pregnancy an intensified development and atresia of follicles, from which interstitial cells are formed. As we have seen in Chapter V., this explanation is in reality identical with Fellner's.

In all the above-mentioned experiments the augmentation of the uterus was made use of as a quantitative test of the hormonic effect of a given extract. By the same method Fellner arrived at the conclusion that the extract of a placenta is equivalent to that of an extract of forty corpora lutea. There were never any changes in the kidneys. Though there was a great hypertrophy of the mammary gland, milk secretion was never observed.

Herrmann (1915) investigated the effects of extracts prepared by ether. He made a comparative study of extracts of corpora lutea excised from ovaries, of extracts of ovaries without corpora lutea and of extracts of the placenta. By different chemical methods Herrmann obtained a thick yellow oil which became solid when cooled. This substance showed the characteristic reactions of cholesterine and contained carbon, hydrogen and oxygen. According to Herrmann it is possibly a derivate of cholesterine, soluble in alcohol, ether, petrol-ether, acetone and benzol, but insoluble in water. Herrmann examined the physiological effects of all the different fractions obtained in preparing the above-mentioned oily substance. The experiments were made on fully grown castrated rabbits and on young animals eight weeks old. By injecting the extracts the atrophy of the uterus which normally follows castration was inhibited, and the changes characteristic of the normal "heat" took place in the uterus. Very striking results were obtained on young animals (*Fig.* 123). After three injections an extraordinary development of the uterus began; there were changes in the mucosa and in the muscle layer. The infantile uterus increased enormously, and the blood vessels were very enlarged. There were glands in the mucosa and the muscle layers were much more pronounced after the fifth injection. The stroma of the mucosa now consisted of cells very like decidua cells. Extraordinary changes took place also in the vagina, in the tubes, and in the mammary glands. The latter began to secrete, and a quantity of clear fluid could be pressed out. These phenomena were observed also with young animals previously castrated. Similar changes in the mammary gland occurred with injected males.

It is of great interest that the ovary also is influenced by the extract (*Fig.* 124). The ovary of the young rabbit consists mainly of primary follicles (*Fig.* 124 A), but there are also some follicles just entering upon development. In the ovary of an animal which received five injections numerous ripening follicles were to be found (*Fig.* 124 B), and some of them had even already attained maturity.

It follows from these experiments that the extract prepared by Herrmann may cause in animals of about eight weeks a development of the sex characters such as is found at an age of about six to seven months. The genital organs may even develop so far as to become like those during heat or at the beginning of pregnancy. As far as I am aware, Herrmann obtained all these changes by injecting preparations of the corpus luteum and the placenta, but not by preparations of ovaries from which the corpora lutea had been excised. Herrmann concludes from his experiments that the corpus luteum and the placenta contain a substance which can excite the development of the genital organs and mammary glands.

Herrmann (1917) has employed his extracts in cases of hæmorrhage of ovarian origin and found that there were good results in 95 per cent. of 73 cases after injection of extracts of the corpus luteum or placenta. His paper may be consulted for details of the cases.

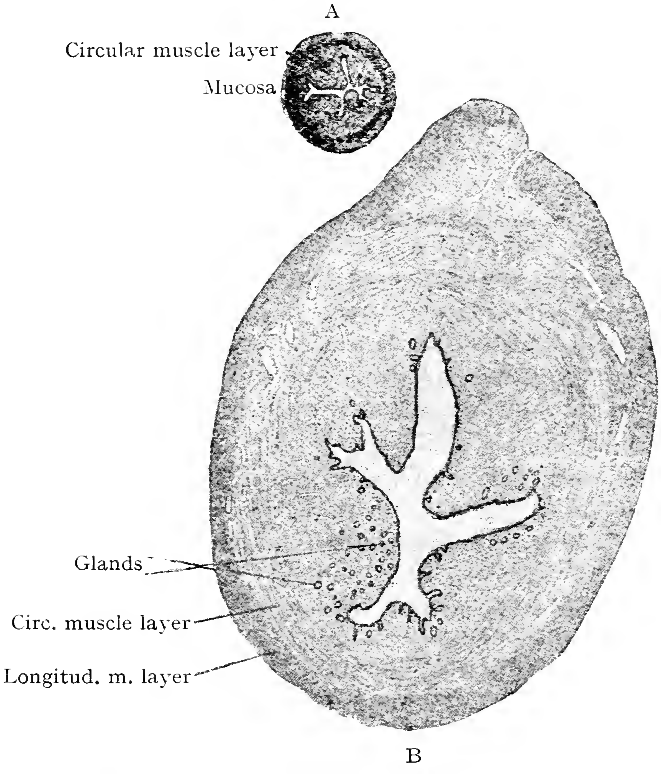


FIG. 123.—*Influence of extracts of corpus luteum on the uterus.*—From Herrmann.

A. Uterus of a rabbit 8 weeks old. Normal. x 22.
B. After 3 injections. x 22.

We have already mentioned that the influence of the extract was observed also on the mammary glands of male rabbits. This shows that the extract of the ovary or of certain parts of the ovary may act in a sex specific manner. The question of the sex specifity of this action has been studied lately more fully by *Herrmann* and *Stein* (1919, 1920, 1921) and by *Fellner* (1921). Herrmann and Stein stated that the extract of the corpus luteum inhibits the development of the generative tissue in young male rats; if spermatogenesis has already started, degeneration of the generative tissue takes place. All the male sex characters—the penis, the prostate, the vesiculae seminales, etc.—were in a state of extreme underdevelopment (signs of castration). In male rabbits there was on the one hand hypertrophy of the mammary glands and in some cases even secretion of colostrum, and on the other signs of castration in the different accessory genital glands. It is

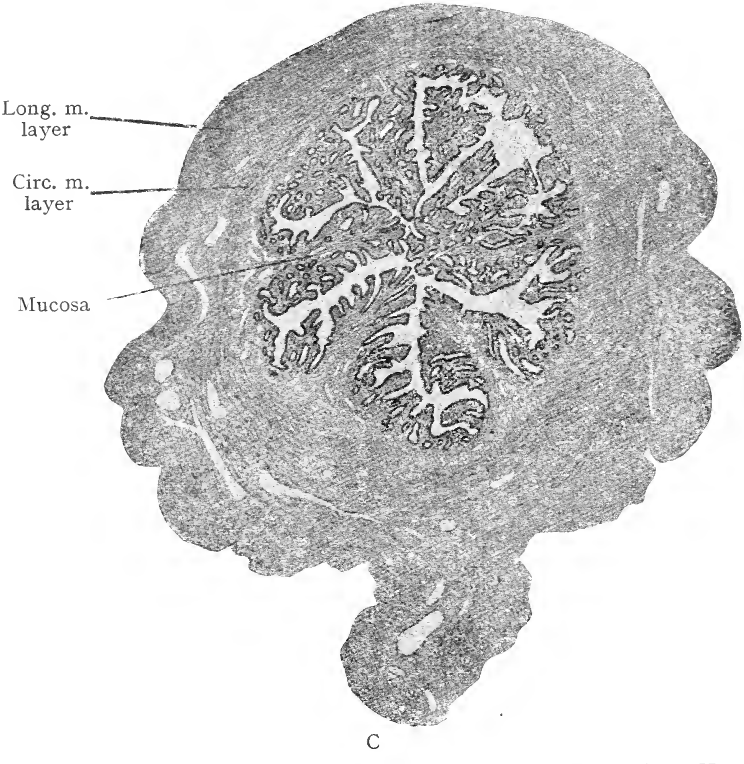


FIG 123.—*Influence of extracts of corpus luteum on the uterus.*—From Herrmann.

C. After 5 injections. x 22.

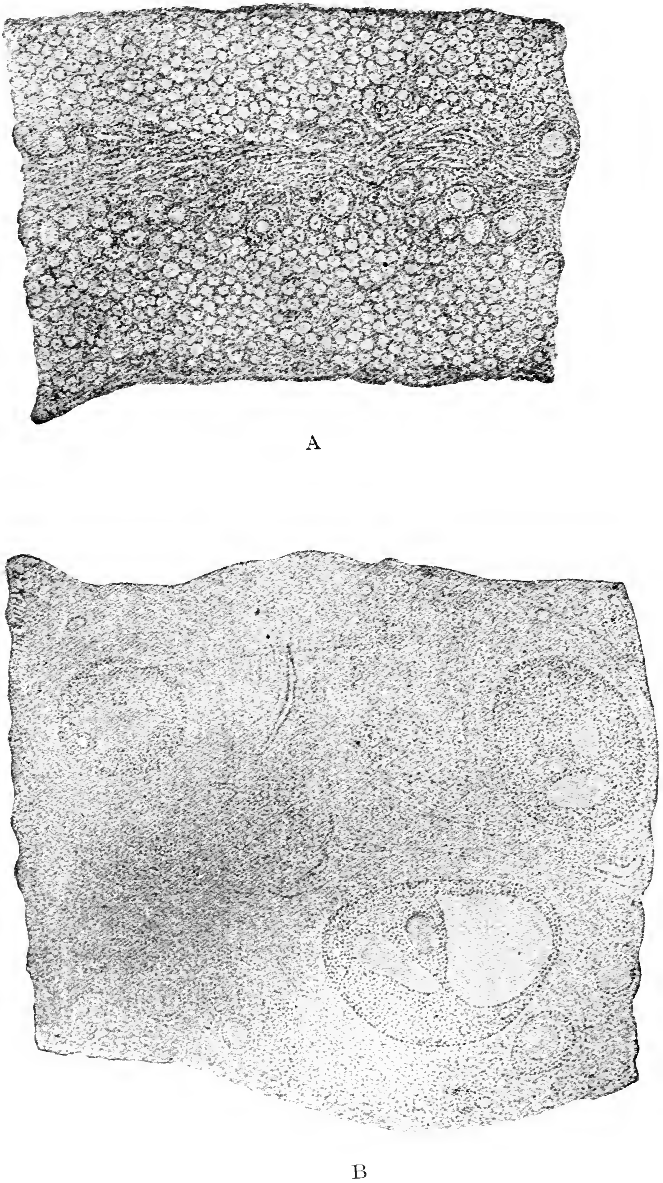


FIG. 124.—*Influence of extracts of corpus luteum on the ovary.*—From Herrmann.
A. Ovary of young normal rabbit. × 35.
B. After 5 injections. × 35.

of great interest to note that the uterus masculinus, which is greatly developed in this species, showed marked thickening of the muscle layers of the wall after injection of the above-mentioned extracts. The muscle layers of the uterus masculinus of the rabbit are considered by some authors as arising from the Müllerian ducts. If this is really so, we have an example of an organ homologous with the uterus (that is, an essentially female organ) reacting to female sexual hormones in the male organism. *Stein and Herrmann* (1921) have made similar statements about male guinea pigs in which an hypertrophy of the mammary glands also took place. But on account of certain discrepancies in their individual experiments on rabbits they think that further confirmation is needed in regard to the matter of the transformation of the uterus masculinus.[1]

Fellner (1921) has made the interesting statement that the inhibitory action which female extracts have on the testicle, may be obtained also by injecting lipoid-containing extracts of other organs, and even by injecting an extract from the testicle itself. This testicular extract also promotes hypertrophy of the uterus and of the mammary gland. Fellner concludes from his experiments that female sexual hormones are present in the testicle though in a lesser quantity than in various parts of the ovary.

There is an interesting disparity between the results of Herrmann and Fellner. Whereas Herrmann and Stein have described, as already recorded, an inhibition of the development of the vesiculae seminales and of the prostate gland in rats, rabbits and guinea pigs, injected with an extract of the corpus luteum, no such effects were observed by *Fellner* (1921, pp. 200, 204). The latter author failed also to observe the secretion from the hypertrophied mammary glands in injected males as noted by Herrmann. I think that this absence of agreement is to be explained by differences in the quantity of the injected hormones. Where the injected quantity is relatively small there will be a reaction only on the part of the generative tissue of the testicle which is very sensitive; where the injected quantities are greater there will be an inhibition of other sex characters also. In Chapter IX. we shall

---

[1] According to Wertheimer and Dubois (see Ch. VIII., p. 338) the "uterus masculinus" of the rabbit is nothing else than a seminal vesicle. Stein and Herrmann were possibly mistaken when making all the above statements.

see again that the results of the transplantation experiments in which male and female hormones were simultaneously present in the same organism were also very conflicting; and I think that in these latter experiments the disparity can be explained only on quantitative lines.

Basing his position on Herrmann's and Stein's results, *Harms* (1922) drew attention to the fact that there may be signs of castration, though interstitial cells are present in the degenerated testicle. He declared these experiments to afford further evidence for the conclusion that the interstitial cells are not the hormone-producers in the testicle. The absence of agreement between Fellner and Herrmann on the question of the behaviour of the sex characters of injected male animals shows clearly enough that the conclusion of Harms is without justification. Harms has evidently overlooked the disparity between Fellner and Herrmann, as he quotes Fellner's experiments in support of his assumption.

It seems at first thought that the changes obtained by Fellner and Herrmann in their experiments correspond with those of normal puberal development and early pregnancy. It may be pointed out that the transformation of the mammary gland caused by injection of the extract into the male animal corresponds with that observed by Steinach and others after transplantation of ovaries into the male organism. But have we any guarantee that all these changes, as described by Fellner and Herrmann, are really caused by a definite chemical substance? This is not very probable. As we have already pointed out, it is most likely that the internal secretion of the sex gland does not consist of *one* hormone, but rather of many different hormones.

An experimental comparison between the action of extracts of the corpus luteum and that of the hilum ovarii was undertaken by *Itagaki* (1917) in the laboratory of Schafer. He stated that the action of these extracts upon the movements of the living uterus of the rat are antagonistic to one another, the first causing a distinct increase of tone, the second causing inhibition. But the uterus of other animals reacts differently; in the rabbit, cat and guinea pig extracts of both the corpus luteum and the hilum produce an increase of tone. Sometimes however the extract of corpus luteum may produce inhibition. Itagaki suggests that this difference of effect is possibly due to a difference in the samples of corpus luteum. He assures us that there are apparently two principles in the corpus luteum having an antagonistic action upon the uterus. Both these principles can be extracted, according to Itagaki, by Locke's solution; the principle causing inhibition of the uterine contractions is soluble in alcohol, the principle causing increase of tone is soluble in water. *Athias* (1920) has recently confirmed the stimulating action of the ovary and of the corpus luteum on the uterus.

It may be of interest to note that *Weil* (1920) recorded a difference in reaction to subcutaneous injections of testicular extracts according to the sex of the injected animal. There was a sudden decrease in the output of CO_2 followed by a sudden increase beyond the normal output in young males, "castrates" and pregnant females, but no influence in adult males and females. On the other hand, ovarian extracts were without any influence on adult males, but caused decrease and increase in the CO_2 output in females and young or castrated males. Weil refers to this as a "sex specific" reaction.

The experiments of *Dittler* (1920) may be mentioned here, though only in an indirect relation to the problems discussed in this chapter. Dittler made intravenous injections of fresh sperm into female rabbits and stated that sterility can be caused by repeated injections. Sterility was not caused when the sperm of a man instead of rabbit's sperm was used. This effect is at first thought similar to that caused by injection of extracts of corpus luteum. But there is a very marked difference between sperm and corpus luteum, since sperm does not inhibit ovulation, according to Dittler, whereas the corpus luteum has this effect.

BIBLIOGRAPHY FOR CHAPTER VII.

ANCEL *et* BOUIN. 1906. Action de l'extrait de la glande interstitielle du testicule sur le développement du squelette et des organes génitaux. *C. R. de l'Acad. d. Sc.*, 142, p. 232.

ATHIAS. 1920. Action d'extraits et produits dérivés d'organes à sécrétion interne sur l'uterus isolé, particulièrement après la castration totale. *Arch. internat. de Pharmacodynamie et de Thérapie*, 25, p. 423.

BIEDL. 1913. *Innere Sekretion*, II., 2nd edit. Berlin–Wien.

—— 1922. *Innere Sekretion*, I. 1, 4th edit. Berlin–Wien.

BELL (W. Blair). 1920. *The Sex-Complex.* 2nd edition. London.

DITTLER. 1920. Die Sterilisierung des weiblichen Tierkörpers durch parenterale Spermazufuhr. *Münch. medizin. Wochenschr.*, p. 1495.

—— 1920. Studien zur Physiologie der Befruchtung. *Zeitschr. f. Biol.*, 72, p. 273.

FELLNER. 1913. Experimentelle Untersuchungen über die Wirkung von Gewebsextrakten aus der Plazenta und den weiblichen Sexualorganen auf das Genitale. *Arch. f. Gynäkol.*, 100.

—— 1917. Über die Tätigkeit des Ovariums in der Schwangerschaft (interstitielle Zellen). *Monatsschr. f. Geburtsh. Gynäkol.*, 54, p. 88.

—— 1920. Über das spezifische Ovarialsekret. *Zentralbl. f. Gynäkol.*, 44.

—— 1921. Über die Wirkung des Placenta- und Hodenlipoids auf die männlichen und weiblichen Sexualorgane. *Pflügers Archiv*, 189, p. 199.

FOGES. 1914. Keimdrüsen. In Jauregg u. Bayer, *Lehrbuch der Organotherapie.* Leipzig.

FRAENKEL. 1903. Die Funktion des Corpus luteum. *Arch. f. Gynäkol.*, 68.

—— 1910. Neue Experimente zur Funktion des Corpus luteum. *Arch. f. Gynäkol.*, 91.

—— 1914. Normale u. patholog. Sexualphysiologie des Weibes. *Handb. d. ges. Frauenheilkunde*, III. Leipzig.

GLEY. 1914. *Les sécrétions internes.* Paris.

HARMS. 1922. Keimdrüsen und Alterszustand. *Fortschr. d. naturwissensch. Forsch.*, 11, p. 189.

HERRMANN. 1915. Über eine wirksame Substanz im Eierstocke und in der Plazenta. *Monatsschr. f. Geburtsh. u. Gynäkol.*, 41.

—— *und* STEIN. 1916. Über die Wirkung eines Hormones des Corpus luteum auf männliche und weibliche Keimdrüsen. *Wiener klin. Wochenschr.*, 29, No. 25.

—— 1917. Der Einfluss eines Corpus luteum-resp. Plazenta-Lipoids auf Blutungen, menstruellen Zyklus und Ausfallserscheinungen. *Monatsschr. f. Geburtsh. u. Gynäkol.*, 54, p. 152.

—— *und* STEIN. 1919. Heterologe Reizstoffwirkung auf bestimmte System-bezw. Geschlechtsmerkmale bei männlichen Kaninchen. *Zentralbl. f. Gynäkol.*, 43.

—— *und* STEIN. 1920. Ist die aus Corpus luteum bezw. Placenta hergestellte wirksame Substanz geschlechtsspezifisch? *Zentralbl. f. Gynäkol.*, 44.

ITAGAKI. 1917. The influence of Corpus luteum extracts upon plain muscle, especially that of the uterus. *Quart. Jl. of Experim. Physiol.*, 11, p. 1.

—— 1917. On the action of various extracts obtained from the cow's ovaries upon the muscular tissue of the uterus, intestine and blood-vessels. *Ibid.*, p. 27.

—— 1917. The action of certain gland extracts and drugs upon the uterus of the rat. *Ibid.*, p. 39.

MARAÑÓN. 1922. *Problemas actuales de la doctrina de las secreciones internas.* Madrid.

PÉZARD. 1911. Sur la détermination des caractères sexuels secondaires chez les Gallinacés. *C. R. de l'Acad. d. Sc.*, 153, p. 1027.

STEIN *und* HERRMANN. 1921. Über künstliche Entwicklungshemmung männlicher sekundärer Geschlechtsmerkmale. *Arch. f. Entw.-Mech.*, 48, p. 447.

WEIL. 1920. Geschlechtsspezifische Wirkungen von Keimdrüsenextrakten. *Pflügers Archiv*, 185, p. 33.

Chapter VIII.

The Seminal Vesicles and the Prostate Gland in Relation to the Development of the Sex Characters.

Is there an influence on the part of the seminal vesicles and prostate gland on the somatic sex characters and on the psycho-sexual behaviour? This question was discussed more than thirty years ago by *Tarchanoff* (1887) in relation to the seminal vesicles; a similar question was recently raised in connection with the prostate gland by various clinical observations. It seems, however, to have been demonstrated recently that the seminal vesicles and the prostate have no influence on the sex characters, more especially by *Steinach* (1894) and *Lichtenstern* (1915, 1916), who performed experiments dealing with this question in Steinach's laboratory. Further, the experiments of Kölliker, Fürbringer, Steinach, Nussbaum, Exner, Hirokava and Wischnewsky have shown that the seminal vesicles and the prostate have distinct functions apart from the production of hormones.[1]

A. PHYSIOLOGY OF THE SEMINAL VESICLES.

1. Experiments on Frogs.

It was already known to *Spallanzani* (1786) that even serious injuries to the male frog, as, for instance, mutilation of both hind legs, do not necessarily inhibit the clasp reflex. Tarchanoff showed that the male continues to clasp for some time even when internal organs are mutilated or excised. But he claims to have shown also that incision and emptying of the seminal vesicles or extirpation of the latter inhibit the clasp reflex in *Rana temporaria*. Tarchanoff suggests that the stimulus which makes the male seek the female, and which excites the clasp reflex and causes its persistence, originates

---

[1] For the literature on this question see the papers of *Tarchanoff*, *Steinach* and *Lichtenstern* quoted above; see also *Marshall* (1922, ch. VI.), *Busquet* (1910), *Nussbaum* (1912), *Biedl* (1913, vol. II of the 2nd ed.), *Stigler* (1918).

in the seminal vesicles. According to Tarchanoff a distention of the walls of the vesicles by the fluid content produces a mechanical irritation of the nerve-endings, and he suggests further that their excitation may be increased by the spermatozoa hitting against the walls of the vesicles. Steinach was able to show that Tarchanoff's assumptions were not justified. In frogs which had already been clasping for several days the seminal vesicles were found to be empty, for the filling of the vesicles takes place only after the clasp begins. It is clear that the sexual instincts of the frog during "heat" and the clasp reflex cannot be caused in the manner supposed by Tarchanoff. Further, Steinach showed experimentally that spontaneous clasping or clasping after stimulation is still possible when the seminal vesicles have been extirpated. In animals from which the seminal vesicles have been removed, however, the clasp continues for only about ten days. But according to Steinach, this is to be explained by the fact that in extirpating the seminal vesicles the ureters are severed, and the urine flows into the abdominal cavity. The experimental animals show many pathological symptoms and die about twenty days after the operation. Nussbaum's experiments gave further support to Steinach's conclusions.

It is clear that in the frog the seminal vesicles have nothing to do with the erotization of the central nervous system. This effect is due only to the testicle.

2. EXPERIMENTS ON MAMMALS.

Steinach removed both seminal vesicles from rats ten to eleven months old. The experimental animals about ten days after the operation displayed a marked sexual behaviour, just like normal ones. But breeding experiments performed by Steinach showed that by removing the seminal vesicles the fertility may be much diminished. Only a very small percentage of the females with which the operated males copulated became pregnant; the number of young in the litter was about half that of the normal. One might object that the diminished fertility was possibly caused by obstruction of the vas deferens, but such an objection is not justified, since each male was able to impregnate at least once.

Similar observations were made by *Camus* and *Gley* (quoted from *Camus et Gley*, 1899) on the guinea pig, the fertility of which was likewise diminished after removal of the seminal vesicles.

One might indeed object that the diminution of fertility was caused by the testicles having suffered from the abdominal operation. As we pointed out in Chapter IV. the testicle is of an extraordinary sensitiveness. If the abdominal operation is performed without complete aseptis one often notices considerable changes in the generative part of the testicle. But it is naturally impossible to say how far this factor might have been involved in the experiments of the authors referred to.

But what is the real function of the seminal vesicles? It was formerly thought that they serve as receptacles for spermatozoa, and hence the name of the organ. But spermatozoa are not always present in the seminal vesicles, and if present they are only in small quantities. In guinea pigs I have many times examined the contents of the seminal vesicles without having found spermatozoa. Most probably the mucosa of the seminal vesicles has a secretory function, the secretion not always having exactly the same significance for the various species. Leuckart seems to have been the first to call attention to the fact that in the guinea pig the fluid secreted by the seminal vesicles has the power of coagulation. Any one working experimentally with guinea pigs is familiar with this fact. The ejaculated fluid becomes solidified in about one minute. It is the so-called "*bouchon vaginal.*" *Camus and Gley* (1896, 1921, 1922) have carefully examined the mechanism of the coagulation. They showed that the prostate produces an enzyme which causes coagulation of the secretion of the seminal vesicles; they called this enzyme "*vesiculase.*" Only traces of it are present in the new-born animal; its quantity increases during sexual maturation. The enzyme is not specific for a given species (1922 b). The *bouchon vaginal* is found in the vagina of the female, and according to Leuckart prevents the spermatozoa from leaving the vagina Mechanical functions were ascribed to the *bouchon vaginal* by Gley in another sense also. He suggested that the more abundant secretion of the vesicles and of the prostate favours the transportation and ejaculation into the vagina of the small quantities of secretion which are produced in the testicle and in the epididymis. This question was lately examined more fully by Amantea in the laboratory of Baglioni. For the study of this question in the guinea pig *Amantea* (1920) employed what he called an "artificial vagina." He stated that the seminal fluid containing the spermatozoa does not mix with the secretion of the seminal vesicle. He could always find these two portions of the genital secretion distinctly separated from one another in the artificial vagina of the guinea pig, and only a very small number of spermatozoa could be discovered in the coagulated secretion of the seminal vesicles.

There may be a difference as to the function of the seminal vesicles in different species. In the seminal vesicles of man spermatozoa are said to be always found. This has again been affirmed lately by *Wertheimer and Dubois* (1921). On injecting a fluid into the vas deferens of a man, they obtained a distension of the vesicles before so much as a drop had entered the urethra (the experiment of Régnier de Graaf). On the contrary, in the bull and in the ram the injected fluid passes directly into the urethra; in these species spermatozoa are not to be found in the seminal vesicles. Also the "uterus masculinus" of the rabbit, according to *Wertheimer and Dubois* (1922), is nothing else than a seminal vesicle containing spermatozoa which are more mobile than those in the vas deferens. The experiment of Régnier de Graaf gives a positive result in the rabbit, contrary to what is to be observed in the guinea pig and in the rat.

B. PHYSIOLOGY OF THE PROSTATE GLAND.

It is known to the surgeon that various nervous and psychical troubles sometimes follow the removal of the prostate in man. It has been said, that prostatectomy involves an even more severe operative interference than castration, especially in young individuals. But the number of patients showing nervous troubles after prostatectomy is relatively small. Lichtenstern relates having observed psychical troubles in only one out of a great number of individuals after prostatectomy. As *Haberern* (quoted from *Lichtenstern,* 1916) pointed out, these troubles are due to injuries in the neighbouring tissues; a conclusion with which *Lichtenstern* (1916) concurs.

1. The Effect of Prostatic Injections.

Some authors are of the opinion that the troubles arising after prostatectomy are caused by lack of an internal secretion of the prostate. A great number of experiments has been made with a view to demonstrating this internal secretion. Especial attention has been paid to the changes which are caused by injection of extracts of the prostate. Very profound changes have been observed after injection of a glycerine or water extract of the prostate of the bull; a remarkable rise of blood pressure followed by a fall, and a stoppage of the heart together with convulsions, were observed. An acceleration of the respiratory movements also has been recorded after injection of smaller quantities of the extract. Similar experiments have been performed also by *Biedl* (1913) on the dog. Biedl points out that these observations are totally insufficient for demonstrating the existence of a specific internal secretion of the prostate, and that the changes observed can be explained as due to intravascular coagulation.

Some authors claim to have observed specific effects of the prostatic secretion on the muscles of the bladder. But as we have pointed out already in Chapter VII., experiments with injection of extracts are of a theoretical value only in those cases where control experiments have been made with extracts of other organs prepared in exactly the same manner. We never know what changes the complex chemical compounds of the different tissues undergo when preparing an extract, and it is very likely that the effects of an extract are often merely the result of substances which are artificially produced in making it. Due consideration is not always taken of this possibility. Much critical study is necessary in this field of experimental and clinical research, and this is especially true for experiments with extracts of the prostate. This applies to the experiments of *Bogoslavski and Korenčevski* (1921) who stated that an emulsion of prostate gland may give rise to a very considerable increase in the metabolism in dogs, especially if they are previously castrated. The experiments of *Macht* and his co-workers (1920) are also of interest here. Macht fed tadpoles of different amphibians with dried prostate gland for several weeks; controls were fed with liver, ovary, corpus luteum and other glands. He recorded an acceleration of growth and metamorphosis under the influence of the prostate. He stated further that the prostate gland of the bull is more efficient than that of the ox. Macht and Matsumoto examined the influence of prostatic extracts on different organs such as the bladder, the ureter, the uterus, etc., of rats, guinea pigs and other animals. There was always an increase of tone. None of these experiments supply evidence of an endocrine action for this organ. The same may be said about experiments with removal of the prostate; we shall deal with these experiments in the following section.

2. Simultaneous Removal of the Seminal Vesicles and of the Prostate.

Steinach removed the seminal vesicles together with the prostate from rats about ten months old. Only the lateral lobules were removed, the prostatic tissue surrounding the urethra remaining intact, since removal of this part of the gland causes severe injury to the animal. The sexual behaviour was peculiar for some weeks, but afterwards the operated animals behaved normally. Against these experiments the objection may be made that the prostate was not completely removed, and that the small quantities of prostatic tissue which remained were sufficient to replace functionally the whole prostate in relation to sexual instincts. We shall discuss this question later.

With rats from which the seminal vesicles and the prostate gland had been removed, Steinach performed breeding experiments which lasted about three months. The operated males copulated with normal females as frequently as normal males do. But, nevertheless, not one of all the twelve normal females became pregnant, though spermatozoa were detected in the vagina of the females after coition.

From these experiments Steinach concluded that by simultaneous removal of the seminal vesicles and prostate fertility is definitely destroyed. Since spermatozoa passed into the vagina, he thought that evidently the functional activity in regard to the power of fertilization of the spermatozoa is influenced by the secretions of the seminal vesicles and prostate.

But experiments have been performed which do not corroborate this conclusion. Iwanoff induced pregnancy in various mammals by injecting into the female passages a fluid taken directly from the epididymis. It is very likely, as supposed by Rauther (quoted from *Marshall*, 1922), that the diminished fertility after removal of the seminal vesicles and the absolute sterility after removal of both the vesicles and the prostate were due in the experiments of Steinach to failure to form the *bouchon vaginal.* On the other hand, it may be mentioned that Iwanoff diluted the seminal fluid obtained from the epididymis with a five per cent. solution of sodium carbonate; we shall see later that alkalinity is a very important factor in functionally activating the spermatozoa. It is possible that by mixing the seminal fluid with a solution, as just mentioned, one is really replacing the normal secretion of the seminal vesicles and of the prostate.

3. Removal of the Prostate.

As already mentioned above, the first experiments of Steinach with removal of the prostate are open to the objection that here a small quantity of the prostate remained unaltered, and performed the hypothetical endocrine function of this organ necessary for a normal erotization. One might object that a complete removal of the prostate would cause a complete disappearance of sexual desire and sexual activity. This objection has been studied experimentally by Lichtenstern. He removed the prostate from male rats at an age of five to eight months when they were already sexually mature. In this first series of experiments Lichtenstern never succeeded in removing the prostate completely, small pieces of glandular tissue always remaining around the bladder. Nevertheless, sexual activity was only seen in some of these animals. This was evidently due to the many injuries to the neighbouring tissues which cannot be avoided if the attempt is made to remove the prostate completely from an adult animal. But in a second series of experiments on young rats four to five weeks old, Lichtenstern succeeded in completely removing the prostate without any injury to the surrounding tissues. Sexual instincts and sexual activity developed in these animals in normal strength, though with some delay. Also such somatic sex characters as the seminal vesicles and the penis, which are markedly affected by the absence of sexual hormones, were normal.

The experiments of Lichtenstern show that development of the somatic sex characters and of the psycho-sexual behaviour is independent of the presence of the prostate and of any endocrine function which this organ might possess. When there is, as in man or in the adult animal, an effect on the behaviour following prostatectomy this is merely due to operative interference in a region very sensitive to injury, and not to the absence of some specific prostatic hormones. The fact that there may be considerable abnormality in the psycho-sexual behaviour, even when the prostate is not completely removed, is very significant. Unfortunately, Lichtenstern has not examined the question as to whether sterility follows complete prostatectomy without removal of the seminal vesicles.

Similar experiments have been performed by *Macht* and *Bloom* (1921). They examined the psychical behaviour of twenty young rats from which the prostate gland was removed. In their experiments they employed a labyrinth or maze through which the rats learned to pass, the time taken being a test of intelligence or memory. The experimental animals passed through the labyrinth as quickly as the control animals in which the abdomen had been opened without prostatectomy being performed. In later experiments by *Macht* and *Ulrich* (1922) rats trained to walk along a rope did not lose their power to do so after prostatectomy. But when prostatectomy was performed before the rats were completely trained, they could not be properly trained afterwards. But, according to Macht and Bloom, the mental deficiency shown by these animals could be alleviated by the administration of dried prostatic tissue.

Serralach and Parès claimed to have shown that prostatectomy is followed by azoospermia. In three dogs after prostatectomy they found an atrophy of the testicle which showed no signs of spermatogenesis. Further, the same authors point out that two to three days after injection of an extract of the prostate spermatozoa reappeared in the ejaculation. They concluded from their experiments that the prostate produces an internal secretion which influences the testicle and stimulates spermatogenesis. But the experiments of Serralach and Parès are by no means convincing. It is highly probable that in those cases where a degeneration of the generative part of the testicle took place a seminal passage was interfered with during the operation; this objection, I think, cannot be avoided in such an operation as prostatectomy. Further, Lichtenstern showed that spermatogenesis proceeded quite normally in his rats from which the prostate was completely removed at an early age. These observations are opposed to the conclusion of Serralach and Pares, especially as in the experiments of the latter it is probable that there was never a complete removal of the prostate, this operation being almost impossible in the adult animal.

The interstitial tissue of the testicle in animals prostatectomized at an early age was found by Lichtenstern to be also quite normal.

C. THE SECRETION OF THE GENITAL PASSAGES IN RELATION TO THE VITALITY OF THE SPERMATOZOA.

It was stated above that, although the seminal vesicles and the prostate have no influence on the somatic sex characters and on the psycho-sexual behaviour, they are nevertheless necessary for normal fertility. As we have learned that spermatogenesis also is independent of the seminal vesicles and the prostate gland, it seems likely that decrease or absence of fertility after removal of the seminal vesicles and the prostate is due to a change in the vitality of the spermatozoa. We have already touched upon this question above.

The question as to the influence of the secretion of the male accessory glands on the spermatozoa is a very old one. Kölliker stated that the secretion of the uterus masculinus of the rabbit and that of the seminal vesicles of man has the power of stimulating the movements of spermatozoa, these becoming quicker and lasting longer. Similar statements have been made by Fürbringer about the secretion of the prostate. Steinach studied the influence of the secretion of the seminal vesicles and of the prostate on the spermatozoa of the rabbit, guinea pig, mouse and rat. He found that in the secretion of the prostate the movements of spermatozoa last longer than in a physiological salt solution. The most effective fluid, according to Steinach, is a solution of the prostatic secretion with a few drops of physiological salt solution. According to Hirokava the alkalinity of the prostatic secretion is of a special importance for the vitality of the spermatozoa; it was already known to Kölliker that weak alkaline solutions can stimulate the movements of the spermatozoa. Recently *Amantea and Krzyškowsky* (1920 b) repeated these experiments using different physiological solutions, and again showed how spermatozoa can remain alive in salt solutions for a very considerable period, though in the secretion of the sex gland itself the normal movement is more prolonged. A more exact investigation of the question of the hydrogen ion concentration most suitable for mammalian spermatozoa has been made by *Wolf* (1921 a), who succeeded in keeping spermatozoa of the rabbit in movement for nine days. But there was no evidence that these spermatozoa were capable of fertilization (1921 b).

In view of these considerations one might assume that the secretion of both glands has some influence on the spermatozoa; this would not be contrary to the above-mentioned experiments of Iwanoff. It is possible that sterility as observed after removal of the vesicles and of the prostate is due to the fact that the spermatozoa have lost the great vitality by which they are normally able to swim from the vagina to the tubes where fertilization takes place. This would explain why fertilization occurred in the experiments of Iwanoff, where the seminal fluid obtained from the epididymis was directly introduced into the female passages. The question is a much more complicated one than was formerly supposed. It seems very likely that the vitality of the spermatozoa depends not only upon the secretion of the vesicles and of the prostate, but also on that from other accessory glands. According to *Stigler* and *R. Pollitzer* (1918) motility and resistance of spermatozoa depend also on a secretion of the epididymis; they concluded from their experiments that there were in the secretion of the epididymis some stimulating substances not present in the secretion of the vesicles.

The question of the secretory function of the epididymis has been studied also histologically by various observers in such animals as the lizard, in which there is a periodical spermatogenesis and a secretory activity of the epididymis beginning during spermatogenesis and highly developed during the passage of the spermatozoa through the excretory ducts of the gonad. The question has been dealt with again by *Courrier* (1920 a), a pupil of Bouin. In the bat a great quantity of spermatozoa remain in the epididymis during the whole of hibernation.

Now Courrier stated that in the epididymis of the bat a secretory activity also goes on during hibernation. Evidently, as Courrier points out, this exceptional secretory activity during hibernation is rendered necessary on account of the presence of living spermatozoa in the epididymis in this species at a time at which they are absent in other species. The spermatozoa seem to be attracted by the secreting cells. It may be noted that spermatogenesis is at this time suppressed in the testicle, only cells of Sertoli and spermatogonia being present in the seminiferous tubules. On the other hand the interstitial cells are very well developed; they are very active and full of secretory granules.

It is probable that along the whole passage in the male and female there takes place a secretion of substances which influence the movements of the spermatozoa, and it seems possible that each of these secretions has its specific effect. Various histological observations tend to confirm this. As to the vas deferens the question has been recently studied in a more detailed manner in the mouse by *Benoit* (1920) in Bouin's laboratory. He records signs of very intense secretory activity in the epithelium of the vas deferens even more pronounced than in the epididymis. According to Benoit there is evidently some kind of tropism on the part of the spermatozoa towards the secretion of these cells, the spermatozoa being often found attracted to the secretory masses of the epithelial surface.

A fine example of secretory activity of the *uterine epithelium* for maintaining alive the spermatozoa is that afforded by the uterus of the bat. In this animal the spermatozoa are introduced into the uterus before the winter begins, whereas ovulation and fecundation take place only in the spring. *Courrier* (1920 b, 1921) stated that the uterine epithelium assumes its secretory activity just before copulation and the introduction of the seminal fluid, and persists during the whole winter. According to Courrier the spermatozoa are attracted by those cells which are full of secretory granules. He considers the uterine secretion to act in a manner similar to that in the epididymis of the male bat.

Böttcher (1920) assumes that the secretion of the prostate and of the seminal vesicles may inhibit the noxious influence on the spermatozoa of the acid content of the vagina. According to J. Loeb and others (*Clowes and Bachman*, 1921) the egg of a sea urchin also produces a substance stimulating the movements of the spermatozoa.

The question as to the dependence of the spermatozoa both in their vitality and in their movements upon different factors is of a practical interest, since it is very probable that chemical substances present in the secretion of the vagina or the cervix uteri may exert a considerable influence. This suggestion was supported by *Weil* (1921). Weil's experiments are not very convincing, but the question deserves further experimental consideration.

BIBLIOGRAPHY FOR CHAPTER VIII.

[* *Not seen in the original.*]

AMANTEA. 1920. Sulla funzione secretoria delle vesichette seminali. *Congrès de Physiologie, Paris.*

—— *et* KRZYŠKOWSKY. 1920 b. Osservazioni sulla biologia degli spermatozoi. *Congrès de Physiologie, Paris.*

*—— *et* KRZYŠKOWSKY. 1921. Ricerche fisiologiche sugli spermatozoi. *Riv. de biol.*, 3, p. 569 (quoted from "Berichte").

BENOIT. 1920. Sur l'existence de phénomènes sécrétoires dans le canal déférent. *C. R. de la Soc. de Biol.*, 83, p. 1640.

BIEDL. 1913. *Innere Sekretion*, Vol. II., 2nd edit.

*BÖTTCHER. 1920. Über die Bedeutung der Sekrete der männlichen akzessorischen Geschlechtsdrüsen. *Münch. med. Wochenschr.*, 67, p. 45 (quoted from "Berichte").

*BOGOSLAVSKI *and* KORENČEVSKI. 1921. On the influence of the internal secretion of the testicle and of the prostate on the metabolism. *Russki Fisiol. Jurn.*, 3, p. 48 (quoted from "Berichte").

BUSQUET. 1910. *La fonction sexuelle.* Paris.

*CAMUS *et* GLEY. 1896. Action coagulante du liquide prostatique sur le contenu des vésicules séminales. *C. R. de la Soc. de Biol.*, 48, p. 787.

*—— 1897. Note sur quelques faits relatifs à l'enzyme prostatique (vésiculase) et sur la fonction des glandes vésiculaires. *Ibidem*, p. 787.

—— 1899. Rôle des glandes accessoirs de l'appareil génital mâle dans la reproduction (recherches de physiologie comparée). *Bull. du muséum d'hist. natur.*, p. 253.

*Camus *et* Gley. 1921. Action du liquide prostatique sur le contenu des glandes vésiculaires des cobayes nouveau-nés ou très jeunes. *C. R. de la Soc. de Biol.*, 84, p. 250.

—— 1922a. Action coagulante du liquide prostatique de la viscache sur le contenu des vésicules séminales. *C. R. de la Soc. de Biol.*, 87, p. 207.

—— 1922b. Action coagulante du liquide prostatique de la gerboise sur le contenu des vésicules séminales. *C. R. de la Soc. de Biol.*, 87, p. 320.

*Clowes *and* Bachman. 1921. On a volatile sperm-stimulating substance derived from marine eggs. *Proc. of the soc. f. exp. biol. a. med.*, 18, p. 120 (quoted from "Berichte").

Courrier. 1920a. Sur l'existence d'une sécretion épididymaire chez la chauve-souris hibernante et sa signification. *C. R. de la Soc. de Biol.*, 83, p. 67.

—— 1920b. Sur l'existence d'une sécrétion de l'épithélium utérin chez la chauve-souris hibernante. Sa signification. *C. R. de la Soc. de Biol.*, 83, p. 243.

—— 1921. Sur le rôle physiologique des sécrétions utérine et tubaire chez la chauve-souris hibernante. *C. R. de la Soc. de Biol.*, 84, p. 571.

Lichtenstern. 1915. *Anz. d. Akad. d. Wissensch.*, Wien, No. 16.

—— 1916. Untersuchungen über die Funktion der Prostata. *Zeitschr. f. Urologie*, 10.

*Macht. 1920. Physiological and pharmacological studies of the prostate gland. I. Effect of prostate feeding on the growth and development of tadpoles. *Journ. of Urol.*, 4, 115 (quoted from "Berichte").

*—— *and* Matsumoto. 1920 b. II. The action of prostatic extracts on excised genito-urinary organs. *Journ. of Urol.*, 4, 255 (quoted from "Berichte").

*—— *and* Bloom. 1921. III. Effect of prostatectomy on the behaviour of albino rats. *Journ. of Urol.*, 5, 29 (quoted from "Berichte").

*—— *and* Ulrich. 1922. Effect of prostatectomy on integration of muscular movements of the white rat. *Americ. Jl. of Physiol.*, 59, p. 482 (quoted from "Berichte").

Marshall. 1922. *The physiology of reproduction.* 2nd edition. London.

Nussbaum. 1912. Über den Bau und die Tätigkeit der Drüsen. *Arch. f. mikroskop. Anat.*, 80, Abt. II.

Spallanzani. 1786. *Versuche über die Erzeugung der Tiere und Pflanzen.* German translation. Leipzig.

STEINACH. 1894. Untersuchungen zur vergleichenden Physiologie der männlichen Geschlechtsorgane, insbesondere der akzessorischen Geschlechtsdrüsen. *Pflügers Archiv*, 56.

STIGLER. 1918. Der Einfluss des Nebenhodens auf die Vitalität der Spermatozoen. *Pflügers Archiv*, 71.

TARCHANOFF. 1887. Zur Physiologie des Geschlechtsapparates des Frosches. *Pflügers Archiv*, 40.

WEIL. 1921. Die chemischen Ursachen der Spermatozoenbewegung. *Arch. f. Frauenkunde u. Eugenik*, 7, p. 238.

WERTHEIMER *et* DUBOIS. 1921. L'expérience de Régnier de Graaf et les fonctions des vésicules séminales. *C. R. de la Soc. de Biol.*, 85, p. 504.

—— 1922. Sur les fonctions des vésicules séminales de quelques rongeurs. *C. R. de la Soc. de Biol.*, 86, p. 35.

*WOLF. 1921a. The survival of motility in mammalian spermatozoa. *Jl. of Physiol.*, 55, p. 246 (quoted from "Berichte").

*—— 1921b. The survival of motility in mammalian spermatozoa. *Jl. of agric. science*, 11, p. 310 (quoted from "Berichte").

Chapter IX.

Intersexuality.[1]

A. TRUE HERMAPHRODITISM AND PSEUDO-HERMAPHRODITISM.

THERE are individuals which combine within themselves characters of both sexes. Such individuals are generally divided into two groups: the so-called true hermaphrodites and the pseudo-hermaphrodites. An individual is said to be a true hermaphrodite when within the organism there are combined not only somatic characters but also generative cells of both sexes. We speak of pseudo-hermaphrodites when only somatic characters of both sexes are combined in an individual in which generative cells of one sex are to be found. Most hermaphrodites in man and other mammals belong to the second group.

In many species of invertebrates both generative cells and accessory organs of both sexes, serving for the expulsion of the secretion of the gonad and for copulation, are normally present in the same individual. When speaking of true hermaphroditism occurring rarely as a monstrosity in mammals and man we are thus referring to a condition which is normally present in these species of invertebrates. When speaking of pseudo-hermaphroditism we imply a condition which deviates from normal hermaphroditism, since, although generative cells of only one sex are present, somatic characters of both sexes are combined in the same individual.

There is another principle tacitly implied in such a classification. After learning that somatic sex characters are conditioned by the internal secretion of the gonad, it seems to be very strange to find somatic characters of both sexes in one individual with generative cells of only one sex. The want of consistency apparently implied in this condition could not be better expressed than in the term pseudo-hermaphroditism.

Now, we have seen in Chapter IV. that male sex characters can be normally developed when no spermatozoa or different stages of male seminal cells other than spermatogonia are present; and we learned further that female sex characters

---

[1] The term has been introduced by Goldschmidt (1917).

attain their climax after the expulsion or degeneration of the ripened ovum when follicular cells are histologically prevalent in the ovary. There is evidently no direct relation between fully developed generative cells and full development of somatic sex characters. It is clear that a knowledge of these facts renders the case of the pseudo-hermaphrodite less contradictory. Furthermore, if one adopts the view that the internal secretion is to a certain degree independent of the generative part of the gonad, the contradiction presented by the pseudo-hermaphrodite may quite disappear, generative cells not being necessary at all, according to this view, for full development of the sex characters. Various authors have tried to introduce this standpoint into the discussion of hermaphroditism. *Biedl* (1913, p. 209) pointed out, that the normal gonad is in the beginning possibly "bisexual," and that remains of endocrine tissue of the other sex persist after a sexual differentiation of the gonad has taken place, and that pseudohermaphroditism may thereby be caused. *Steinach* (1912, p. 86) speaks of an incomplete differentiation of the gonad, which may be sexually indifferent in the beginning; such an incomplete differentiation implies persistence of male endocrine cells in the ovary and persistence of female endocrine cells in the testicle, and these heterosexual endocrine cells may exert under certain circumstances their respective hormonic influences on the body. The opinion that the hermaphrodite state of an individual may be caused by an hermaphrodite state of the endocrine tissue of the gonad without an hermaphroditism of the generative part being necessary, was also held by *Tandler and Gross* (1913, p. 83).

We see that two important questions are to be considered in regard to intersexuality in mammals and man. *First,* the question has to be experimentally examined whether combination of male and female somatic sex characters is really caused by simultaneous presence of gonads of both sexes in the same individual. And *secondly,* if the first question is to be answered in a positive sense, whether such an "hormonic intersexuality," to adopt an expression of Goldschmidt, is caused by male and female endocrine cells other than generative cells of any stage simultaneously functioning in the same organism. These two great questions will be examined in this chapter.

There is still another question to be discussed here. We saw that the psycho-sexual behaviour also depends on the internal secretion of the gonad. It seems possible that pathological deviations of all kinds in the psycho-sexual behaviour may be caused by deviations in the endocrine function of the gonad. As I have said already (see Chapter III., p. 102) this may be true, but only to a certain degree. We should never forget that the psycho-sexual behaviour must depend partly upon the state of the nervous system which is principally involved in all psycho-sexual reactions. It thereby follows that external conditions are very important factors in the psycho-sexual behaviour. But on the other hand, there can be no doubt that deviations in the psycho-sexual behaviour may be caused also by the interference of sexual hormones. Now the question arises whether some cases of homosexuality can be considered as a kind of hermaphroditism or condition of intersexuality in the psycho-sexual behaviour as caused by an intersexuality in the production of sexual hormones. *Halban* (1903, p. 291) suggested that homosexuality was a kind of pseudo-hermaphroditism, and *Bloch* (1909, p. 590) pointed out that it might be really caused by some defect in the endocrine function of the sex gland. Such an assumption would be in agreement with the opinion of Hirschfeld, the most learned expert in this special branch of sexual pathology, that homosexuality is in the majority of cases a congenital condition.[1]

B. EXPERIMENTAL HERMAPHRODITISM.

Steinach (1916) and *Sand* (1918 a, pp. 152–182) have shown experimentally that the simultaneous presence of the male and female sex gland in the same individual can transform the latter somatically and psychically into an intersexual individual. It is very interesting to note that Steinach and Sand performed their experiments on mammals independently of one another, the experiments of Steinach with feminization

---

[1] Hirschfeld's view is best expressed in the following passage: "It seems to me quite certain that the homosexual individual bears from the beginning the stamp of its somatic and psychical peculiarity. The latter is present from earliest youth, whereas it is absent in other people educated in a similar manner and grown up in a similar *milieu*. Every homosexual individual remembers to have been different from ordinary boys. In many cases the condition is already clearly seen at the age of the schoolboy, though the real cause is not yet understood. More than himself, his relations and those with whom he comes into touch, recognize that he possesses certain girlish peculiarities in his behaviour." (See *Hirschfeld*, 1918, p. 207.)

and masculinization having been for Sand an incentive to carry out experiments upon the simultaneous implantation of both glands, and he started on these in 1914. Afterwards similar experiments were performed by other investigators on mammals and fowls, especially by Pézard, Goodale, Moore and Minoura (in Lillie's laboratory), Zawadowsky, and by Lipschütz and his co-workers, Krause and Voss. Most of these experiments gave full support to the conclusions of Steinach and Sand.

1. THE ANTAGONISM BETWEEN TESTIS AND OVARY.

We learned in Chapter VI. that there is a certain antagonism between the male and female sex glands. We discussed the question whether sex characters which are favoured in their development by male sexual hormones, could be inhibited by female sexual hormones, and *vice versâ*. The antagonism between the male and female sex gland was a subject of discussion also in another sense. According to *Steinach* (1916) an ovary which had been implanted in an ordinary male guinea pig, and a testicle which had been implanted into an ordinary female, will not "take" and will not continue to function in the new host, but will finally undergo resorption. A similar statement was made about the guinea pig by *Athias* (1915). Numerous experiments have been made by *Sand* (1918) on rats and guinea pigs, the result always being a negative one. Any parts of the graft which were still present were found to be in a state of degeneration.

According to Steinach and Sand this antagonism between the male and female gonad can be overcome if the host is previously castrated and both testis and ovary are simultaneously engrafted into such a sexually "neutralized" organism, as Steinach says. But even by this method Steinach did not succeed as well as in ordinary experiments with testicular or ovarian grafts, the number of successful experiments with simultaneous implantation being much smaller than those with ordinary crossed or heterosexual transplantation. According to Steinach, in simultaneous transplantation the graft does not survive so long as in an ordinary transplantation, and he explains this as due to the antagonism between both glands persisting to a certain degree also in the previously castrated host. In the experiments of Sand there was only one successful case, a castrated male guinea pig, into which testis and ovary were simultaneously engrafted; in all the other experiments the gonad of the opposite sex or even both gonads underwent degeneration.

Sand obtained better results by a new method introduced by himself. He implanted the ovary directly into the testicle *in situ*. By this "intratesticular" transplantation of the ovary performed on rats and guinea pigs, Sand succeeded in preserving the engrafted ovary for several months (*Fig.* 125), often without interfering with normal spermatogenesis (*Fig.* 126) or normal development of interstitial tissue in the testicle, whereas follicles, interstitial tissue and even corpora lutea were present in the engrafted ovary.[1] Both the testicle and the ovary

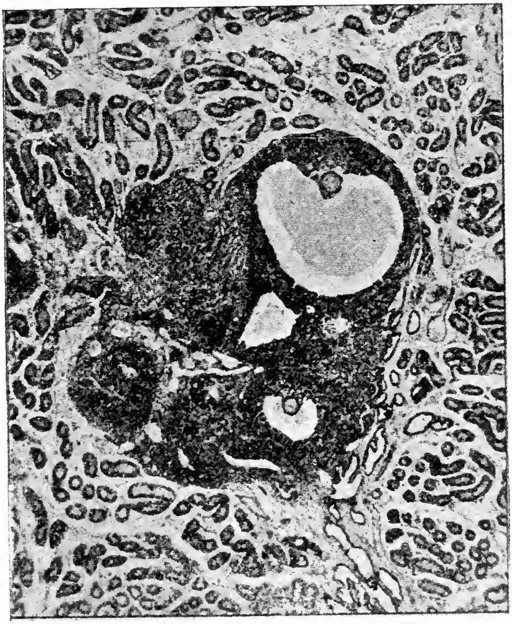


FIG. 125.—*Artificial ovariotestis in the guinea pig*, 4 months after transplantation of ovary into an animal 1 month old. Ripe follicles and theca-lutein cells; no corpora lutea. The testicle remained infantile; no spermatozoa. Normal quantity of interstitial cells.—From Sand.

---

[1] Sand speaks of an *ovariotestis* (Møller-Sørensen) instead of an "ovotestis"; the first expression is indeed more suitable.

performed their characteristic endocrine functions. Sand concluded from these experiments that the antagonism of the two kinds of gonads is not such as to involve a direct influence of one on the other, but that there is in the normal organism some kind of "immunity" against the heterosexual gonad. According to Sand this "immunity" arises owing to the presence of certain substances in the organism which are necessary for the normal development of both gonads; the gonad which is in its normal place has more facility for obtaining these substances than the engrafted gonad; the latter perishes on account of lack of the necessary substances. When both glands are in the rôle of grafts, or when an intratesticular implantation is made, both glands are similarly conditioned, neither of them having a preference.

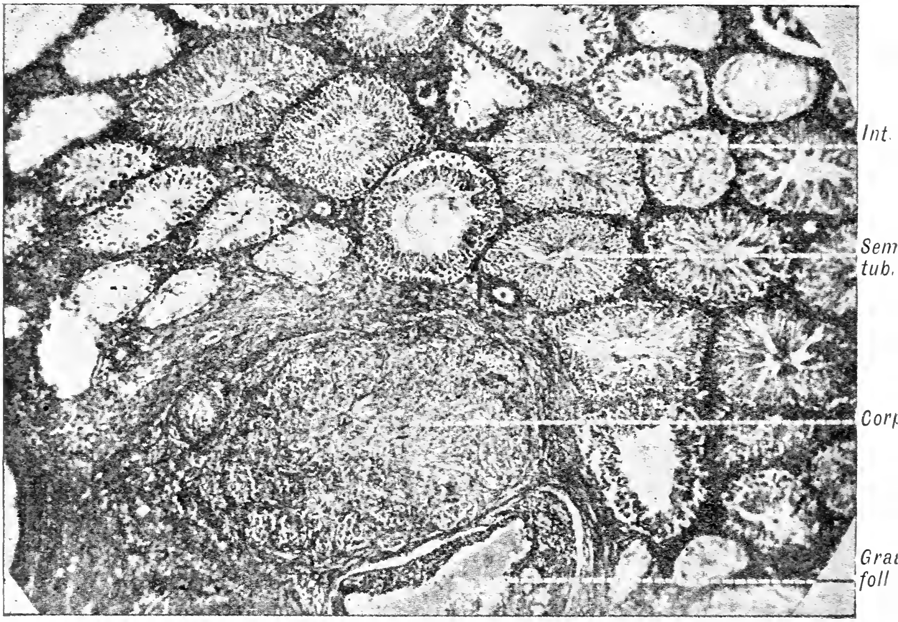


FIG. 126.—*Artificial ovariotestis in the rat*, 4 months after transplantation of an infantile ovary into an animal 5 weeks old. Both ovary and testicle have developed; ripe follicles and corpus luteum in the ovary, spermatogenesis in most of the tubules.—From Sand.

Certain observations have been made which seem to be contrary to the statements of Steinach and Sand. *W. Schultz*

(1910) found that in the guinea.pig the ovary can survive and develop normally even when engrafted into a normal male. Lately new experiments on this question have been published by *Moore* (1920, 1921), who like Schultz succeeded in successful transplantation of ovaries into male rats possessing a normal testicle. The graft became vascularized and was observed for at least eight and a half months. All the characteristic structures of the normal ovary, excepting corpora lutea, were present. On the other hand, pieces of testis were engrafted into female guinea pigs possessing one normal ovary; the graft persisted for at least eight months. The graft behaved like the testicular graft in general, i.e., the seminiferous tubules underwent degeneration. In view of all these experiments Moore comes to the conclusion that there is no indication of an antagonism between the ovary and the testis. *Fisher* (1923) at the suggestion of Moore engrafted intraperitoneally or subcutaneously two ovaries into male rats having *both testicles in situ*; in seven out of eight animals operated, one or both grafts persisted for at least three to five months. But it may be added that with guinea pigs Moore, like Steinach and Sand, always had negative results (*Moore,* 1921 a, p. 136). This, however, does not signify much in view of the older experiments of Schultz on guinea pigs and of those of Moore and Fisher on rats.

I think that the question of the antagonism between the glands of both sexes is by no means negatively decided by Moore's and Fisher's experiments. It is very significant that, according to these observers, there was never any influence upon the somatic and psychical sex characters in those experiments in which an ovary or a testicle was implanted in the body of the other sex without previous castration of the host; on the contrary, in the related experiments of Steinach and Sand where ovarian and testicular grafts were made simultaneously, or where an intratesticular ovarian graft was performed, both glands exhibited a very pronounced influence on the somatic and psychical sex characters, as we shall see below. It must, however, be pointed out that male rats are not very suitable for observing the feminizing influence of the ovary, since teats and mammary glands are absent in the male; as to the female with a testicular graft, Moore does not mention whether, like Sand, he examined the condition of the clitoris. But, on the other hand, a recent observation of *Sand* (1922 c) is of great interest in this connection; in guinea pigs, so suitable for demonstrating the feminizing effect of ovarian hormones, Sand found in three cases of intratesticular transplantation, persistence of normal ovaries without any influence on the sex characters having been exhibited. This statement of Sand was recently confirmed in our laboratory by Voss. It seems to me very likely that the fate of the graft and its hormonic effect are not necessarily concomitant phenomena. The hormonic effect of the graft depends evidently upon *quantitative* relations between the two heterosexual glands. The experiments hitherto made were such as did not admit of the possibility of making definite statements on this point, but the question seemed to me well worthy of experimental study, in which the quantities of the respective grafts should be varied.

With Krause and Voss I made an extensive experimental study of this question in guinea pigs on quantitative lines. These experiments proved (*Lipschütz and Krause*, 1923; *Krause*, 1923) that an ovarian fragment can survive and reveal a maximal feminine hormonic effect when engrafted by the intratesticular method of Sand, both testicles being present in the body. If one testicle is removed previously to the ovarian implantation, the number of successful cases is highly increased and the time of latency, i.e., the time between the operation and the first appearance of the hypertrophy of the teats, is much diminished. If previously to ovarian transplantation the testicular mass is so far reduced that only a small testicular fragment is present in the body, which, however, is sufficient for normal masculinization, there will be almost 100 per cent. of positive cases, i.e., the fragment will "take" and exhibit its hormonic effect practically in all the cases operated (unpublished experiments with intrarenal ovarian grafts[1], experiments with Voss). The time of latency is so extraordinarily diminished, under the indicated quantitative conditions, that the hormonic effect of the ovary may reveal itself as early as 12 to 14 days after implantation, even when the ovary is taken from an animal only two weeks old. Our experiments leave no doubt that ovarian fragments can resist against two testicles *in situ* and that testicular fragments can

---

[1] Intrarenal ovarian grafts were first made by *Marshall and Jolly* (1908). The technique I adopted differs in some respects from the original method of Marshall and Jolly.

resist against two ovaries engrafted, both causing sex specific hormonic effects. But the chance of survival of the ovarian graft *seems* to depend upon the quantity of testicle simultaneously present in the body, and the time of latency of the feminine hormonic effect *surely* depends upon the quantity of testicle. In those experiments in which an intrarenal ovarian transplantation was made, both testicles remaining *in situ*, we *never* obtained a positive feminine effect. If in similar negative experiments the testicles are removed about 7 to 8 weeks after the ovarian transplantation there may be a positive feminine effect after a short time of latency. These latter experiments show in a most striking manner that *an antagonism exists between the gonad in situ and the engrafted gonad.* But this antagonism is not necessarily to be understood in the sense that the development of the graft is *definitely inhibited*; an inhibitory influence might reveal itself in retarding follicular development and the production of sex hormones; consequently again the time of latency might be lengthened, and the chance of survival also diminished. Whether this antagonism is an antagonism of *hormones* simultaneously circulating in the body cannot yet be said. Some experiments (Lipschütz and Voss; Lipschütz, Lange and Tiitso) in which there was only an operative interference on the testicle without the testicular mass being reduced, were also positive and the time of latency was rather a short one.[1] It is possible that the antagonism between the gonad *in situ* and the engrafted gonad is not of a sex specific order, i.e., that the ovarian graft also in females will exhibit an hormonic effect only when the gonads *in situ* have been previously removed or reduced. We cannot go into further details here. But on the basis of our new experiments it seems clear that *the problem of the antagonism of the sex glands is very far from being negatively settled.*

As to the fowl the situation seems at first glance a conflicting one, and I think that here also a quantitative factor is involved.

Goodale's experiments (1918, p. 283) on fowls gave mostly negative results. Nine young cocks were unilaterally castrated or one testicle was injured and an ovary was engrafted; the

---

[1] The fact that the *intratesticular* ovarian graft can exhibit an hormonic effect, even when both testicles are present, might be due to the operative interference on the testicle as in the above experiments of Lipschütz and his co-workers.

birds were killed after sexual maturity was attained, and in seven cases ovarian tissue could not be detected. All the birds showed normal somatic and psychical masculinity, even those birds in which ovarian tissue was found. *Zawadowsky* (1922) implanted one testicle into the normal hen. Six experiments of this kind were made. In one case the graft persisted for a longer time. There was no decided influence of the testicular graft on the ovary, and *vice versâ*, as the hen showed all the female sex characters and even laid eggs at a time when the comb had already begun to hypertrophy. Further, Zawadowsky engrafted ovaries into normal cocks; five experiments of this kind were made. In one case the graft took and exhibited its influence on the sex characters. There was also a decided antagonism of the sex glands in the experiments of Minoura (see p. 311). This antagonism does not, however, exclude the possibility of experimental hermaphroditism in the fowl as shown by the above-mentioned experiments of Zawadowsky and by those of Pézard, Sand and Caridroit (see p. 410), all depending, as I think, upon the quantities and the condition of testicle and ovary simultaneously present.

It is of great interest to note that in Arthropoda, where there is no hormonic activity of the sex gland, the gonad develops normally in every respect when engrafted into an animal of another sex which has been unilaterally castrated.

New experiments of *Matsuyama* (1921) should also be referred to here. Matsuyama made observations on rats in parabiosis, uniting normal and castrated males with normal and castrated females. He found that the testicle of a male united with a normal female several months afterwards undergoes degenerative changes like those after ligation of the vas deferens, transplantation, irradiation and so on; the ovary undergoes changes which seem to me to be similar to those after transplantation or irradiation. At first thought one might be disposed to consider these results as caused by an antagonism between the gonads of different sexes. Now, it is of great interest that similar degenerative changes in the testicle occur also if the normal male or female has been united with a castrated partner of the opposite sex. There never was feminization or masculinization of the castrated partner. Evidently here certain factors are involved which are beyond our actual knowledge. As far as I can see from

Matsuyama's experiments there was no endocrine influence even on the partner if a normal male was parabiotically united with a castrated male. When a castrated female was united with a normal one, degeneration of the ovaries took place as with a transplanted or irradiated ovary; there was an intensified development of the mammary gland of the normal partner, whereas the mammary glands of the castrated partner behaved like those in an ordinary castrated female. Similar observations were recently made by *Goto* (1922). It seems to me very difficult to judge from the description given by Matsuyama how far the question of the mutual influence of parabiotically united partners has been decided by his experiments, but I think that the experiments should provide incentive for further research by the method indicated.

Lillie (1923) considers that the description of the organs of the freemartin (see p. 388) are a further proof of an antagonism between the male and female hormone-producing gonads.

2. SOMATIC CHARACTERS OF THE EXPERIMENTAL HERMAPHRODITE.

In castrated male guinea pigs, into which a simultaneous implantation of both testicle and ovary had been made, the penis and the seminal vesicles were well developed; the proportions and also the filling of the seminal vesicles were normal (*Sand*, 1918); the coagulation of the vesicular content under the influence of prostatic secretion takes place in a normal way (*Lipschütz and Krause*, 1923 a). The hormonic action of the ovarian graft was easily seen in the teats; the length of the teats was in Sand's experiments more than ·5 cm., as compared with 1 to 2 mm. in the normal male; the teats were like those of an ordinary female, sometimes like those of a female during pregnancy or even lactation (*Figs.* 127, 128). In some of the cases recorded by *Steinach* (1916 b, p. 322) and *Sand* (1918, pp. 163 and 171) milk secretion occurred as well. Evidently the testicle was not able to inhibit the development of the female sex characters, or to hinder the hormonic action of the ovarian graft, whereas the engrafted ovary was not able to inhibit the growth of the male sex characters. It seems that the stimulating action of both sex glands can take place in the experimental hermaphrodite, but that the inhibiting action of both glands is suppressed. A similar statement was made by Moore: the

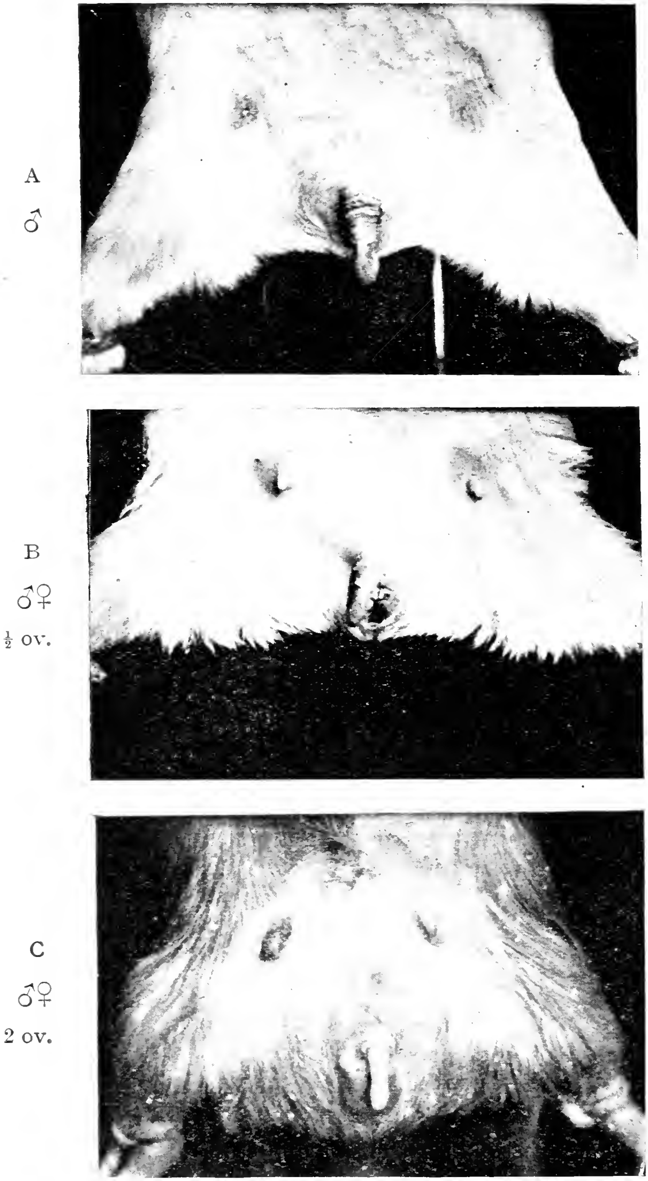


FIG. 127.—*Experimental hermaphroditism in guinea pigs.* (Operated by Dr. W. Krause by the intratesticular method of Sand.)

A. Normal male (610 gr.).

B. Male (415 gr.) with both testicles *in situ* and half an ovary engrafted into one testicle about six months previously at an age of 2–3 weeks and at weight of 160 gr.

C. Male (450 gr.) with two whole ovaries engrafted into the testicles *in situ* about six months previously at weight of 170 gr.

—Photos of Vešnjakov.

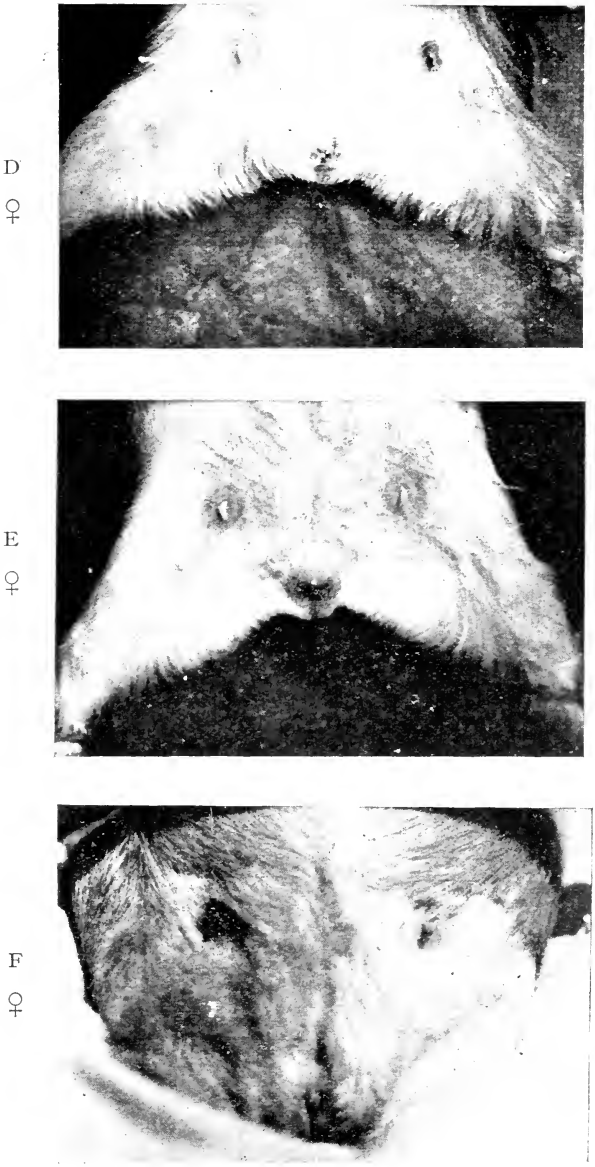


Fig. 127.—*Experimental hermaphroditism in guinea pigs.* (Operated by Dr. W. Krause by the intratesticular method of Sand.)

D. Normal virginal female (475 gr.).
E. Normal female (430 gr.) which has been pregnant once (aborted).
F. Normal adult female. —Photos of Vešnjakov.

growth of the penis and seminal vesicles was not inhibited by the engrafted ovary. Moore and Fisher were evidently mistaken when writing that Steinach asserted that the ovarian graft will inhibit certain male sex characters in hermaphrodites. Steinach's statement is just the opposite of this. The fact that male characters are not inhibited by the ovary engrafted simultaneously with a testicle into a male animal, was explained by Steinach as due to the antagonism of the male and female sex glands continuing to exist to a certain degree also after successful implantation. If this is true, one can understand why full inhibition of the hormonic action of the successfully engrafted gland occurs, as possibly in the above-related experiments of Moore, and certainly in some experiments of Sand, and of our own with Krause and Voss, all evidently depending upon the *quantities* and the *condition* of the respective heterosexual tissues simultaneously at work. On the other hand, in the experiments which we have performed with Voss engrafting ovaries into the kidney of male guinea pigs with testicular fragments only, we had the impression that there was a temporary incomplete inhibition of development of male sex characters at the time when the ovarian hormonic activity had attained its

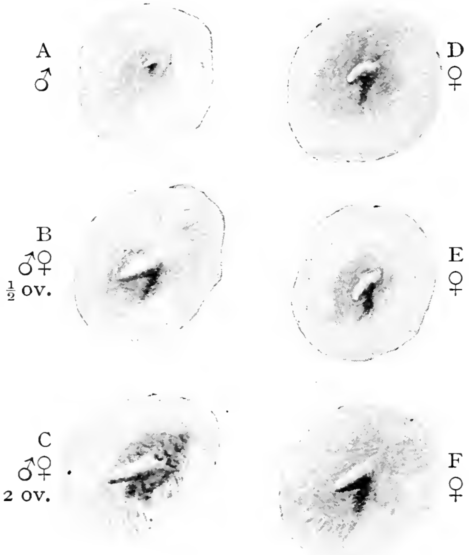


FIG. 128.—Same as Fig. 127. Drawn from nature.

point of culmination, though nothing definite could be stated as to this.

Very good results were obtained by *Sand* (1922 c) by intratesticular ovarian transplantation in infantile guinea pigs and in those having just attained sexual maturity. In six out of sixteen operated animals he obtained complete success, the penis being normal and the mammary glands secreting milk or being better developed than in virgin females. Four experiments of the same kind performed on guinea pigs a year old gave negative results. In the experiments of Krause (*Lipschütz and Krause,* 1923 b) in which the intratesticular method of Sand was used, and in which the respective quantities of testicle and ovary were varied, there were twelve positive cases (female and male characters simultaneously present) out of 36. In my experiments with Voss (testicular fragments *in situ* and ovaries into the kidney) nearly all our results were positive (16 out of 17 operated), eight of them with milk secretion. We observed milk secretion even in an animal operated when it had attained a weight of about 800gr.; the age of this animal must have been no less than about a year and a half.

The control experiments of Steinach and Sand are also of great interest. When about six to eight weeks after transplantation the development of the teat and of the mammary gland begins, this development can be stopped by removal of the ovarian graft. If, on the contrary, the testicular graft is removed, the teat and the mammary gland continue to grow, and further development of the penis stops; the animal becomes feminized (experiments of Steinach). Sand removed both the engrafted testicle and ovary; the animal became an ordinary "castrate," the turgor of the penis diminishing and the teats becoming shorter and looser. All these experiments show that the combination of male and female sex characters in the same animal was due to the simultaneous presence of male and female sexual hormones.

In Chapter VI. we gave an account of experiments by Foges and Pézard on fowls; a condition of hermaphroditism was caused by engrafting the heterosexual gland in an incompletely castrated bird. Similar observations were made also by *Zawadowsky* (1922). Two castrated hens with regenerated ovary and successful testicular graft exhibited normal somatic sex characters, but the comb became bigger than in the ordinary hen. Similar results were obtained with implantation of testicle into a normal hen. Zawadowsky also performed experiments with implantation of ovaries into normal cocks or into castrated cocks with regenerated testes. There was in the first case feminization of the cock, in regard to plumage; the comb was bigger than in the ordinary hen. A castrated cock with regenerated testicle and implanted ovary exhibited the male comb, but a more or less female plumage. A general review of the six experiments of Zawadowsky with experimental hermaphroditism (three "would-be-cocks" and three "would-be-hens") is of great interest. All the six birds had the plumage of the hen, or, in other words, the ovary exerted its action on the plumage in the presence of the testicle. The growth of the spurs was more or less inhibited in birds with implanted ovaries. All the birds showed an exaggerated growth of the head apparel under the influence of the engrafted testicle, though there was a great variability in the head apparel and likewise in the sexual instincts. This, I think, can easily be explained as due to variation in the time at which the graft was made or "took," and by the quantity of graft which survived in the respective experiments. There are indeed very great variations in the development of the head apparel also in normal hens.

3. THE PSYCHO-SEXUAL BEHAVIOUR OF EXPERIMENTAL HERMAPHRODITES.

According to *Steinach* (1916) and *Sand* (1918) their experimental animals exhibited a very pronounced intersexuality also in the psycho-sexual behaviour. Steinach relates that the "would-be-male" transformed into an experimental hermaphrodite shows in the beginning a male behaviour, fighting with normal males, emitting the characteristic call of the normal male, following the female and making attempts to leap. Some weeks afterwards a change in the behaviour was observed, the animal now becoming shy, unwilling to fight with normal males and not following normal females. On the contrary, the animal is now followed by normal males which try to copulate, whereas the hermaphrodized male defends himself by the averting reflex. There is, according to Steinach, a periodic change of male and female erotization in the "would-be-male" made hermaphrodite. During the period of female erotization there is sometimes also a milk secretion. According to *Sand* (1918) changes in the psycho-sexual behaviour from male to female and *vice versâ* may take place even within half an hour. Sand describes an animal which showed characteristic female tendencies, such as licking the young and smoothing them down, and which showed soon afterwards male reactions when a castrated sister was brought into its cage; the "would-be-male" now emitted the characteristic male call, followed the female and performed characteristic copulatory movements. Such a *bisexual* behaviour was observed by Sand in two experiments. The period of bisexuality was a transitory one; this period was followed by a male one, which became gradually more and more accentuated; finally only traces of female reactions were present. Such a transition from bisexuality to a male period took eight days. These latter observations corroborate those of Steinach mentioned above. But it may be said that according to my own observations on normal and castrated guinea pigs it is very difficult to draw any detailed conclusions about the psycho-sexual behaviour.

As to the sexual instincts of the fowls made experimentally hermaphrodite, Zawadowsky states that there were some indications of a simultaneous influence from both glands.

All these experiments leave no doubt that combination, not only of male and female somatic, but also of psychical sex characters, can be experimentally caused by combining male and female sex glands in one organism.

4. Histological.

The first of the questions propounded by us has been answered positively. Intersexuality can be experimentally caused by the simultaneous presence of gonads of both sexes. The second question as to whether endocrine cells of both sexes other than generative cells simultaneously functioning in the same organism are the real cause of the experimental hermaphroditism, will now be examined.

Testicular and ovarian grafts in the experimental hermaphrodite undergo the same changes as such grafts usually do. There is a degeneration of the seminiferous tubules; there is an increased follicular atresia, and an increased production of those cells in the ovary which are derived from atretic follicles, and to which an endocrine function has been ascribed.

From the histological examination of an ovarian graft removed from an experimental hermaphrodite at a period of female erotization, Steinach concluded that milk secretion and female erotization in experimental hermaphroditism is due to the fact that there is an increased follicular atresia and an increased production of female sexual hormones. Some histological observations of Sand might also be taken as evidence of such an assumption. The ovarian graft removed by Sand from an animal at a time when male erotization predominated contained more or less mature follicles, but only a few theca-lutein cells, whereas the ovariotestis removed from another animal at a bisexual period contained a considerable number of theca-lutein cells. But in some of the above-mentioned negative cases of *Sand* (1922 c, d) the ovary was normally developed, and Sand states that "there is not always a correspondence between the anatomical condition and the physiological state." This phenomenon can be explained only on the experimental lines, as discussed above (on p. 356).

Steinach concluded that intersexuality is caused not by the simultaneous presence of both male and female generative cells, but by the simultaneous presence of special endocrine cells. As to pseudo-hermaphroditism, Steinach assumes "that in the many cases where homologous and heterologous sex characters are combined in an individual, although the gonads seem to be of only one sex, they are of one sex only in the matter of generative cells, and are hermaphrodite in the endocrine cells, these gonads containing in reality an hermaphrodite puberty gland" (*Steinach,* 1916, p. 328). Such a suggestion means that there is no justification for classifying cases of intersexuality as those of true and of pseudo-hermaphrodites, the latter being as much true hermaphrodites as the "true hermaphrodites" of the old terminology.

Against this assumption various objections have been urged. First, the degeneration of the generative part in the testicular graft is not a complete one, sex cells at early stages, or at least spermatogonia, almost always still being present in the testicular graft, the periodic regeneration of the seminiferous tubules being thereby not excluded. This is the same objection as that so often made to the experiments of Ancel and Bouin and of Steinach with ligation of the vas or with transplantation. But the fact remains that notwithstanding the extraordinary degenerative changes which take place in the generative part of the ovarian or testicular graft the latter is still able to change the sex characters to a certain degree in the direction of the sex of the graft.

On the other hand, many objections to Steinach's theory have been urged by pathologists. These will be discussed below.

C. INTERSEXUALITY IN MAN, MAMMALS, AMPHIBIANS AND INSECTS.

Intersexuality is very widespread in birds, mammals and man. There is an enormous variability in regard to the somatic and psychical characters of intersexual individuals. There is also great variability in the time at which the individual becomes intersexual.

We shall deal in the following sections with such cases only as serve to elucidate the morphogenetic basis of intersexuality. Our main problem will be the following: how far is any abnormal condition of the endocrine function of the sexual gland or of some other internally secreting gland involved in intersexuality?

I. Man.

(*a*) *Homosexuality.*

According to clinical observations there are many cases of homosexuality where there is a periodic change in the psychosexual behaviour. This periodicity relates to men as much as to women. Sometimes even changes in the condition of the somatic sex characters may take place. Steinach is inclined to consider these periodic changes as analogous to those observed in experimental hermaphroditism. One might suppose that in such individuals there is an hermaphrodite gland and a periodic change in the quantities of male and female sexual hormones produced. Examining the testicles of homosexual individuals, *Steinach* (1919 c, 1920 b) found that the interstitial tissue contained large epithelioid cells, not resembling the ordinary male interstitial cells of the testicle, but rather like the luteal cells of the ovary. Steinach is inclined to ascribe homosexuality to female sexual hormones produced by these cells. As long as the male sexual hormones quantitatively prevail, the activity of the cells producing female sexual hormones will be inhibited according to the law of antagonism between the hormones of both sexes. The individual will show normal somatic characters and a normal psycho-sexual behaviour, though male and female sexual hormones can be produced owing to the intersexual condition of its sex gland. "If now the vitality of the male cells should sooner or later decrease for some reason and their endocrine function should cease, the female cells present will be released from inhibition and become activated" (*Steinach*, 1916 b, p. 327). The female endocrine cells activated owing to some pathological condition of the male cells will now exercise their endocrine function and influence the somatic and psychical sex characters.

The above-mentioned statement of Steinach that special endocrine cells like luteal cells are to be found in the testicle of homosexual individuals has not been confirmed, as pointed out especially by *Benda* (1921), *Hirschfeld* (1921) and *Sternberg* (1921). The proportions of the interstitial cells in the normal testicle vary very much. According to my observations on the guinea pig the variation seems to be especially great when there is a degeneration of seminal tubules and a concomitant reaction on the part of the surrounding interstitial tissue. There can be no doubt, therefore, that Steinach was mistaken about those large interstitial cells.

Though Steinach failed to show that there are really special endocrine cells of both sexes in the testicle of the homosexual individual it nevertheless remains very likely that his assumption about the periodic changes in the psycho-sexual behaviour being caused by periodic changes in the production of sexual hormones is not without foundation. We must assume that the different parts of the organism will react to the changed quantities of the hormones of both sexes in the same individual in a way that is not uniform. They will change very little if already *fixed* previously by ordinary growth or by the action of sexual hormones; they will change more if they still maintain a certain degree of *growth intensity,* and if they still possess great plasticity or lability like the central nervous system. On such an assumption one can explain how it is that homosexuality or an intersexuality concerning the psycho-sexual behaviour only is much more widely spread than somatic intersexuality

Goldschmidt (1916) has elaborated a theory of homosexuality on the basis of his very interesting experiments on moths. He considers the possibility of homosexuality being a genetic intersexuality like that caused by crossing different races of *Lymantria dispar.* There might be in man, according to Goldschmidt, a normal endocrine function of the sex gland, but an intersexual state of the soma; in this case the normal hormone production would be insufficient to bring about a normal development of sex characters, and an intersexual condition would result. On the other hand, there might also be an intersexual condition of the hormonic sex gland. This is why Goldschmidt as long ago as 1916 proposed to try gonadal injections or transplantations for curing homosexuality. The latter treatment was tried by *Steinach and Lichtenstern* (1918) before Goldschmidt's paper was published. They removed the testicles from an homosexual patient and engrafted the testicle of a normal individual. The patient was a man of thirty with some signs of somatic eunuchoidism, such as accumulation of fat on the breast and the hips, and insufficient growth of hair in the characteristic places. The man was homosexual from his fourteenth year, like a brother and two sisters. At twenty-nine the left testicle and the right epididymis were removed on account of tuberculosis. The patient became sexually impotent after this operation; but the above-mentioned somatic indications were already present from his seventeenth year. Lichtenstern removed the remaining testicle and engrafted a retained testicle of a sexually normal individual. As soon as about two weeks after the operation normal male sexual desire and ability appeared. Six weeks later coition took place followed by full satisfaction and happiness. The general behaviour of the man, which before the operation was clearly feminine, now became more masculine.[1] About a year after the operation the man married. It is truly very difficult in such cases to exclude the influence of suggestion on the psycho-sexual behaviour. But the man showed also a change in his somatic sex characters; the accumulations of fat on the breast and hips disappeared, and the hairiness became much more pronounced.

Similar attempts at surgical treatment of homosexuality

---

[1] Through the kindness of Professor Steinach I had opportunities of examining this patient before and after the operation.

have been repeated by several doctors. Successful results are described by *Mühsam* (1922), *Pfeiffer* and others, whereas *Kreuter* (1922) and *Stabel* (1922) deny any success. Stabel is even of the opinion that it is impossible to change the psycho-sexual behaviour of the homosexual individual by implantation, as this behaviour is already definitely fixed in the central nervous system after puberty is attained. Stabel's view does not agree with the statements of Mühsam and Kreuter, who described cases in which the homosexual behaviour disappeared after castration. One is inclined to explain the negative results partly by castration not having been performed previously to transplantation. It may be said that in three of his successful cases Mühsam previously removed one of the testicles of the patient. But according to Stabel a successful treatment of homosexuality by transplantation is impossible even when both testicles are previously removed.

The divergent results of the different surgeons may be partly due to the fact that in some cases of homosexuality the sex gland is not the direct cause of the abnormal behaviour, some other organ of internal secretion being primarily involved and influencing the hormonic activity of the testicle. In such cases no transplantation of a normal testicle could help or be successful even when castration is previously performed. In such cases really *nothing* is changed by castration if followed by testicular homoiotransplantation, whereas castration alone will "cure" this homosexual individual in the sense that he will become an ordinary "castrate," as in the cases of Mühsam and of Kreuter.

There is still another possible explanation of some cases of homosexuality. It seems to me likely that certain forms of this sexual perversion are nothing else than special cases of fetishism on the basis of a more or less pronounced eunuchoidism. Lately *Weil* (1921, 1922) having measured a great number of homosexual individuals came to the conclusion that the bodily proportions of male and female patients are on the average like those of eunuchoids, but Weil's statements have been contradicted by other authors. The success attained by Steinach and Lichtenstern with the above-mentioned homosexual individual could be explained, on the basis of my assumption, as a cure of eunuchoidism by means of transplantation.

Whatever the real cause of homosexuality may be, we must assume that it is somehow due to disturbances in the endocrine function of the sex gland or of some other organ of internal secretion, or by the suppression of the endocrine function of these glands. But this does not imply that external factors are without any significance and should not be taken into consideration in explaining homosexuality. It is not impossible even that in some cases external factors are alone sufficient to account for the abnormal condition. The psychosexual behaviour of a given individual is always the result of interference of a great and very variable complex of external factors with a given but also changeable somatic organisation. Some years ago *Kraepelin* (1918, p. 118), in opposition to Hirschfeld, said that there is no proof of the assumption that homosexuality is an inborn condition. I think that Weil's measurements supply definite evidence that many cases of homosexuality are caused, as said above, by some disturbance of an endocrine order. But I should like to insist that this endocrine disturbance is not necessarily always of an *intersexual* order, and it is by no means impossible that external factors may in some instances be responsible for the homosexual condition.

(*b*) *Other forms of intersexuality in man.*

In the medical literature many cases are known, where during childhood or after puberty a change of sex characters to those of the opposite sex took place. According to *Neugebauer* (1908) there were in Warsaw about thirty hermaphrodites (or pseudo-hermaphrodites in the old terminology) in a population of 800,000. It is not possible and not necessary to give here a detailed description of the different cases of hermaphroditism in man, which show indeed a very great variability. Two cases, however, may be described, as they may be taken as examples of two etiological possibilities in similar cases.

The *first* was that of a girl, who up to the age of three developed like a normal female. Then the clitoris hypertrophied and came to resemble a penis of that age. Pubes of female appearance and male characters such as the low male voice and beard developed, the first signs of the latter having already appeared in the third year. This case was examined by many specialists, and at an age of about nine carefully described by

Asch (1911, 1921) in Breslau. The skeleton was not that of a child, the epiphyses being partly ossified. The larynx was like that in a man after puberty. Some kind of menstruation took place about twice in the year. The patient developed intellectually in a satisfactory manner. Physically the development finally stopped; at the age of eighteen the body height was 121 cm., or the same as it was at the age of nine. The body weight was 30 kgr. at the age of nine and 40 kgr. at the age of eighteen. A tumour in the right hypochondrium was found when the patient was examined at the age of eighteen. The tumour grew rapidly during the last year, and it was supposed to be an hypernephroma. The tumour was removed, and it was stated to be really an hypernephroma weighing about 3 kgr., and filling up almost the whole abdominal cavity. A small but normally developed uterus and tubes were present. Both ovaries were white, smooth, without visible corpora lutea, and without cysts. The patient died soon after the operation.

Similar cases in which masculinization of a female individual was caused by an hypernephroma or a neoplasm of the adrenals are not very rare. In the "Institut für Sexualwissenschaft" in Berlin, I had the opportunity of seeing a new-born child, brought there for examination in order to ascertain the sex. There was a penis-like organ, much bigger than in a normal new-born boy; the organ was hypospadic. There was a formation resembling an empty scrotal sac. The general impression based on the examination of the external genitalia was that it was a boy with an hypospadic penis and undescended testicles. The child died some months afterwards. The examination made by Dr. Weil revealed normal female internal genitalia and somewhat hypertrophied adrenals.

Besides those cases where an hypernephroma causes masculinization of a female individual, others are known where a male individual undergoes a rapid development to male sexual maturity, the cases of so-called pubertas praecox or sexual precocity. *Krabbe* (1921) lately has given a summary of all the cases described in the medical literature. Krabbe concluded from his description that the hypernephroma, being a masculinizing factor, will cause masculinization in the female and acceleration of sexual development in the male. But there are also cases where a feminization of a male individual was caused by an hypernephroma. *Matthias'* paper (1921, 1922) may be referred to here.

The *second* case I will mention is that of *Blair Bell* (1920). The patient was seen the first time at an age of seventeen. Menstruation commenced during the fourteenth year and had stopped eighteen months before examination. The voice had got deeper. Nothing abnormal was felt in the abdomen or *per rectum.* When the patient presented herself about two years later it was at once noticed that she had become more masculine in appearance; she had a slight moustache, and the distribution of hair on the trunk and legs was masculine. The clitoris was much enlarged (two inches in length) and there was a well marked prepuce; *per vaginam* the left genital gland could be felt somewhat enlarged; no tumour was discovered in the suprarenal region; there was still complete amenorrhoea. Pieces of both genital glands were taken for histological examination, and it was stated that the right genital gland contained a large corpus luteum and an almost mature Graafian follicle; the left ovary was thought to contain a carcinoma. After this pathological diagnosis both ovaries and the uterus were removed. After the operation the patient underwent very marked changes. When examined eight months subsequently all the hair of the legs and of the upper lip was found to have disappeared. "The voice was slightly higher in tone, and the figure and skin were greatly altered towards the feminine type. The breasts, however, showed very little development, but this was not to be expected in the absence of ovaries." The patient suffered from slight menopausal symptoms, but somatically reverted, as seen from the description, entirely to the feminine or neutral type. When Blair Bell examined the sections of the left genital gland himself, he came to the conclusion that the first histological diagnosis of the pathologist was erroneous; the left genital gland was an ovariotestis and not the seat of a carcinoma. The organ (*Fig.* 129) consisted of a thin capsule of normal ovarian tissue (Graafian follicles, primordial ova and stroma) surrounding a central portion which was most likely an underdeveloped testis. This portion contained tubules and an interstitial tissue between them. The tubules were mostly lined with several layers of epithelial cells, among which cells with big nuclei, possibly spermatogonia, were to be seen. In the

FIG. 129.—*Section of ovariotestis from the case described in the text.* Above, central testicular portion; infantile seminal tubules surrounded by interstitial tissue. Below, outer capsule of ovarian tissue containing a follicle in the lower part of the field.—From Bell.

interstitial tissue large eosinophile cells, resembling exactly the interstitial cells of the testicle, were present.[1]

This case of Blair Bell is of a particular interest. Here, a marked change of sex characters took place, and the developed male sex characters disappeared after removal of the sex glands. Was the intersexual state of the genital gland the real cause of the intersexuality of the characters as observed in this case? As no signs of any abnormality in the adrenals could be detected, it seems justifiable to give a positive answer to this question. The case seems wholly to correspond to the experimental hermaphrodites of Steinach and Sand, the male sex characters being indeed more marked. The objection might be made that this case was really one of intersexuality or masculinization caused by an hypernephroma, since absence of any abnormalities in the adrenals does not exclude the possibility of an hypertrophy of these organs. I do not think, however, that the intersexuality of the sex characters was due to the adrenals; were it so, the patient could not have wholly recovered after castration, as she seems to have done, according to Blair Bell. But even if we adopt the view that in this case masculinization was due to an intensified function of the adrenals, it follows, from what Blair Bell observed after the operation, that the masculinizing effect of the adrenals is possible *only when a sex gland is present*, and further, that the masculinizing influence of the adrenals on the sex characters was due primarily to the masculinizing of the sex gland itself.

Cases of a gonadal intersexuality in man have been studied clinically or pathologically by *Salen and Pick* (see *Pick*, 1916) as well as by other observers, and lately by *Sand* (1922 b).

After seeing from the clinical cases related above that intersexuality in man may be caused by hormonic disturbances, the question arises as to how far an hormonic basis can be adopted for the great number of cases of intersexuality known to the clinician or to the pathologist. The question has been carefully examined in recent years by several authorities since the experiments of Steinach and Sand showed that intersexuality in mammals can be caused experimentally by combining ovarian and testicular implantation in the same individual. We shall now discuss some of the cases described

---

[1] As to the ovarian tumours of a seminiferous type the papers of *Peyron* (1922) may be referred to.

in the last few years in relation to the problem as to the existence of an endocrine basis for intersexuality.

Polano (1920) described a case of a "girl" of twenty-two with an hypertrophied penis-like clitoris. On the left side there were an ovary and a testicle containing rather infantile seminal tubules and interstitial cells. On the right side there was a malignant tumour. An uterus and tubes were present also. This case gives full support to the hormonic theory of hermaphroditism. It is the same with the case described by *Sand* (1922 b) of a "boy" of ten with a highly hypospadic penis or an hypertrophied clitoris and labia, together with an uterus and tubes, and a testicle on one side and an ovary on the other, as determined by histological examination of pieces excised from the respective glands for this purpose prior to deciding whether to operate. *Berblinger* (1923) has recently described a case very similar to that of Bell. In a girl at the age of twelve some growth of beard had taken place, but nevertheless menstruation set in at the age of sixteen. At the age of twenty-one a tumour of the proportions of a walnut was removed from the right labium. The psychical development, which was till then indifferent, became now typically female. The histological examination revealed that the tumour was an ovariotestis containing typical Graafian follicles, corpus luteum and spermatogonia, but no spermatozoa.

Mittasch's case (1920) was a man of 54; the genitalia were externally male, but the scrotal sac was empty; an uterus and more or less developed tubes were present. Besides the female internal organs there was a vas deferens, seminal vesicles and a prostate. The gonads were testicles containing seminal tubules with spermatogonia and spermatocytes. There was an hypertrophy of the adrenals. A similar case (a man of 77) was recently described by *Priesel* (1921) but without any hypertrophy of the adrenals being described. These cases might be classified as those of an hormonic intersexuality, if we assume with *Sauerbeck* (1909, 1911) that the male or female generative part of an intersexual gonad may disappear during embryonic or postembryonic development, and that such an intersexual gland may become afterwards unisexual. This assumption means, as Sauerbeck pointed out many years ago in view of his own observations and those of others, that it is very difficult to draw a sharp line between true and false hermaphroditism in mammals based upon an examination of the sex gland. The same view was held by Pick. To this group belong also cases like that of *Bolognesi* (1921), in which an uterus and tubes may be present in an otherwise normal man with a normal functioning testicle.

Let us now consider the cases of intersexuality described in recent years by *Bab* (1920), *Benda* (1921), *Blair Bell* (1920), *Schmincke and Romeis* (1920), *Sternberg* (1921), *Peyron* (1922 b) and others. Most of these cases belong to what is called pseudo-hermaphroditismus masculinus externus. The external sex characters of these individuals are rather female, though some traces of maleness may be also present; the internal sex characters are either male or underdeveloped female. The gonad was found in general to be an underdeveloped testicle in which seminal tubules in an infantile stage were to be found; most of the authors claim to have found also real interstitial cells sometimes even in great quantities. When confining attention to what is present at the moment of clinical or pathological examination, an extraordinary discrepancy may appear to exist between the sex of the gonad and the sex characters, and most of the authors who observed such cases are opposed to the assumption that an hormonic intersexuality of the sex gland was involved. But I think that the question is by no means negatively decided by these numerous observations. Ovarian tissue present during embryonic life or during childhood may have disappeared in some of these cases, and the interstitial cells, as present in the underdeveloped testicle, may be functionally inactive. Further, it must be taken into consideration that the result of an hormonic activity of a sex gland will depend, not only upon the mutual quantities of male or female active endocrine tissues, but also upon the condition of the soma, which varies greatly according to the stage of development.

The clinical and pathological observations likewise supply no evidence as to the question whether generative cells or special endocrine cells (interstitial cells) are actively involved in the glandular intersexuality. Moreover it must not be forgotten that a disturbance of some other endocrine gland may have temporarily interfered with the hormonic activity of the gonad itself, as shown by those cases of intersexuality where interference of hypertrophied adrenals is evident.

Some of the cases described above could be explained as adrenal cases; one might suppose that an intensified masculinizing action by the adrenals had temporarily interfered with and changed the female sex glands, which primarily were present, and had already begun their feminizing hormonic activity, into male ones. These cases recall in many details what Minoura observed in his experiments with testicular and ovarian transplantation in hens' eggs (see pp. 310, 311).

In view of these considerations I come to the conclusion that there are many indications of an hormonic basis for intersexuality in man, though the cases of the so-called glandular hermaphroditism, i.e., cases where ovary and testicle have been simultaneously present, are extremely rare. The hormonic basis may be an *adrenal* or a *gonadal* one. In the first instance there will be more chance that the sex glands will be monosexual, an almost complete transformation of the gonad into the opposite sex having taken place. In the second instance the chance of observing glandular intersexuality will be greater. If the hormonic basis is an adrenal one, this does not mean that the adrenals have a direct masculinizing influence on the sex characters; *the primary effect seems to be masculinization of the sex gland, by the intermediation of which the masculinization of the sex characters takes place.* I also hold the opinion that many cases adduced by various authors as evidence against the theory of a gonadal hormonic intersexuality in man, can be explained as having been formerly true hermaphrodites, who became afterwards false hermaphrodites owing to the degeneration and disappearance of one or both sex glands. With Sauerbeck and Steinach I believe that there is no sharp limit between true and false hermaphroditism.

When claiming that intersexuality in man may be caused by an intersexual hormonic activity of the gonad or by some other hormonic disturbance, I do not wish to deny that intersexuality in some cases may be caused by an abnormality relating to the somatic basis only, as supposed by many authors.

(*c*) *Is hypospadia a symptom of intersexuality?*

As mentioned above, the clitoris of the masculinized guinea pig becomes transformed into a penis-like organ, that is, into a kind of hypospadic penis. Now the question arises whether hypospadia, as observed in man, could be explained as due to masculinizing hormones during embryonic development entering into play or becoming activated more or less suddenly after the soma had originally begun its sexual differentiation in a female direction. There would under these circumstances be a masculinization, not of an asexual soma, but of a soma which had already undergone the influence of female sexual hormones, that is, a masculinization of a soma in which female sex characters had already become fixed to a certain degree. One must suppose that from such an abnormal condition an hypospadia might result. The degree of hypospadia will depend on the time at which male sexual hormones became activated and female sexual hormones ceased to be active. Such an assumption means that hypospadia may in some cases be a symptom of intersexuality which existed only during embryonic life when simultaneously or successively feminizing and masculinizing sexual hormones exerted their influence on the soma.

The assumption of hypospadia being a symptom of intersexuality, and the assumption that intersexuality is sometimes only a temporary one, being present only during embryonic life, was held at first by Sauerbeck as a result of his careful anatomical investigation of hermaphroditism in animals and men. Pick afterwards made a similar suggestion.

It seems to me probable that the number of abnormalities caused by temporary intersexuality in general is much greater than was formerly supposed. If we adopt the view that hypospadia is a symptom of intersexuality, the number of hermaphrodites becomes extraordinarily great. According to Lagneau (quoted from *Neugebauer*, 1908, p. 624) there are in France five cases of hypospadia among every 1000 recruits. As Neugebauer pointed out, men with higher degrees of hypospadia, or those with a hypospadia peniscrotalis, are mostly educated as girls.

2. MAMMALS.

(*a*) *Different forms of intersexuality in mammals.*

It is of great interest to examine the question of hormonic intersexuality in the different groups of mammals.

It is a very striking fact that true glandular intersexuality is not very uncommon in some species such as pigs and goats. As to the pig the detailed observations of *Pick* (1916) are to be mentioned in the first instance. He examined about half a million pigs in the Berlin slaughter-house; six cases of true glandular hermaphroditism were found. This means that there is one true hermaphrodite in 80,000 animals. In his cases the internal genital organs were intersexual, there being an ovariotestis, while both the uterus and the vasa deferentia were developed. In some cases the external genitalia were female, in others decidedly male or transitional between female and male. Both the ovary and the testicle could be recognised beyond any doubt. The seminal tubules were in an infantile stage, but the quantity of interstitial cells was very great. Ripening of the follicles had been going on in the ovary, as well as cystic degeneration. I had the opportunity of seeing in Prof. Landau's clinic in Berlin the preparations of Pick's animals, and I had the impression that transitional stages from a well developed ovary to a cystically degenerated one were present; in one case the ovary was transformed into a thin capsule of a great cyst. On the other hand Pick stated that in a case where there was a testicle on one side and an ovary on the other, remains of a testicle could be seen on the surface of the ovary or in the fibrous tissue between the corpora lutea. The observations show in a most striking manner that in those cases where an ovary and a testicle are simultaneously present, there is also a somatic intersexuality. Further Pick's observations make it very probable that in some cases the ovary was on the way to disappear or, in other words, that in an intersexual individual the gonad of one sex may finally disappear, the intersexual gland thus being transformed into a monosexual one. The result is an individual belonging to the group of pseudo-hermaphrodites with the gonad of one sex no longer corresponding to the intersexual condition of the sex characters.

Cases of glandular hermaphroditism in the pig have recently been described by *Ancel* (1920) and by *Bujard* (1921). Bujard insists that the bilateral glandular intersexuality is much more common than is generally admitted; the fact is often overlooked that the ovarian part of the ovariotestis may be much reduced so as to be found only when a very careful histological examination is made.

Many cases of intersexuality in the goat, pig, horse, cattle and sheep have been examined by *Crew* (1923 b and different papers in *The Veterinary Journal*, Vols. 78 and 79; *Fell*, 1923 a). As to the genital organs they belonged to the type described by Pick; an hypertrophied clitoris, vasa deferentia, seminal vesicles, prostate, an uterus and a vagina were present. The gonads microscopically resembled a retained testicle; there were undeveloped seminiferous tubules and interstitial tissue, sometimes hypertrophied. These cases can be explained as having been primarily glandular hermaphrodites in which the ovarian endocrine tissue has afterwards disappeared.

Observations on goats have been recently made by *Krediet* (1921, 1922), who examined 30 new-born goats and several adult ones. Krediet described in one case a true ovariotestis. The internal genital organs were feminine, but there was also an epididymis. A goat seven years old giving plenty of milk revealed a general male appearance, a bisexual behaviour, and the smell of a male. The genital organs were feminine, but there was an ovariotestis with ova and spermatogonia on both sides. In a second case of a similar kind, spermatogonia were absent in the ovariotestis. Another case of Krediet is also of great interest. He unilaterally castrated a goat a few days old. The gonad was stated to be an ovariotestis. Four months afterwards the second gonad was removed, and it was stated to have also been an ovariotestis but without spermatogonia, the whole testicular part being in a state of atrophy. Krediet thinks that the second gonad changed during the four months which had elapsed since birth, and he says that this animal, which during youth was a true hermaphrodite, would afterwards have possibly become a female individual. He expresses the matter very well when he says that an individual which is to-day a false hermaphrodite may have been a true one yesterday. *Steinach* (1920 a) has described a goat with normally developed female sex characters, but with a decidedly male sex behaviour. There were no signs of heat. Later on the skull became broader than that of the female. The animal was killed at an age of ten months. The genital organs were female and there were ovaries in their normal places. The microscopical examination revealed that the ovaries were really ovariotestes. Steinach explains this case in the following manner. Primarily the female endocrine gland of the ovariotestis dominated over the male one, and female sex characters such as the vagina, uterus and mammary gland could develop normally. But subsequently the function of the female gland was impaired and the male gland was activated; a male erotizing influence on the central nervous system and a male influence on the growth of the skeleton then took place. A decidedly homosexual individual was the result.

There are, however, observations which do not conform with our conception of intersexuality as being caused by simultaneous or successive intersexual hormonic activity of the sex gland. I should like to mention here the case of *Pearl and Surface* (1915); a perfectly normal cow eventually assumed the secondary characters of the male, in respect of both body proportions and behaviour. The uterus and the tubes were in an infantile condition. The only change which could be detected in the gonads was the absence of corpora lutea and the formation of follicular cysts. The interstitial cells were normal, but no real luteal tissue was present. So the authors concluded "that the absence of luteal substance in the ovaries was causally connected with the assumption of secondary male sex characters." That this conclusion is not justified is shown by an observation of *Crew* (1922) on a goat. There was an absolute sterility associated with persistent oestrum and a male smell. The internal genital organs were typically female. There was a bilateral cystic degeneration of the ovary. Microscopically ovarian tissue was identified; there were cells similar to those of the membr. granulosa and luteal cells in abundance; widely degenerate atretic follicular cysts were to be found. "The persistence of luteal cells in quantity can account for the disturbance of the oestrous cycle and in part for the widespread follicular degeneration."

Another case of great interest is that of *L. Loeb* (1918). He observed a guinea pig with a male sexual behaviour, but without any somatic sex characters: neither a vagina or uterus on the one hand, nor a penis, vas deferens or descended testicle on the other, could be found. Near the place where the ovaries are normally situated round bodies were discovered which consisted microscopically of testicular tissue. The seminal tubules were infantile; the interstitial cells were extraordinarily developed. The mammary gland was much further developed than in an ordinary male. Loeb explains the male sexual behaviour as due to the highly developed interstitial tissue. Since no other male sex characters were present, and since the mammary gland was developed rather after the manner of a female, Loeb assumes that the effect of the hormonic influence on the soma depends not only upon a specific action of the interstitial cells, but primarily upon the system on which the hormones act. The somatic system will have in one case the tendency to react rather to the male side, in another case rather to the female side. In an individual with a tendency towards a female reaction even a strong male hormonic influence will not be able to prevent development of certain female sex characters; the case described might have been such a one. I do not think that it is necessary to explain this case as Loeb does. The animal perhaps began its development rather as a female, but afterwards changed to a male without the male sex gland at the beginning being in a very active condition; when greater hormonic activity displayed itself, only the more variable sexual behaviour reacted, the other characters being already in a fixed condition. So Loeb's case might possibly be understood as due to the successive influence of hormones of both sexes.

(*b*) *The case of the freemartin.*

The observations made independently of one another by *Keller and Tandler* (1916) in Austria and by *Lillie* (1916, 1917, 1923) in America, on the freemartin, are of the greatest importance for a true understanding of intersexuality in mammals, giving support to the assumption that intersexuality may be caused during embryonic life by the simultaneous or successive influence of hormones of both sexes on the soma.

It has long been known that sometimes female twins in cattle show abnormalities in sex characters. These abnormal animals are generally called freemartins. They are sterile even when the external genital organs seem to be well developed; sometimes there are abnormalities also in the external genital organs, the clitoris being enlarged and transformed into a penis-like organ. A more detailed examination reveals a marked abnormality of the internal genital organs, whereas externally the animals resemble "castrates." There is a great variability in the condition of the internal genital organs. The ovaries are in general rudimentary, resembling in some cases rudimentary testicles. The uterus is as a rule underdeveloped, being small and thin. According to Keller and Tandler the underdevelopment of the organs originating in the female from the Müllerian ducts is particularly marked when the rudimentary gonad resembles a testicle. In these cases the ducts of Gartner (the remains of the Wolffian ducts) are particularly well developed, giving the impression of vasa deferentia. In some cases there was even a partial descent of the testis-like gonads. Some kind of seminal vesicles can be detected, and they are especially well developed if the other genital organs are of a more male type. Thus we see that the freemartin is a case of intersexuality, which might be designated in the old terminology as a pseudo-hermaphrodite showing a combination of characters of both sexes, those of the female being as a rule more marked.

Both twins in cattle are normal, when both are of the same sex, whether it be male or female. When the twins are of different sexes, the male one is always normal, whereas the female one is normal only in very rare cases, according to Keller and Tandler, only in six per cent. Now the question arises whether there are any structural differences in the mutual relations between the foetuses, which could explain why the female twin is generally abnormal, but is nevertheless normal in some cases. For this purpose they examined the membrane relations and the circulation in twins of cattle. Although there were generally two corpora lutea, there was as a rule a fusion of the two chorions. There were also in most cases *connecting blood vessels between both foetuses* (*Fig.* 130). Besides this some cotyledons had vessels arising from both foetuses. It seems, according to Lillie, that the connection between the circulation of both twins is already established at a very early stage; he found a fusion of the two chorions at a stage when the foetuses had a length of only 10 to 20 mm.

A detailed anatomical examination of the foetuses supplied evidence that in opposite-sexed twins the female foetus has abnormal internal genital organs, when there is a fusion of the two chorions and a well developed connection between the blood vessels. On the other hand, *the female foetus was found to be normal when there was no connection with the blood vessels of the male foetus.* It is the same in other mammals with normal twins of different sexes or of the same sex (*Fig.* 131).

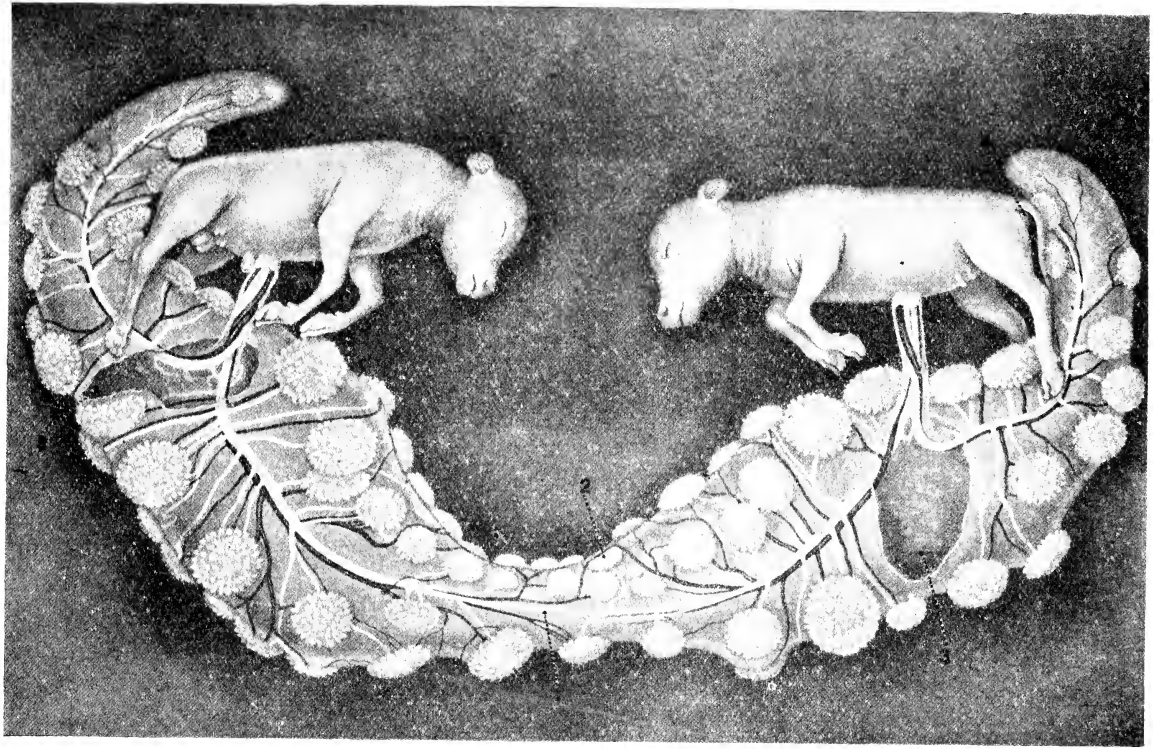


FIG. 130.—*Twins in cattle.* x 1/4. Left, male; right, freemartin. 1. Main arterial trunk. 2. Cotyledon with venous connection with both sides. 3. Amnion sacs opened. 4. Clitoris of freemartin; female arrangement of teats.—From Lillie.

A similar observation was made by *Keller* (1920) on the goat. In triplets two foetuses were male, whereas the third revealed external female genital organs, but the uterus was underdeveloped. The Wolffian ducts were developed like those in the sterile freemartin. The gonads externally resembled testicles, but were to be found in the normal position of the ovaries. Microscopically seminal tubules like those in a retained testicle were found; but genital cords like those of the ovary were present, and the stroma resembled that of an ovary. The examination of the membranes and of the blood vessels showed that there was a great anastomosis between the chorions.

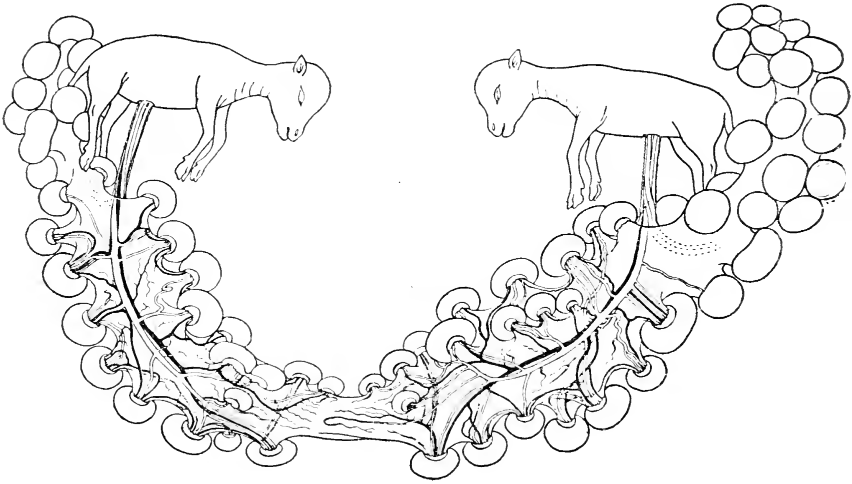


FIG. 131.—*Twins in sheep.* x 2/9. Both females. Fusion of chorionic vesicles, but no anastomosis of blood vessels from the two sides.—From Lillie.

The authors concluded from these observations that the abnormality of the female foetus in opposite-sexed twins is caused by the fact that, owing to the direct communication between both foetuses, the female one undergoes masculinization under the influence of a male sexual hormone entering the blood of the female. The authors consider the condition to be similar to that of the animals employed in Steinach's experiments on masculinization and feminization. But in the case of the freemartin there is presumed to be a masculinization of an embryonic soma, which had begun its sexual differentiation in the female direction. On this assumption there must be not only an inhibition of the female and a stimulus for the growth of the male genital organs (corp. cav. and seminal vesicles), but also an influence of the male sexual hormones on the ovaries, which are in progress of development. There should be a masculinization also of other somatic sex characters as the body proportions of the female foetus sometimes resemble those of the male type. Afterwards, during extra-uterine life, when the influence of the male sexual hormones of the partner ceases, the freemartin appears to acquire the body proportions of an ordinary "castrate."

Certain objections may be made against the assumption that intersexuality as present in the freemartin is caused by the successive or simultaneous influence of hormones of both sexes on the same individual during embryonic life. *Magnusson* (1918, quoted from different authors) holds the opinion that the gonad of the freemartin is testis-like to such a degree that the freemartin can only be considered as an abnormal male. If this is so, then masculinization by sex hormones from the other foetus does not come under consideration. But the standpoint of Magnusson is contrary to certain important facts stated by Lillie and his co-workers. Lillie has shown that the freemartin is genetically a female; if we adopt the opinion that the sterile partner is a modified male, we meet with an absurd sex ratio. Ninety-two cases of bovine twins examined by Lillie give 29♂♂ : 39♂♀ : 24♀♀. Out of the 39 cases of different-sexed twins six were normal. Though, indeed, these figures are small, it is easy to show by calculation that they are intelligible only on the assumption that the sterile animals are modified females and not modified males. In the first instance we have a sex-ratio of 97♂ : 87♀; in the second instance the ratio would be 130♂ : 54♀; such a deviation from the normal ratio 1♂ : 1♀ is outside the probable. Magnusson, however, is of the opinion that the twins in cattle are monozygotic, i.e., derived from *one* ovum; but this assumption is without any foundation, since Keller and Tandler, and also Lillie, regularly found *two* corpora lutea in the ovaries. *Zietzschmann* (1920) has rightly made the same objection to Magnusson's contention. In view of these considerations, it seems for the moment highly probable that the freemartin must be interpreted as a modified female. Further support is given to this assumption by the fact demonstrated by *Chapin* (1917) that in freemartins all transitory stages between an ovarian rudiment and a testicle may be found. Lately *Willier* (1921), also working in Lillie's laboratory, after making a very extensive investigation on the gonad of the freemartin, came to the conclusion that "an indifferent gonad with a primary female determination is changed in the male direction." Even in the cases of Magnusson formations similar to primordial follicles were present in the gonad. As already pointed out, the gonads of the abnormal goat, as observed by Keller, resembled ovaries in many respects. Finally, *Minoura* (1921) has shown experimentally that a testicular or ovarian graft is capable of modifying the heterosexual gonad of the embryo of the fowl in either the male or female direction.

The only fact which at first thought does not seem to conform with the assumption that the freemartin is a female modified by male hormones is that, according to Keller, the mammary gland is more developed than in a normal male. But it must be mentioned that a high development of the mammary gland is often observed also in new-born male children.

The question arises why a masculinization of the female foetus takes place, and not a feminization of the male. Lillie first considered the possibility of there being some kind of a natural dominance of the male sexual hormones over the female ones. This is not very probable, since no such dominance was present, either in the experiments of Steinach, Sand, and Lipschütz and his co-workers with experimental hermaphroditism, or in those of Minoura; it may, indeed, be that during the embryonic development the power of resistance of the ovary to the male sexual hormones (and *vice versâ*) is different from that during extrauterine life. *Pézard* (1918, p. 156) thinks that there is possibly a neutralization of the female foetus through the atrophy of the ovary under the influence of the male sexual hormones, which after this exhibit their masculinizing influence on the soma. But the most probable explanation seems to me that the male sexual hormones, as was suggested by Lillie, begin their action sooner than the female ones; according to *Van Beek* (1921), the female gonad becomes differentiated in cattle when the foetus is about 21 mm. long, whereas the male gonad becomes differentiated in the foetus of 19 mm. According to *Lillie and Bascom* (1922; *Bascom*, 1923), fully differentiated interstitial cells are found from the 3 cm. stage onwards. It may also be that the male sexual gland dominates *quantitatively* over the female, the former, during embryonic life, being sooner or more highly developed than the female gonad. In any discussion of problems of intersexuality one must never forget to take into consideration quantitative and time relations.

It may also be questioned why the female partner does not undergo under the influence of the male hormones a more pronounced masculinization. No answer can be given to this for the moment. Lillie thinks that there is a certain resistance in the female soma against which the male hormone is acting.

Willier stated that the transformed gonad contains interstitial cells, and he thinks that "the interstitial cells of the freemartin gonad bear no relations to the sexual instincts and little, if any, relations to the secondary sexual characters." But are we certain that these cells were normal or functional? I rather agree with Willier when he says that search should be made for any evidence of interstitial cell activity during the period of foetal development in the testis of the male twin, as recently done by Lillie and Bascom, and that it must be determined how far the anastomosis of the extraembryonic blood vessels between the male and female individuals is developed in every individual case. The last paper of *Lillie* (1923) may be here referred to. There is, as already said above, a very great variability in regard to the somatic characters of the freemartin. In some cases the male characters are more marked, in others the female ones. During embryonic life male or female body proportions may prevail, whereas the proportions of the "castrate" are present in extrauterine life. This extraordinary variability of combinations of sex characters corresponds to our theoretical assumption that quantitative and time relations are of the greatest importance in conditioning the sex characters which depend upon the sexual hormones. The question should be susceptible of experimental investigation. It may be mentioned that *A. Mayer* (1918) tried to perform castration of foetuses in the pregnant dog. The animal died four days after the operation from peritonitis. As the four foetuses operated upon showed no pathological abnormalities, Mayer concluded that the death of the foetuses was not caused by the opening of the membranes, and he thinks that it would be possible to operate on foetuses without causing death and artificial abortion. The experiments of Minoura on hens' eggs, referred to in Chapter VI., are the first really successful steps in solving these special problems in this kind of way.

Since *Matsuyama* (1921) and *Goto* (1922) have shown that female sex organs such as the uterus undergo profound degenerative changes when parabiotically united with a castrated male, the question arises whether a similar mechanism might not be at work in the case of the freemartin (*Romeis*, 1922). The question deserves experimental consideration.

Doncaster has studied the question whether the sterile male tortoiseshell cat may also be considered, like the freemartin, as a transformed female, as in general there are only tortoiseshell females from crossings of yellow and black cats. *Doncaster and Bamber* (1922) have examined the blood vessels of 70 cats with 253 embryos; no anastomosis between the chorionic vessels of the individual embryos was found.

3. Birds.

(*a*) *Different forms of intersexuality.*

"Changes of sex" in extrauterine life have been described also in birds. The so-called cock-feathering of old hens has long been well known. Cock-feathering or virility has been observed, according to *Gurney* (quoted from *Pézard*, 1918), in 26 different species of birds. The cock-feathering is evidently in most of the cases due simply to the ovary becoming inactive or insufficient; it is often a climacteric change, or a change due to some other cause inhibiting the hormonic activity of the ovary. The bird assumes the characters of the neutral form, since the latter resembles in many respects the male type, the cock-feathering being erroneously taken for an example of an intersexual condition, though no intersexuality is really present. The condition is best illustrated by an observation made by Pézard on the pheasant. He (1922 a) has described a female pheasant which, at an age of 13 years, assumed the male plumage; spurs did not develop, and there was no male behaviour. The iris kept its chestnut colour, which is characteristic of the female (the iris is light yellow in the male). A year later the bird moulted and again assumed a male plumage. Pézard stated that the ovary and the oviduct were much reduced. Interstitial cells and highly atretic follicles were present. The adrenals were normal. Pézard considers this case as conditioned by a deficiency of ovarian hormonic activity, the ovary having been reduced below the minimal quantity necessary for feminization. A similar case was observed by *Murisier* (quoted from *Pézard*, 1922 a).

There is no intersexuality in the above-mentioned cases, as said above, but only assumption of the neutral form. One can only speak of intersexuality in fowls, if there is, in addition to an assumption of male plumage, an increase of head apparel or change of sexual instincts. Similar cases of intersexuality seem to be not very uncommon in fowls. Several authors have described such cases. *Boring and Pearl* (1918) have published an extensive study of this question. These authors have also carefully examined how far there is a correspondence between the sex characters and the sex glands in hermaphrodite birds. I shall describe these cases, since they afford the best examples available of different forms of intersexuality in birds. Eleven birds were examined. Two guinea chicken hybrids were entirely male in external characters, but indifferent as to sexual instincts. The testicle was not normal; it was probably an undifferentiated gonad, no tubules being present. Interstitial cells and luteal cells were also absent. A hen treading other hens was quite normal as to the gonad. Three hermaphrodite birds revealed during their life history a marked change from femaleness to maleness, in respect both of somatic sex characters and of sex behaviour. They fought both males and females, and crowed and made attempts to copulate, though one of these hens formerly even laid eggs. In two of them the comb was well developed. The carriage was male-like, and the body shape was similarly male in two cases. These two birds assumed also some signs of male plumage. All these hermaphrodite birds had ovariotestes. In one case spermatozoa were present, in another case spermatids; in the third case only spermatogonia and spermatocytes. Interstitial cells and luteal cells were present in the ovarian part in different degrees. The authors consider these cases as females changing to males in respect of the gonad also. Further, they observed five birds with female plumage, with a more or less developed comb, wattles and spurs, and with a more or less male body shape and carriage; these birds never laid eggs, and were indifferent as to sexual behaviour. They showed underdeveloped ovaries; only one possessed both an ovary and a testis which contained spermatozoa. The authors conclude from their observations that the interstitial cells of the ovary have nothing to do with the secondary sex characters, whereas the amount of luteal cells or pigment is in precise correlation with the degree of development of external female somatic characters (p. 29). If the eight hermaphrodite birds are arranged according to their degree of exhibited maleness in regard to external male sex characters or sexual instincts, it will be found that those which revealed more maleness had gonads containing testicular tissue more or less developed. But on the other hand the authors hold the opinion that the "development of comb, spurs and wattles does not stand in direct quantitative relation to the sex of the gonad," whereas body shape and carriage have a general relation to the sex of the gonad.

Hartmann and Hamilton (1922) have described a new case of true hermaphroditism in the fowl; the plumage was a female one, spurs were present, and the head apparel was developed as in a male. The sexual behaviour was an intersexual one, the bird sometimes crowed like a cock and yet clucked like a laying hen. It showed an interest in chickens, but did not sit. It is stated that the bird had once laid an egg. A testicle and an ovariotestis were found. In the ovarian part interstitial and luteal cells were present. Spermatozoa were found.

Lately *Crew* (1923 c) has described a series of female birds changing into males. In one case there was a complete reversal from an egg-laying hen which raised many broods to a functional cock which became the father of two chickens. *Fell* (1923 b) has described the histological condition of the gonads in Crew's cases. There was always development of testicular tissue preceded by ovarian atrophy or disease. Only in one out of eight cases were oöcytes found. The mode of formation of testicular tissue seemed to be almost identical with the embryonic process, sex cords proliferating from the peritoneum inwards into the ovary. There were great quantities of "luteal" cells. Fell is inclined to ascribe to these cells female hormone-production, as they were not found in the gonads of the only cock-feathered bird mentioned above, whereas they were present in all the hen-feathered intersexual hens.

If we go through all the cases of intersexuality in birds as related above, it is clear that only in some of them can a correspondence between the sex characters and the gonad be detected, whereas in others such a correspondence is absent. But, in accepting the hormonic theory of intersexuality, should we expect that in every case of intersexuality conditioned by some pathological disturbance there will be a correspondence as required by the theory? Should we expect such a correspondence, when we see that even in experimental feminization and masculinization or in experimental hermaphroditism it is not always possible to predict the same positive result? Notwithstanding the fact that many things the authors observed do not wholly agree with the hormonic theory of intersexuality, I think that these observations give support to this theory. It may be, however, that the hormonic factor is sometimes counteracted temporarily by somatic factors.

There might be also cases in birds where some other endocrine gland is the primary cause of intersexuality. *Berner* (1923) has described a hen which exhibited a male-like large erect comb and spurs; the plumage was a female one, but eggs were never laid. There was a big suprarenal tumour; the ovary was small, but contained ova surrounded by groups of lutein cells.

Considerable support to the hormonic theory of intersexuality is given by the experiments of *Morgan* (1919–20) on the Sebright and Campine cocks. In the Sebright race the cock is normally hen-feathered, but becomes cock-feathered when castrated. It is the same with the Campines, where there are in some stocks only hen-feathered males, in other stocks both hen-feathered and cock-feathered males. It is evident that the intersexual condition being the rule in these races is caused by the hormonic activity of the testicle. According to Morgan and Boring luteal cells are to be found in the testicle of the Sebright cock; similar cells were found in the testicle of the hen-feathered Campine. Morgan ascribes to these cells the hormonic activity of the testicle which leads to hen-feathering. Doubt has been thrown on this view by

Pease (1922), who examined 28 testicles of normal and hen-feathered cocks of different ages and at different seasons. Pease stated that the luteal cells are to be found in the testicle only in young birds before sexual maturity, but both in hen-feathered and in normal cocks. These cells disappear when spermatogenesis begins, and they are absent when the bird becomes older. Pease inclines to the view that the luteal cells have a nutritive function, and he thinks that the contrary conclusion of Morgan was due to an insufficient number of hen-feathered birds having been examined. *Nonidez* (1922), a pupil of Morgan, has re-examined the question of the luteal cells in birds, and stated that they are derived from young seminiferous tubules, the cellular elements of which undergo fatty infiltration. Since similar cells in the ovary arise from the degenerating sexual cords, "there can be little doubt about the homology of the cells in both organs." The process takes place in late embryos and young chicks, and not only in the Sebright race, but also in other breeds, as, for instance, in the Rhode Island Reds and in the Leghorn.

Lately *Yocum* (1923, quoted from *Morgan*, 1923) and *Morgan* (1923) stated that luteal cells are absent in the testis of the phalarope, whereas these cells are to be found in the ovary. In this species the female is more highly coloured than the male. Morgan concludes, therefore, that the failure of the male phalarope to develop a highly coloured plumage cannot be ascribed to luteal cells.

Castration experiments of Marshall (see *Punnett and Bailey*, 1921) on henny-feathered Sebright cocks may also be mentioned here. Three out of six unilaterally castrated animals developed some feathers of the cocklike intermediate type, and these were almost entirely confined to that side of the body on which the testicle was removed. Two of three birds later on became fully henny on both sides (the third was killed previously).

(*b*) *Experimental.*

An interesting statement was made by *Goodale* (1916 a) about castrated Brown Leghorn hens. He found that certain castrated hens having acquired, as is the rule, the male plumage, may some time afterwards change the plumage again towards the female type. The plumage may then be changed a second time to a male one. Such an observation Goodale made on six birds. One would suggest that the reappearance of a female plumage was due to the regeneration of pieces of ovary left in the body unintentionally. This would most likely be true in many of the cases. But on the other hand Goodale found that in some of the birds observed no regeneration of ovarian tissue took place, no trace of ovarian tissue being present at all. An organ *sui generis* had grown. A portion of this organ was removed from each bird for histological examination. The organ resembled more or less that which is sometimes present in normal females on the right side. But it is impossible to assert that the new organ resulted from the hypertrophy of the latter. There are, according to Goodale, reasons for drawing such a conclusion, but "to demonstrate the assumed relationship between the structure will require a considerable series of stages, which are not at present available, and whose collection will require some time." As in the hens observed by Goodale there was not only a change of plumage to the male type, but sometimes also a male-like development of the head-apparel, one must assume that these changes were due to a masculinizing factor present in the body of the castrated hen. That this assumption is true is shown by the observations of Pézard and of Zawadowsky.

Pézard (1922 a) made his observations on two hens which were castrated, and which received a testicular implantation into the peritoneal cavity. These birds did not assume male plumage, this being a sign of the oöphorectomy having been an incomplete one. Five years later both hens manifested a male growth of head apparel and male sexual instincts. This maleness lasted only about four months, but in the next year maleness was again reassumed. When dissecting these two birds Pézard found no testicular graft; an ovarian fragment was found in the normal position of the ovary, and near this fragment a small body. The histological examination of the ovary revealed interstitial cells and degenerating follicles sometimes with a thick granulosa. As to the lateral body the interpretation is a rather difficult matter. There were cords of cells mostly without any cavity, possibly originating from the primary sexual cords. The adrenals were normal. The explanation Pézard gives of these two cases is the following. The ovarian quantity was very much reduced, but yet remained above the minimum necessary for conditioning female plumage and for inhibiting the growth of the spurs. On the other hand the lateral bodies behaved, as to hormonic activity, like a testicle. Since the quantity of male hormones produced evidently only just attained to the efficient minimum, a seasonal diminution of hormonic activity necessarily caused a corresponding disappearance of maleness.

Observations wholly identical with those of Goodale were made by *Zawadowsky* (1922) on five castrated hens which assumed male plumage; development of a male comb and of decidedly male sexual instincts was observed. There was in every case a development of the right rudimentary ovary. But this body is evidently not only a masculinizing, but in a certain measure also a feminizing factor, since in some of the cases observed female plumage was reassumed, as in the experiments of Goodale. On the other hand, it seems, according to Zawadowsky, that sometimes even the regenerating *left* ovary can have both a feminizing and a masculinizing effect, as observed in a bird which after castration assumed male plumage and growth of spurs, but subsequently assumed female plumage and showed a *male* development of the comb. No ova were present in the regenerated left ovary.

The above-described observations of Goodale, Pézard and Zawadowsky give full support to the hormonic theory of intersexuality. But do these observations tell in favour of the sex gland, or in favour of some other organ of internal secretion conditioning intersexuality? First, these observations show clearly that *generative cells are not necessarily involved in conditioning intersexuality.* Secondly, they render it very probable that *the adrenals are not involved in masculinization,* since no adrenal disturbance of any kind was observed. Thirdly, the observations suggest that *cells originating from the primary sexual cords may have a masculinizing influence*; if the interstitial cells, as was suggested by *Rubaschkin* (see p. 118), really originate from the primary sexual cords, we have in the above-mentioned observations *a very strong support for the theory of the endocrine function of the interstitial cells.*[1]

When discussing intersexuality in man we insisted that

---

[1] Lately *Benoit* (1923, 1924) has stated that the right organ developing after early ovariotomy may reveal the typical structure of a testicle with spermatogenesis though an incomplete one. If Benoit's statement is to be understood in the sense that it is *always* so, then the conclusions as drawn above would be naturally not justified.

the adrenals, if really conditioning maleness, can have this influence only by the intermediation of the sex gland, the latter forming some kind of a junction point between the sex characters and other endocrine glands. Blair Bell's case shows this very clearly. The question of such an intermediation of the sex gland has been experimentally studied in birds. *Torrey and Horning* (1922) showed that hen-feathering can be induced in cocks by feeding with thyroid. Further, these observers stated that the sex gland is a necessary factor in this result, since no castrated male assumed female plumage when fed with thyroid. Experiments in which normal and castrated females were fed with thyroid also gave negative results. The experiments of Torrey and Horning lead to the conclusion which we have always supported, that feminization and masculinization are the sex specific effects of the sex glands, and that in so far as any other endocrine gland influences the sex characters this is done by *the intermediation of the sex gland.* The action of the thyroid on fowls has been recently studied also by *B. M. Zawadowsky* (1923). He claims that by thyroid feeding a premature moulting can be caused; the new feathers are poor in pigment. There was in one cockerel an underdevelopment of the head apparel and an almost complete absence of spurs; no sexual instincts were present. It is difficult to say how far the results of B. M. Zawadowsky corroborate those of Torrey and Horning. *Crew and Huxley* (1923 a) repeated the experiment of Torrey and Horning on twelve male and female chicks; the animals developed in the usual manner. The most probable explanation is that the positive or negative result depends on the quantity of thyroid hormones introduced.

There are, however, facts which seem at first sight to be contrary to our theory, such as the cases of lateral intersexuality observed both in mammals and in birds, but especially in the latter. These cases will be discussed in the last section of this chapter.

4. Amphibians.

Intersexuality in frogs has repeatedly been the subject of observation and experiment. Intersexual frogs have been described by various authors, and the condition has been induced under different experimental conditions. The whole question as to the bearing of the internal secretion of the sex gland on intersexuality in frogs has lately been discussed from a general point of view by *Witschi* (1921) and by *Crew* (1921), whose papers may be referred to here. The most important points are the following. Though there is in frogs a great variability as to the degree of intersexuality, it may be said that somatic intersexuality corresponds to that of the gonad. All transitions between female and male as to the development of the ducts of Müller and Wolff have been observed, and it can be stated that the Müllerian ducts are the better developed the more the ovary is developed, and *vice versâ* in regard to the Wolffian ducts and the testicle. The Müllerian ducts of an intersexual or a male individual are the better developed the longer the gonads remained female, and the later the time at which the gonad changed to maleness. There is a change of somatic sex characters parallel to that of the gonads, but the change of the former takes place somewhat later. If there is an ovary only on one side, the Müllerian duct will be found reduced on the other side, whereas the male pads and the seminal vesicle are normally developed in the same individual on both sides, notwithstanding that only one testicle is present. Witschi concludes from these observations that there is a sex specific dependence of the somatic sex characters upon the sex gland, but that this dependence is not an endocrine one. This latter conclusion is founded on Witschi's observations on asymmetrical hermaphrodites. On the contrary, Crew concludes that "the mechanism by which the individual is thus transformed is one which acts through the internal secretion of the gonads."

In my view there is one weak point in Witschi's arguments. The influence which the gonad has on such sex characters as the excretory ducts need not necessarily be an endocrine one, as we shall show in some detail in Chapter XI. But on the other hand certain facts mentioned by Witschi are contrary to his conclusion that there is no morphogenetic endocrine influence of the sex glands on the sex characters, since in his asymmetrical hermaphrodites there was at the same time a symmetrical development of male sex characters, though the testicle was present only on one side. When making these objections against Witschi's conclusions, I do not say that there is necessarily only an endocrine basis for intersexuality in frogs. What I wish to point out is merely that the observations available are not sufficient for drawing definite conclusions in the opposite sense, as Witschi does, and that some observations can be explained on the ground of the hormonic theory, as Crew assumes. Though Witschi holds the opinion that there are no morphogenetic processes in the frog depending upon sexual hormones, he recognises on the other hand that sexual processes such as that of the clasp reflex may depend upon these hormones.

The position Witschi takes up in relation to the question of the function of the interstitial cells is a very interesting one. He points out that the testicle at the time of heat is, so to speak, free of fatty inclusions in the interstitial tissue, and he concludes that the hormone production of the testicle during heat cannot take place in this tissue. But on the other hand he thinks that the masculinizing effect produced by different conditions on the frog is brought about by the intermediation of interstitial cells disposed between the primary sexual cords. His opinion is based on purely histological observations.

We have already mentioned in the foregoing chapters *Wagner's* (1923) experiments with feeding tadpoles on ovaries, without a sex specific influence having been observed. *L. Adler* (1920) found, however, that low temperature causes masculinization in frogs. He found the thyroid gland to be highly developed in these animals, and he concluded that the thyroid was the masculinizing factor. But it may be objected that in these experiments the external factors conditioning masculinization possibly influenced directly both the thyroid and the sex gland.

As to the toad, we have already mentioned in Chapter VI. the observations and experiments of *Harms* and of *Guyénot* and his co-workers.

Finally, the observations of *Champy* (1922) on the triton may be mentioned here. He observed a gradual transformation of the male external sex characters into female ones. The gonad was stated to be an ovary. Champy does not doubt that the condition of the ovary, as described by him in detail, and some other sex characters, are signs of the transformation having taken place only recently. The most important point is that the transformation of the sex characters is correlated with the transformation of the sex gland, but there was no formation of mature generative cells. Were these sex characters dependent upon the sex gland? Or were the two processes of transformation caused by a factor common for both? Champy considers it possible to state merely that the first change on the part of the gonocytes towards sexual differentiation is correlated with development of certain sex characters, and that he is unable to say what the nature of this correlation is, or whether the first change has any direct influence on the second.

5. INSECTS. GOLDSCHMIDT'S EXPERIMENTS.

Intersexuality is very widespread in insects, and in this group also there is a great variability in the different degrees or types of intersexuality.

It seems at first thought impossible to postulate an hormonic basis of intersexuality in insects, as no hormonic dependence of the sex characters upon the sex gland appears to exist in this class. Intersexuality cannot be experimentally induced in insects by gonadal transplantation, though the engrafted gonads "take" easily.

On the other hand, intersexuality in insects can be experimentally controlled, as Goldschmidt has shown in his experiments on the gipsy moth. We shall deal here with *Goldschmidt's* (1917–22) work only in so far as certain general points are involved.

By crossing definite races of gipsy moths with one another Goldschmidt failed to obtain the expected normal numerical sex ratio, some of the "would-be-males" or of the "would-be-females" being intergrades between normal males and females. Goldschmidt stated that the number of intergrades or intersexual individuals, and the degree of intersexuality, i.e., the degree of transformation of one sex into the other, is constant for a given cross of races. There is also for every cross a constancy as to the time at which the transformation takes place. The degree of intersexuality is the more pronounced, the sooner the heterosexual transformation sets in during ontogenetic development. The behaviour of the individual parts of the body of an animal undergoing heterosexual transformation is very different. Those organs which differentiate very early during embryonic development rarely undergo heterosexual transformation, whereas those organs which differentiate later show a great tendency to heterosexual transformation. The first-mentioned organs, for instance the gonads, will be found in heterosexual transformations only in those crosses where the turning point to the other sex is a very early one; the transformation of the gonad will take place only in those crosses in which all the somatic organs are already changed.

Some examples of Goldschmidt's may be given in his own words (1920 b, p. 82). If a male of the Japanese race of Gifu is crossed with a female of the race of Kumamoto, all the females of the first generation will be slightly intersexual. The antennae will be slightly hairy like those of the male; there will be a little of the male brown on the white female wings; the number of eggs will be reduced, but the copulatory organs will be normal and reproduction be possible. If the same males of Gifu are crossed with females of Hokkaido or of Schneidemühl, the degree of intersexuality in the females of the first generation will be a somewhat more pronounced one. All the somatic sex characters are more male-like; but the instincts are still female, the males being attracted without fertilization being possible, though ova are present. If a male of Gifu is crossed with a female of Fiume, females with a high degree of intersexuality will be the result. The somatic sex characters are almost male; the instincts are midway between the two sexes; no copulation takes place, and would, indeed, be impossible; but the ovary is still to be found, though in an undeveloped condition. If a male of another Japanese race (of unknown origin) is crossed with a female of Schneidemühl, the females of the first generation will be highly intersexual. It is almost impossible to distinguish them from males, though a careful examination will reveal a strain of female somatic characters; the instincts are wholly male; the gonad shows all transitions between an ovary and a true testicle with mature spermatozoa. If males of Oggi or Amori are crossed with females of Fiume, Schneidemühl or Hokkaido, all the females of the first generation will be transformed into true males. There is a whole scale of female intersexuality or a gradation from female to male.

I shall abstain from reviewing and discussing other observations and experiments made on similar lines with various *Arthropoda*. The papers of *Goldschmidt*, of *de la Vaulx* (1921–22) and of *Sexton and J. Huxley* (1921) may be referred to here. It may be mentioned that de la Vaulx made very extensive observations on the intersexuality of the crustacean

Daphnia atkinsoni, and Sexton and Huxley on the crustacean *Gammarus chevreuxi*, a brackish water amphipod.

Two points stand out in Goldschmidt's results which are of special importance for us. First, no doubt can be possible as to the conclusion that the factor causing intersexuality and controlling its degree, in the case of the moth, is not the gonad; and, secondly, that the variability so characteristic in every domain of intersexuality may be understood as a function of time.

Goldschmidt calls the intersexuality observed in insects a *zygotic* one, as opposed to the *hormonic* intersexuality present in mammals and birds. Zygotic intersexuality means that the result is already determined at the moment of fertilization as in insects, whereas in mammals and birds the somatic and psychical characters can be changed by the action of hormones. This terminology of Goldschmidt is not a very fortunate one, as probably also in mammals and birds the result or the degree of intersexuality may already be determined, though not necessarily at the moment of fertilization. The difference between insects on the one hand and mammals and birds on the other is evidently only that in the first case the factor causing the turning over to the other sex is not localized in the sex gland, but rather, as Goldschmidt assumes, in all the cells and tissues of the organism, whereas in the second case the factor may be certainly located in the sex gland and possibly also in some other organ of internal secretion. There is really in both cases a "zygotic" intersexuality.

It is of great interest to note that Goldschmidt adverts in a certain degree to hormones when explaining the individual phenomena of what he calls zygotic intersexuality in the moth. He assumes that in every individual hormones of both sexes are present, the quantitative relation between the two hormones being constant for every sex of a given race. Intersexuality develops when this normal quantitative relation is disturbed, the quantity of hormones of one sex becoming greater than normal; such a disturbance is caused when crosses between races with different normal quantitative hormone relations occur. Further, Goldschmidt supposes that the time at which the turning over to the other sex takes place also depends on the quantitative relation between male and female hormones in the same individual; the inversion will take place the earlier, the greater the quantity of the heterosexual hormone above the normal. Since the degree of transformation into the other sex is the higher the earlier the inversion takes place, the degree of intersexuality, according to Goldschmidt's supposition, will be a function of the quantitative relation between the male and female hormones.

Sexton and Huxley also are inclined to explain the differences as to the degree of intersexuality in *Gammarus* by a time factor.

We have emphasized the experiments of Goldschmidt, because they show us that the great variability of intersexual types, as experimentally produced in Goldschmidt's crosses, may be understood as caused by a variation in the quantitative relations between the male and the female hormones, and by a variation in the time at which the antagonistic action of the one becomes dominant. The explanation Goldschmidt gives of his experiments corresponds to what we proposed in foregoing sections in explaining the phenomena of variability in the domain of intersexuality among mammals and birds.

D. CLASSIFICATION.

Though it is not yet possible to demonstrate how far intersexuality in mammals and birds or other vertebrates is really caused by an intersexuality of the sex gland, and though the question cannot be definitely answered whether the generative part or some other part of the sex gland is the factor conditioning intersexuality, it seems clear that, in the face of the numerous experimental data obtained since Steinach's work, the notions of *true hermaphroditism* and *false hermaphroditism* no longer correspond to our knowledge of the *morphogenetic* basis of intersexuality. Neither does this classification take a due account of the great *variability* observed in the field of intersexuality.[1] As already remarked, the old division into true and false hermophroditism tacitly expresses the assumption that there exists a genetic dependence of the sex characters upon the generative cells, or that "sex" is characterized only by the gonad. But all we know for certain is that there may be an hormonic intersexuality, the hormones being produced

---

[1] For a careful description of cases of intersexuality in man see especially *Neugebauer* (1908); also *Hirschfeld* (1918, vol. 2). For different classifications of intersexuality see especially *Halban* (1903), *Neugebauer* (1908), *Meisenheimer* (1909), *Sauerbeck* (1909, 1911), *Hirschfeld* (1918).

either by the sex gland or, as some authors suppose, by other organs of internal secretion. It would appear also that the generative cells may be dependent upon sexual hormones, since the sex of the gonad can be experimentally induced or changed by hormonic action. If we imply by the notion "secondary" sex characters some kind of genetic hormonic dependence, the gonads of mammals and birds, in the light of Willier's and Minoura's work, are themselves secondary sex characters conditioned by sexual hormones!

Though I hold that it is not possible to demonstrate that all cases of intersexuality in mammals and birds are caused by an intersexuality in hormone-production, I think it should be of great interest to attempt a classification of intersexuality based on that assumption. It may well serve as a working hypothesis. But such a classification cannot yet be made very satisfactorily, our knowledge of the morphogenetic rôle of the sex hormones in somatic and psychical intersexuality being still very incomplete and of a more general order. We suppose that male and female sexual hormones circulate sometimes *simultaneously*, sometimes *successively* in the same individual. We may also suppose that abnormal hormone-production often takes place only *during embryonic development*, whereas seemingly in the same individual during extrauterine life the production of hormones is only of *one* sex. But in such cases there will be a somatic intersexuality during the whole of life as some sex characters are already *fixed* during embryonic development. Further, if there is in an adult a successive production of hormones of two sexes, a *periodic change* of some sex characters might take place; this change will concern especially those characters which have retained a certain *growth intensity* and plasticity, as, for instance, the hair or the mammary glands, or such organs as are of great lability like the central nervous system.

It is clear that such a classification cannot be based on direct clinical observation, but only on deduction from what we know concerning experimentally produced intersexuality. The use of such a classification would rather be to present a general view of the enormous variability shown by cases of intersexuality, and to provide a working hypothesis for further research. But such a classification will not serve our purpose, if we require a better designation of individual cases of intersexuality. For this purpose we need a classification in which particular characters accessible to direct observation are emphasized. Such a classification cannot, indeed, be a very profound one; but it is *necessary* to have it. The particular characters which should serve as the basis for such a classification are the *sex characters*, and the cases of intersexuality would be here classified according to whether the appearance of these characters is simultaneous, successive, temporary or periodic.

Accordingly I have proposed two *schemes* of classification:—

A. Classification according to sexual hormones.

1. *Simultaneous intersexuality.*
   - (*a*) Male and female hormones act simultaneously during *embryonic development.* Afterwards an establishment of a seemingly *normal* hormone-production may take place.
   - (*b*) Male and female sexual hormones act simultaneously during the *whole of life.*
2. *Successive intersexuality.*
   - (*a*) Heterologous sexual hormones enter into play during embryonic development. A change to a seemingly *normal* hormone-production or to *simultaneous intersexuality* is possible.
   - (*b*) Heterologous sexual hormones enter into play during extrauterine life.
     - (i) The heterologous sexual hormones remain active *for the whole of life.* A change to *normal* hormone-production or to *simultaneous intersexuality* is possible.
     - (ii) Heterologous sexual hormones remain active only *temporarily.*
     - (iii) Heterologous sexual hormones enter into play *periodically.*

The above scheme is only a further development of the following *hypothetical thesis* :—

Intersexuality in the vertebrates is caused by intersexuality in hormone-production, hormones of both sexes acting simultaneously or successively in the same individual.

B. Classification according to sex characters.

1. *According to degree and quality.*
   - (*a*) *Complete* intersexuality: *somatic, psychical* and *generative* sex characters (generative cells) of both sexes are combined in the same individual.
   - (*b*) *Partial* intersexuality.
     - (i) *Somatic* intersexuality: somatic characters of both sexes are combined in the same individual.
     - (ii) *Psychical* intersexuality: instincts of both sexes are exhibited.
     - (iii) *True homosexuality*: the sexual instincts do not correspond to the sex of the somatic and generative characters.
2. *According to the time.*
   - (*a*) *Simultaneous* intersexuality: characters of both sexes are *continuously* and *simultaneously* combined in the same individual; female somatic characters may be combined with male psychical and generative characters and *vice versâ.*
   - (*b*) *Successive* intersexuality: the more or less sexually differentiated organism acquires at a given moment of embryonic or extrauterine life characters of the other sex, a certain number of somatic, psychical, or generative characters becoming transformed into those of the other sex; the transformation may be a more or less complete one.
     - (i) The transformation is a *definite* one.
     - (ii) The transformation is only a *temporary* one.
     - (iii) The transformation takes place *periodically.*

This scheme corresponds to the following *definition*:—

Intersexuality is an abnormal condition in which more or less rudimentary characters of both sexes are combined in the same individual; somatic, psychical, and generative characters of both sexes may be present simultaneously or successively.

Scheme *A* does not need further explanation. As to Scheme *B* some consideration is necessary. The limits between the different groups are not very sharp either in Scheme *A* or in Scheme *B*; there are transitions from one group to the other. This is especially true of the different groups in

Scheme *B*. This is easy to understand, if we take into consideration the fact that a qualitatively uniform change in the activity of male or female sexual hormones will cause very different changes in the somatic and psychical sex characters, according to the *time* at which the activation of the hormones of the other sex takes place, and according to the *quantity* of the heterologous sexual hormone which enters into play. This is why it is very difficult to limit different groups or types of intersexuality in a classification based on sex characters.

By "complete" intersexuality we do not mean that there are cases where the male and female modifications of every sex character are simultaneously present in the same individual, but only that there are cases where besides different somatic and psychical characters of both sexes generative characters of both sexes are also present. Complete intersexuality, which is the rule in some invertebrates and in many plants, is a very rare phenomenon in vertebrates, and especially in man. As Blair Bell says, very few cases would pass the test if the described condition of complete intersexuality is considered critically. Most of the cases belong to partial intersexuality. There are cases where only somatic characters of both sexes are present, and other cases where there is only a psychical bisexuality. Further, a combination of somatic characters of one sex with psychical characters of the other sex is possible as in ordinary homosexuality.

The somatic and psychical sex characters in intersexual individuals are as a rule incompletely developed or rudimentary; this can be explained on the assumption that these characters are derived from an antagonistic, simultaneous or successive action on the part of the hormones of both sexes. But sometimes one or more somatic, psychical or generative sex characters may be completely developed. Underdevelopment of heterologous sex characters in the intersexual individual will be all the more marked the later the heterologous hormones enter into action. Since the reaction of the different sex characters to the sexual hormones will be very different according to time, it follows that *variations in time and variations in the quantity of the hormones of both sexes will cause an extraordinary variability of intersexual types.* One may say without any exaggeration that there are no two intersexual individuals in man completely resembling one another.[1] This is why I should like to emphasize that a classification of cases of intersexuality according to sex characters, though very useful for orientation in this field, will not help in further research, if general morphogenetic factors with their time and quantitative relations are not taken into consideration. No doubt, for the moment it is not possible to build up definitely the theory of intersexuality in mammals and birds on an hormonic basis. But on the other hand it cannot be denied that an extraordinary progress has been made in this field since Steinach began his experiments with feminization and masculinization, i.e., since investigators began to work in this field on an hormonic basis. There are a great number of different problems concerning intersexuality which might be explained on this basis, especially if time relations and quantitative relations are considered. An example may be given. *Hirschfeld* writes (1918, p. 103): "Is the great variability of symptoms in intersexuality due to the reaction of the breasts, or the larynx, or other parts involved being different in individual cases, or is it due, as it seems to me probable, to a *specific* composition of the sexual hormones, the chemical formula of which must be surely a very complex one?" It cannot be denied that the development of different normal sex characters at different times could be caused by the sexual hormones produced at different stages of individual development being different from one another. But if we adopt Hirschfeld's standpoint in explaining the enormous variability of symptoms in intersexuality we must assume that there is an enormous variability in the quality of the sexual hormones. But nothing is thereby really accounted for, one unknown factor being replaced by another. I am rather of the opinion that the question can be decided best on the assumption that the different parts of the organism react differently to the hormones, and that their reaction varies with age.

There is one fact, however, which does not conform with the

---

[1] A very striking example of how the time factor interferes in intersexuality, causing an extraordinary variability, is given by observations of *Goodale*, (1916 b) on feathers of castrated fowls which were moulting at the time of the operation. "Individual feathers from such breeds often show both male and female colors, color patterns, and even shapes, the area occupied by each depending upon the age of the feather germs..." Lately special attention has been given to this question by *Pézard*, *Sand*, and *Caridroit* (1923 b, 1923 c) who experimented on engrafted fowl.

conception of an hormonic intersexuality. There are individuals which have the external characters of one sex on the right side of the body and of the other sex on the left side; this is not uncommon in insects, and has been observed also in other species. In insects there is a very great variability in regard to this "lateral" intersexuality. In some cases the internal sexual organs correspond to those of the external; in others there is no such parallelism, internal female sexual organs, for instance, being present on the side of external male characters. There are also cases where the internal organs are only of one sex, whereas externally a marked unilateral intersexuality is present. *Meisenheimer's* paper (1909, Chapter V.) may be referred to. Examples have been described in moths, ants, bees, Crustacea and other Arthropoda. In ants the variability is particularly great. Here the external male and female sex characters differ from one another very markedly in colour and structure; as *Forel* (1874, pp. 139–143) points out, it is possible to state with certainty to which sex every segment or even every part of a segment appertains. I could assure myself of this in examining Forel's beautiful collection. Such a lateral intersexuality has been observed also in mammals and in birds, in which, however, these cases are extremely rare. In birds examples have been recorded by *Poll, Weber,* and *Bond* (quoted from *Doncaster,* 1914). Poll's bullfinch had the male and female plumage sharply separated on the two sides of the body, the right side being male, the left side female. A testis and an ovary were present on the corresponding sides. In Bond's pheasant the male and female plumage was not so sharply separated, and there was a gonad only on the left side; this gonad contained both ovarian and testicular tissue. At first sight it seems impossible to explain such an abnormality by the hormone theory; both kinds of hormones circulate in all parts of the body, and it would seem impossible to interpret the sharp separation of the male and female plumage. Most authors agree that the recorded condition of intersexuality is "due to differences in the tissues of the body, and the activity of the ovary or testis must be regarded rather as a stimulus to their development than the source of origin" (*Doncaster,* 1914, p. 99). The conclusion was drawn from these observations that the tissues of the male normally differ from those of the female. Doncaster assumed that "the extent to which the tissues of the two sexes differ must vary in different animals and in respect of different characters; in birds . . . the difference must be considerable, while in mammals Steinach found that each sex could be made to assume to a very great extent the characters of the other by cross-grafting of ovaries and testes." The experiments of Goodale, Pézard and Zawadowsky have shown that there is in this matter no difference between mammals and birds. I think that it is impossible to draw any general conclusions opposed to the theory that the sex characters are conditioned by sex specific hormones from the observations on birds with lateral intersexuality. It is not impossible that the condition is caused by an hormonic intersexuality complicated by some other abnormality. I have pointed out that possibly some abnormality in the distribution of the blood vessels during embryonic development might be one of the causes of lateral intersexuality. It suffices to recall the important rôle played by the abnormal distribution of the blood vessels in conditioning the development of the freemartin. On the other hand, I have considered the possibility of *an hormonic intersexuality complicated by some other teratological condition, an hormonic and a somatic abnormality being coincidently present.* On more or less similar lines, *Pézard* (1922 b) has lately elaborated in detail a theory explaining lateral intersexuality in birds. His starting point is the assumption that there is a coincidence of two different abnormal conditions, a somatic and an hormonic one. Normally both sides of the body react to the threshold quantity of female hormones in a similar manner, and female plumage develops likewise on both sides. But now suppose with Pézard that the threshold quantity is abnormally high for one side, and that at the same time only the threshold quantity of female hormones is produced in this individual. A lateral intersexuality as to plumage will result, since the quantity of hormones produced will be able to feminize only that side of the animal which is normal, whereas the abnormal side will reveal the neutral plumage, which is almost identical with the male one. *Pézard, Sand* and *Caridroit* (1923 a, 1923 b) have induced experimentally lateral intersexuality in birds by plucking the feathers of the back and tail of a Leghorn cock on one side in December, and engrafting an ovary into the testicle. In about six weeks a new plumage appeared, which was a female one. This was to be expected, since, as Zawadowsky has shown, the plumage is a female one when both the ovary and the testicle are present simultaneously in the body. The experimental bird was as to its external appearance a true lateral intersex. Indeed, it must be supposed that this bird would at the moulting become female on both sides, as in the experiments of Zawadowsky. But on the other hand this experiment gives a good idea how the coincidence of certain abnormal somatic and hormonic conditions may cause intersexual types, which at first thought might seem to be without any relation to the hormonic theory.

In view of the extraordinary variability in intersexuality in the animal kingdom it seems to me inadvisable to set on one side a theory which can explain a great number of facts from a general point of view, because we meet with some facts which cannot be explained by this theory or which seem to contradict it. It is not impossible, as said above, that such a seemingly contradictory fact as, for instance, lateral intersexuality, is a special case, which is subject to the general law of the genetic dependence of the sex characters upon sexual hormones influencing the characters of the asexual embryonic tissues, and which at the same time is subject to certain other factors not yet known to us. If we are never to be content with any theory or hypothesis without its explaining everything, it would be impossible to make any step forwards amid the labyrinth of biological facts.

In the above discussion on intersexuality we have so far omitted a very important question. We spoke of the hormones normally present in every individual as being only of one sex. But it is not absolutely necessary that this should really be so. It is possible that the normal gonad produces simultaneously male and female hormones, but not in similar quantities, one of the two dominating over the other. Such an assumption implies that the normal gonad is *bisexual* in regard to hormone-production, male and female individuals being different from one another in that the hormones produced by their sex glands differ *only quantitatively*. One might suppose then that hormonic intersexuality is caused by changes in the quantitative relations between the two hormones (or groups of hormones). There would be normally a "*latent intersexuality*," which becomes manifest when a disturbance in the sex gland takes place. As already indicated in a foregoing section of this chapter, Goldschmidt has built up the theory of intersexuality in the moth on a similar basis. Such a theory is also held by Zawadowsky in view of his observations on birds related above (see p. 312). It may be remembered that he observed masculinization in hens under the influence of a regenerating ovary. Like Steinach and ourselves, *Zawadowsky* (1923) is inclined to explain the change of sex as due to the action of heterosexual hormones which previously could not influence the sex characters on account of these hormones being dominated by those of the other sex. Also the experiments of *Meisenheimer* (1912) on the frog show that the ovary possibly produces some hormones which are similar to those of the testis.

Now a second important question arises: what factors can produce a quantitative disturbance of the hormonic activity of the sex gland in such a way as to influence the sexual characters? It is well known that tumours of the adrenals may have this effect. But what do we know about the mechanism of this influence? I have already pointed out that the hypernephroma which has a masculinizing influence probably does not act directly through male sexual hormones upon the soma, but more likely influences the sex gland producing some disturbance of its hormonic activity. It may be remembered in this connection that, according to Matthias, a hypernephroma may cause not only masculinization of a female individual, but also feminization of a male one.

The different problems touched on in this section are by no means solved. What we need for the moment are working hypotheses to guide us in further experimental research in this field.

BIBLIOGRAPHY TO CHAPTER IX

[* *Not seen in the original.*]

ADLER. 1920. Experimentelle Untersuchungen über die sexuelle Differenzierung bei Rana temporaria. *Pflügers Archiv*, 183, p. 23.

*ANCEL. 1920. Sur l'hermaphroditisme glandulaire. *C. R. de la Soc. de Biol.*, 83, p. 1642.

ASCH. 1911. Frühreifer Scheinzwitter. *Berl. klin. Wochenschr.*, No. 52.

—— 1921. Heterosexuelle Frühreife durch Geschwulstbildung der Nebennierenrinde. *Berl. klin. Wochenschr.*, No. 2, p. 39.

ATHIAS. 1915. L'activité sécrétoire de la glande mammaire hyperplasée, chez le cobaye mâle châtré, consécutivement à la greffe de l'ovaire. *C. R. de la Soc. de Biol.*, 78, p. 410.

BAB. 1920. Neueres und Kritisches über die Beziehungen der inneren Sekretion zur Sexualität und Psyche. *Jahreskurse f. ärztl. Fortbildung.*

*BAMBER. 1922. The male tortoiseshell cat. *Journ. of genetics*, 12, pp. 209–216 (quoted from Berichte).

BASCOM. 1923. The interstitial cells of the gonads of cattle, with especial reference to their embryonic development and significance. *Amer. Jl. of Anat.*, 31, p. 222.

VAN BEEK. 1921. *Microscopisch- en macroscopisch-anatomisch onderzoek naar de ontwikkeling van het ovarium bij het rund.* Proefschrift, Utrecht.

BENDA. 1921. Bemerkungen zur normalen und patholog. Histologie der Zwischenzellen des Menschen und der Säugetiere. *Arch. f. Frauenkunde u. Eugenik*, 7, p. 30.

BENOIT. 1923 a. A propos du changement expérimental du sexe par ovariotomie, chez la poule. *C. R. de la Soc. de Biol.*, 89, p. 1326.

—— 1923 b. Transformation expérimentale du sexe par ovariotomie précoce chez la poule domestique. *C. R. de l'Acad. des Sc.*, 177, p. 1243.

—— 1923 c. Sur la structure histologique d'un organe de nature testiculaire développée spontanément chez une poule ovariotomisée. *C. R. de l'Acad. des Sc.*, 177, p. 1243.

—— 1924. Sur la signification de la glande génitale rudimentaire droite chez la poule. *C. R. de l'Acad. des Sc.*, 178, p. 341.

BERBLINGER. 1923. Hermaphroditismus beim Menschen. *Klin. Wochenschr.*, 2, p. 663.

BERNER. 1923. A case of "virilisme surrénal." Videnskapsselskapets Skrifter. *I. Mat.-Naturv. Klasse*, Nr. 7.

BIEDL. 1913. *Innere Sekretion*, 2nd edit. Berlin–Wien.

BELL (W. Blair). 1920. *The Sex-Complex*, 2nd ed. London.

BLOCH. 1909. *Das Sexualleben unserer Zeit.* Berlin.

BOLOGNESI. 1921. Presenza di testicolo e di utero nel sacco erniario di un uomo. *Arch. Ital. di Chirurgia*, 3, Nr. 4.

BUJARD. 1921. Structures atypiques de deux ovotestis de porc. *C. R. de la Soc. de Biol.*, 84, p. 112.

CHAMPY. 1922. Etude expérimentale sur les différences sexuelles chez les tritons. *Arch. de Morphol. Génér. et Expérim.*, Fasc. 8.

*CHAPIN. 1917. A microscopic study of the reproductive system of foetal free-martins. *Jl. of experim. Zool.*, 23, p. 453.

CREW. 1921. Sex-reversal in frogs and toads. A review of the recorded cases of abnormality of the reproductive system and an account of a breeding experiment. *Jl. of Genetics*, 11, p. 141.

—— 1922. A case of cystic ovary in a goat. *Veterinary Journal*, 78, Nr. 7.

—— *and* HUXLEY. 1923 a. The relation of interstitial secretion to reproduction and growth in the domestic fowl. I. Effect of thyroid on growth rate, feathering and egg production. *Veterinary Journal*, 79, Nr. 10.

—— 1923 b. Studies in intersexuality. I. A peculiar type of developmental intersexuality in the male of the domesticated mammals. *Proc. Royal Soc.*, B., 95.

—— 1923 c. Studies in intersexuality. II. Sex-reversal in the fowl. *Proc. Royal Soc.*, B., 95.

DOENICKE. 1921. Ein Beitrag zur Kenntnis des Hermaphroditismus. *Bruns. Beitr. z. klin. Chir.*, 123, p. 82.

DONCASTER. 1914. *The Determination of Sex.* Cambridge.

FELL. 1923 a. A histological study of the testis in cases of pseudo-intersexuality and cryptorchism, with special reference to the interstitial cells. *Quarterly Jl. of Exp. Physiol.*, 13, Nr. 2.

—— 1923 b. Histological studies on the gonads of the fowl. I. The histological basis of sex reversal. *British Jl. of Exper. Biol.*, 1, p. 97.

FISHER. 1923. The influence of the gonad hormones on the seminal vesicles. *Americ. Jl. of Physiol.*, 64, p. 244.

FOREL. 1874. *Les fourmis de la Suisse.*

GOLDSCHMIDT. 1916. Die biologischen Grundlagen der konträren Sexualität und des Hermaphroditismus beim Menschen. *Arch. f. Rassen- u. Gesellsch-Biol.*, 12, p. 1.

—— 1917. Intersexuality and the endocrine aspect of sex. *Endocrinology*, 1, p. 433.

—— 1920 a. Die quantitative Grundlage der Vererbung und Artbildung. *Votr. u. Aufs. über Entw.-Mech. d. Organismen*, Heft XXIV. Berlin.

GOLDSCHMIDT. 1920 b. *Mechanismus und Physiologie der Geschlechtsbestimmung.* Berlin. English edition, 1923, London.

—— *and* SAGUCHI. 1922. Die Umwandlung des Eierstocks in einen Hoden beim intersexuellen Schwammspinner. *Zeitschr. f. Anat. u. Entw.-Gesch.*, 65, p. 226.

GOODALE. 1916 a. Further developments in ovariotomized fowl. *Biolog. Bull.*, 30.

—— 1916 b. *Gonadectomy in relation to the sec. sex characters of some domestic birds.* Public. Carnegie Instit. of Washington.

—— 1918. Feminized male birds. *Genetics*, 3.

GOTO. 1922. Experimentelle Untersuchung der inneren Sekretion des Ovariums durch Parabiosentiere. *Arch. f. exper. Pathol. u. Pharmakol.*, 94, p. 124.

GRUSS. 1921. A case of pseudo-hermaphroditism. (Tshec with a resumé in French.) *Rozhledů v chirurgii a gynaekologii.*

HALBAN. 1903. Die Entstehung der Geschlechtscharaktere. *Arch. f. Gynäk.*

*HARTMANN *and* HAMILTON. 1922. A case of true hermaphroditism in the fowl with remarks upon secondary sex characters. *Jl. of Experim. Zool.*, 36, p. 185.

HIRSCHFELD. 1918. *Sexualpathologie*, II. Bonn.

—— 1921. Hodenbefunde bei intersexuellen Varianten. *Arch. f. Frauenkunde*, 7, p. 173.

KELLER *und* TANDLER. 1916. Über das Verhalten der Eihäute bei der Zwillingsträchtigkeit des Rindes. *Wiener tierärztl. Monatsschr.*, 3.

—— 1920. Zur Frage der sterilen Zwillingskälber. *Wiener tierärztl. Monatsschr.*, 7, p. 146.

v. KEUSSLER. 1920. Über einige Fälle von Hermaphroditismus, mit besonderer Brücksichtigung der Zwischenzellen. *Beitr. z. pathol. Anat.*, 67, p. 416.

KRABBE. 1921. The relation between the adrenal cortex and sexual development. *New York Med. Jl.*

KRAEPELIN. 1918. Geschlechtliche Verirrungen und Volksvermehrung. *Münch. mediz. Wochenschr.*, No. 5.

KRAUSE. 1923. Über experimentellen Hermaphroditismus. *Deutsch. Med. Wochenschr.*, Nr. 42.

KREDIET. 1921. Ovariotestes bei der Ziege. *Biolog. Zentralbl.*, 41, p. 447.

—— 1922. Eine Untersuchung der Geschlechtsdrüsen von dreissig neugeborenen Ziegen. Ein Fall von wahrem unilateralem Hermaphroditismus. *Anatom. Anz.*, 55, p. 502.

KREUTER. 1922. Hodentransplantation und Homosexualität. *Zentralbl. f. Chirurgie*, No. 16.

—— 1922. Weitere Erfahrungen über Hodentransplantation beim Menschen. *Deutsche Zeitschr. f. Chirurgie*, 172, p. 402.

LILLIE. 1916. The theory of the freemartin. *Science*, 43, p. 611.

—— 1917. The free-martin; a study of the action of sex hormones in the foetal life of cattle. *Jl. of Exper. Zool.*, 23, p. 371.

—— *and* BASCOM. 1922. An early stage of the free-martin and the parallel history of the interstitial cells. *Science*, N.S. 55, Nr. 1432.

—— 1923. Supplementary notes on twins in cattle. *Biolog. Bull.*, 44, p. 47.

(See also Bascom, Chapin, Minoura, Moore, Willier.)

LIPSCHÜTZ. 1918. Umwandlung der Clitoris in ein penisartiges Organ bei der experimentellen Maskulierung. *Arch. f. Entw.-Mech.*, 44.

—— 1918. Prinzipielles zur Lehre von der Pubertätsdrüse. *Arch. f. Entw.-Mech.*, 44.

—— *et* KRAUSE. 1923 a. Recherches quantitatives sur l'hermaphroditisme expérimental. *C. R. de la Soc. de Biol.*, 89, p. 220.

—— —— 1923 b. Temps de latence dans l'hermaphroditisme expérimental. *C. R. de la Soc. de Biol.*, 89, p. 1135.

(See also Krause.)

LOEB (Leo). 1918. The relations between the interstitial gland of the testicle, seminiferous tubules and the secondary sexual characters. *Biol. Bull.*, 34.

LÖSER *und* ISRAËL. 1923. Zur Pathologie und Diagnose des Pseudohermaphroditismus femininus externus als innerer Sekretionsstörung. *Zeitschr. f. Urol. Chir.*, 13.

*MAGNUSSON. 1918. Geschlechtslose Zwillinge. Eine gewöhnliche Form von Hermaphroditismus beim Rinde. *Arch. f. Anat. u. Physiol., Anat. Abt.*, p. 29.

MARSHALL *and* JOLLY. 1908. On the results of heteroplastic ovarian transplantation as compared with those produced by transplantation in the same individual. *Quart. Jl. of Experim. Physiol.*, 1, p. 115.

MATHIAS. 1921. (Necroscopia of the case of Asch, 1911 and 1921.) *Berl. klin. Wochenschr.*, No. 2, p. 39.

MATSUNO. 1923. Zur Kenntnis des Hermaphroditismus beim Menschen. *Arch. f. Gynäkol.*, 199, H. 2.

—— 1922. Über Geschwülste der Nebennierenrinde mit morphogenetischen Wirkungen. *Virchows Archiv*, 236, p. 446.

MATSUYAMA. 1921. Experim. Untersuch. mit Rattenparabiosen. III. Die Veränderungen der Geschlechtsdrüsen und der Organe, die damit im inniger Beziehung stehen. *Frankf. Zeitschr. f. Pathol.*, 25, p. 436.

MAYER (A.) 1918. Über die Möglichkeit operativer Eingriffe beim lebenden Säugetierfoetus. *Zentralbl. f. Gynäkol.*, 42.

MEISENHEIMER. 1909. *Experimentelle Studien zur Soma- und Geschlechtsdifferenzierung*, I. (Ch. V.). Jena.

—— 1912. *Experimentelle Studien zur Soma- und Geschlechtsdifferenzierung*, II.

*MEIXNER. 1921. Der Hoden eines Drüsenzwitters. *Wien. klin. Wochenschr.*, 34, p. 142.

MINOURA. 1921. A study of testis and ovary grafts on the hen's egg and their effects on the embryo. *Jl. of Experim. Zool.*, 33, p. 1.

MITTASCH. 1920. Über Hermaphroditismus. *Beitr. z. Pathol. Anat.*, 67, p. 142.

MOORE. 1920. The production of artificial hermaphrodites in mammals. *Science*, 52, p. 179.

—— 1921 a. On the physiological properties of the gonads as controllers of somatic and psychical characteristics. III. Artificial hermaphroditism in rats. *Jl. of Experim. Zool.*, 33, p. 365.

—— 1921 b. IV. Gonad transplantation in the guinea-pig. *Jl. of Experim. Zool.*, 33, p. 365.

MORGAN. 1919. *The genetic and the operative evidence relating to secondary sexual characters.* Carnegie Institution of Washington, Public. 285.

—— 1920. The effects of castration of hen-feathered Campines. *Biol. Bull.*, 39, p. 231.

—— 1923. The absence of lutear cells in the testis of the male phalarope. *Americ. Naturalist*, 57.

MÜHSAM. 1922. Endergebnisse der Hodenüberpflanzung. *Deutsche mediz. Wochenschr.*, No. 40.

NEUGEBAUER. 1908. *Hermaphroditismus beim Menschen.* Leipzig.

NEWMAN. 1917. *The biology of twins.* The University of Chicago Science Series. Chicago.

NONIDEZ. 1922. Studies of the gonads of the Fowl. III. The origin of the so-called luteal cells in the testis of the hen-feathered cocks. *Amer. Jl. of Anat.*, 31, p. 109.

PEARL *and* SURFACE. 1915. Sex Studies. VII. On the assumption of male secondary characters by a cow with cystic degeneration of the ovaries. *Annual Report of the Maine Agric. Experim. Station.*

—— *and* BORING. 1918. Sex Studies. XI. Hermaphrodite birds. *Jl. of Experim. Zool.*, 25, p. 1.

PEASE. 1922. Note on Prof. T. H. Morgan's theory of hen feathering in cocks. *Proc. Camb. Philos. Soc.*, 21, p. 22.

Peyron. 1922 a. Sur les tumeurs des glandes génitales. (Avec présentation de documents embryologiques.) *Bull. de l'Assoc. Franç. pour l'étude du Cancer*, 11.

—— 1922 b (Menetrier, Peyron, Isch-Wall et Lory). Deux observations de tumeurs de type séminifère, enlevées chez des sujes d'apparence féminine. Hermaphrodisme et pseudo-hermaphrodisme. *Bull. de l'Assoc. Franç. pour l'étude du Cancer*, 11.

Pézard. 1918. Le conditionnement physiologique des caractères sexuels secondaires chez les oiseaux. *Bull. Biol. de la France et de la Belgique.* (Thèse de Paris.)

—— 1922 a. Modifications périodiques ou définitives des caractères sexuels secondaires et du comportement chez les gallinacées. *Annals des Sc. Natur.* (*bot. et zool.*), p. 83.

—— 1922 b. Notion de "seuil différentiel" et explication humorale du gynandromorphisme des oiseaux bipartis. *C. R. de l'Acad. des Sc.*, 174, p. 1573.

—— Sand *et* Caridroit. 1923a. Production expérimentale du gynandromorphisme biparti chez les oiseaux. *C. R. de l'Acad. des Sc.*, 176, p. 615.

—— Sand *et* Caridroit. 1923 b. Le gynandromorphisme biparti expérimental. (Présentation de matériel.) *C. R. de la Soc. de Biol.*, 89, p. 1103.

—— —— —— 1923 c. Gynandromorphisme biparti fragmentaire d'origine male. (Présentation de matériel.) *C. R. de la Soc. de Biol.*, 89, p. 1271.

Pick. 1916. Über den waren Hermaphroditismus des Menschen u. der Säugetiere. *Berl. klin. Wochenschr.*, 53, p. 1142.

*Polano. 1920. Über wahre Zwitterbildung beim Menschen. *Zeitschr. f. Geburtsh. u. Gynäkol.*, 83, p. 114.

Priesel. 1921. Zur Kenntnis des Pseudohermaphroditismus mascul. int. mit "Dystopia transversa testis." *Frankf. Zeitschr. f. Pathol.*, 26, p. 80.

Punnett *and* Bailey. 1921. Genetic studies in poultry. III., Hen-feathered Cocks. *Jl. of Genetics*, 11, p. 37.

Romeis. 1922. Geschlechtszellen oder Zwischenzellen? *Klin. Wochenschr.*, 1, p. 960.

Sand. 1918a. *Experimentelle Studier over Kφnskarakterer hos Pattedyr.* Copenhagen.

—— 1918b. Experimenteller Hermaphroditismus. *Pflügers Archiv*, 173.

—— 1921. Etudes expériment. sur les glandes sexuelles chez les mammifères. *Jl. de Physiol. et Pathol. Génér.*, 19, p. 305.

SAND. 1922 a. Eensidig Gynaekomasti. *Festskrift til Rovsing.* Copenhagen.

—— 1922b. Hermaphroditismus (verus) glandularis alternans hos 10-aarigt individ. *Ugeskrift for Laeger,* 84, p. 921. (Also 1923. *Jl. d'Urologie,* 15, and *Skand. Archiv. f. Physiol.,* 44, p. 59.)

—— 1922c. De l'hermaphrodisme expérimental. *C. R. de la Soc. de Biol.,* 86, p. 1017.

—— 1922d. L'hermaphrodisme expérimental. *Jl. de Physiol. et de Pathol. Génér.,* 20, p. 472.

—— 1923. Experiments on the endocrinology of the sexual glands. *Endocrinology,* 7, p. 273.

SAUERBECK. 1909. Über den Hermaphroditismus verus und den H. im allgemeinen vom morphologischen Standpunkt aus. *Frankf. Zschr. f. Pathol.,* 3.

—— 1911. Der H. vom morphologischen Standpunkt aus. *Ergebnisse der Allgem. Pathol. u. pathol. Anat.,* 15, 1 Abt.

SCHMINCKE *und* ROMEIS. 1920. Anatomische Befunde bei einem männlichen Scheinzwitter und die Steinachsche Hypothese über Hermaphroditismus. *Arch. f. Entw.-Mech.,* 47, p. 221.

SCHULTZ (W.) 1910. Verpflanzungen der Eierstöcke auf fremde Spezies, Varietäten und Männchen. *Arch. f. Entw.-Mech.,* 29, p. 79.

SEXTON *and* HUXLEY. 1921. Intersexes in gammarus chevreuxi and related forms. *Biol. Assoc.,* 12, p. 506.

STABEL. 1922. Zum gegenwärtigen Stand der Hodenüberpflanzung. *Sexualreform und Sexualwissenschaft,* Stuttgart.

STEINACH. 1912. Willkürliche Umwandlung von Säugetier-Männchen etc. *Pflügers Archiv,* 144.

—— 1916 a. Experimentell erzeugte Zwitterbildungen beim Säugetier. *Anz. d. Akad. d. Wissensch.,* Wien, No. 12.

—— 1916 b. Pubertätsdrüsen und Zwitterbildung. *Archiv f. Entw.-Mech.,* 42, p. 307.

—— *und* LICHTENSTERN. 1918. Umstimmung der Homosexualität durch Austausch der Pubertätsdrüsen. *Münch. mediz. Wochenschr.,* No. 6.

—— 1919 a. Künstliche Zwitterdrüsen bei Säugern und Vögeln. *Anz. d. Akad. d. Wissensch.,* Wien, No. 11.

—— 1919 b. Die antagonistisch-geschlechtsspezifische Wirkung der Sexualhormone vor und nach der Pubertät. *Anz. d. Akad. d. Wissensch.,* Wien, No. 11.

STEINACH. 1919 c. Experim. u. histol. Beweise für den ursächlichen Zusammenhang von Homosexualität und Zwitterdrüsse. *Anz. d. Akad. d. Wissensch.*, Wien, No. 11.

—— 1920 a. Künstliche und natürliche Zwitterdrüsen u. ihre analogen Wirkungen. *Arch. f. Entw.-Mech.*, 46, p. 12.

—— 1920 b. Histologische Beschaffenheit der Keimdrüse bei homosexuellen Männern. *Arch. f. Entw.-Mech.*, 46, p. 29 (also *Anz. d. Akad. d. Wissensch.*, Wien, No. 11, 1919).

STERNBERG. 1921. Über Vorkommen und Bedeutung der Zwischenzellen. *Beitr. z. pathol. Anat.*, 69, p. 262.

TANDLER *und* GROSS. 1913. *Die biologischen Grundlagen der sekundären Geschlechtscharaktere.* Berlin.

TORREY *and* HORNING. 1922. Hen-feathering induced in the male fowl by feeding thyroid. *Proceed. Soc. Experim. Biol. a. Medic.*, 19, p. 275.

DE LA VAULX. 1921. L'intersexualité chez un crustacé cladocère. *Bulletin Biolog.*, 55, p. 1.

—— 1922. L'intersexualité. *Revue Génér. des Sciences*, 33, p. 174.

WAGNER (Karl). 1923. Experimentelle Untersuchungen über die Umwandlung des Geschlechts beim Frosch. *Arch. f. Entw.-Mech.*, 52, p. 386.

WEIL. 1921. Die Körpermasse der Homosexuellen als Ausdrucksform ihrer spezifischen Konstitution. *Arch. f. Entw.-Mech.*, 49, p. 538.

—— 1922 a. Körperproportionen und Intersexualität als Ausdrucksformen der inneren Sekretion. "*Sexualreform u. Sexualwissenschaft.*" Stuttgart.

—— 1922 b. Körperbau und psychosexueller Charakter. *Fortschritte d. Mediz.*, 40, No. 22–23.

WILLIER. 1921. Structures and homologies of free-martin gonads. *Jl. of Experim. Zool.*, 33, p. 63.

WITSCHI. 1921. Der Hermaphroditismus der Frösche und seine Bedeutung für das Geschlechtsproblem und die Lehre von der inneren Sekretion der Keimdrüsen. *Arch. f. Entw.-Mech.*, 49, p. 316.

ZAWADOWSKY (M. M.). 1922. *Das Geschlecht und die Entwicklung der Geschlechtsmerkmale.* (Russian with German summary.) Moscow.

—— 1923. *The sex of animals and its transformation* (Russian). Moscow–Petrograd.

—— (B. M.) 1923. Effect on thyroid feeding of fowl. (Russian, with German summary.) *Proceed. of the Sverdlov University in Moscow*, p. 1.

ZIETZSCHMANN. 1920. Über die Genitalmissbildung beiverschiedengeschlechtigen Zwillingen des Rindes. *Schweiz. Arch. f. Tierheilk.*, Heft 6.

Chapter X.

Eunuchoidism and Sexual Precocity.

THROUGHOUT our discussion of intersexuality two important points have been emphasized: first, the *quantity* of male and female sexual hormones simultaneously or successively influencing the soma; secondly, that the great variability observable in intersexuality may be partly due to another quantitative factor, namely, the *time* at which changes in the quantities of male and female sexual hormones take place, and the different response by the individual parts of the organism at different periods.

Quantitative problems will also be the subject of this chapter. If certain quantities of hormones of a monosexual sex gland be necessary for the normal development of the sex characters, for their preservation and for a normal erotization of the individual, the question arises as to how far the sex characters will vary with diminution or augmentation of these quantities.

If the hormonic activity of the sex gland is diminished on account of underdevelopment or atrophy beneath the threshold or the minimal quantity necessary for normal masculinization or feminization, the organism will acquire the characters of the "castrate"; the appearance of these characters will depend very much upon the time at which underdevelopment or atrophy set in; there will be all transitions between an early or a late "castrate." On the other hand, variations in the quantity of the sexual hormones beyond the threshold quantity (see Chapter IV.) will not be prejudicial as long as the response to the sexual hormones on the part of the different tissues or of the soma in general remains normal. But if, owing to some endocrine or other disturbance, the capacity to respond changes, an alteration in the quantity of the hormones may be of very great importance, even if the quantity is far beyond the normal threshold.

Let us now discuss the results of an augmentation in the quantity of the sexual hormones. At first sight it might seem that no change in the development of sex characters will take place, since the maximal hormonic effect is very likely already attained when the threshold quantity of hormones is produced. But one must not forget that the position is really a much more complicated one than it is in an experiment with partial castration. It suffices to recall in how far-reaching a way the hormonic effect in the female seems to be dependent upon the quantity of hormones produced. Further, an augmentation in the quantity of hormones during childhood may cause an accelerated development of all the characters dependent upon the sexual hormones. Sexual puberty will be attained sooner than normally; there will be a sexual precocity. One might suppose that those cases of sexual precocity which are not complicated by other pathological or teratological factors, later on will become sexually normal. If the augmentation in the quantity of sexual hormones sets in at a period at which all the somatic sex characters are already definitely fixed, probably no change as to hormonic effects will take place. The psycho-sexual behaviour which is so variable, might, however, depend upon these quantitative changes; but as already said in a foregoing chapter, the psycho-sexual behaviour in man depends so largely upon different external factors transformed into psychical coefficients that it is very difficult to examine psycho-sexual behaviour on a purely endocrine basis.

We will now examine the question as to how far clinical and anatomical observation is in accordance with these theoretical considerations. The subject presents great difficulty, as we have no way of estimating the quantities of the sexual hormones beyond what we can learn from an anatomical and histological examination of the gonads.

A. EUNUCHOIDISM.

A great many cases of underdeveloped male sex characters have been carefully studied in the last few years. The papers of *Tandler and Gross* (1910), *Hirschfeld* (1916, case A, and 1917), *Wildbolz* (1917), *Josefson* (1915), and *Furno* (1922) may be referred to here. I mention these papers from my own knowledge, but the number of similar observations which I have not verified is very great. The literature will be found in the above-mentioned papers. The individuals with underdevelopment of the sex glands are now usually called *eunuchoids,* as in general type they resemble the eunuch; the term was introduced by *Griffith and Duckworth* (quoted from Tandler and Gross, 1913).

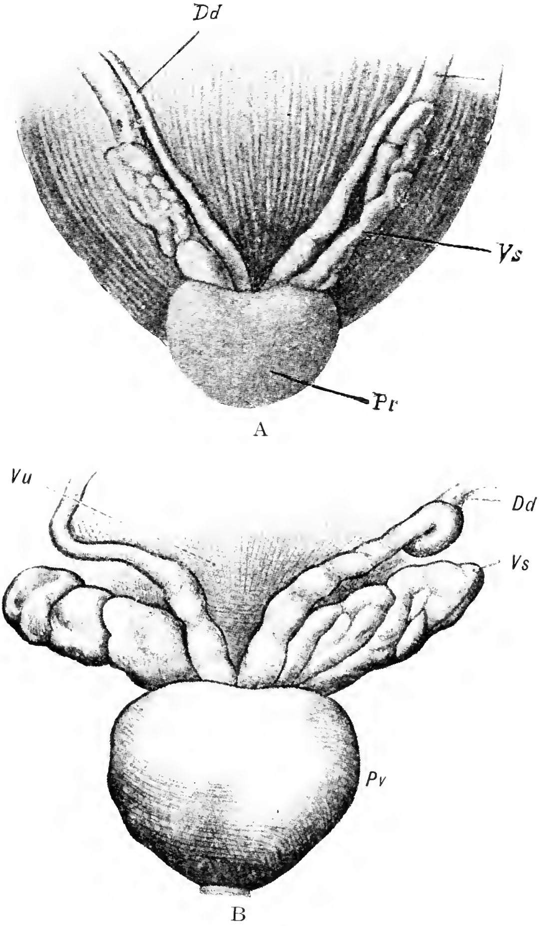


FIG. 132.

A. *Prostate and seminal vesicles of a eunuchoid of 28.* Pr.=prostate; Vs.=seminal vesicles; Dd.=ductus deferens. To be compared with B., where the prostate and the seminal vesicles are larger, the vas deferens broader.—From Tandler and Gross.

B. *Prostate and seminal vesicles of a normal adult man.*—From Toldt.

In the eunuchoid we find all morphological and physiological signs of castration without castration having taken place (*Fig.* 132). The penis, the prostate and the seminal vesicles are smaller than in normal individuals. The face is hairless, whereas the eyebrows and the hair of the head are well developed. Hair is absent on the trunk. The hair in the axillae and in the regio pubis is very poor; the upper limit of the hair in the regio pubis is a straight line. The skin very soon becomes yellowish and wrinkled. If sexual activity still occurs, it is generally incomplete and of a short duration. The testicle is as a rule abnormally small (*Fig.* 133). In some cases it was impossible to find any testis, as for instance in that of Wildbolz, who examined the abdominal cavity during an operation and found no trace of this organ. It is very probable that in such cases testicles, normal or underdeveloped, were originally present, and that they degenerated very early without any obvious cause. *Halban* (1922) recently pointed out that in principle bilateral anorchism may exist, as there are some cases where a unilateral anorchism was observed.

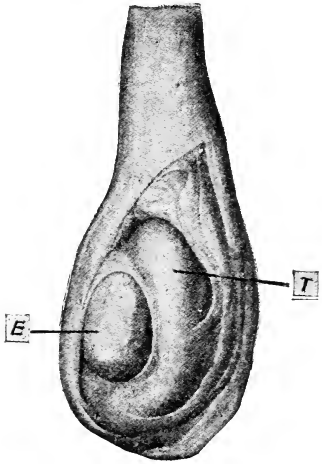


Fig. 133.—*Testicle and epididymis of eunuchoid of* 28. Well developed epididymis and much reduced testicle.—From Tandler and Gross.

There are, as Tandler and Gross showed, different types of eunuchoids such as the "tall eunuchoid" with a much accentuated disproportion in the parts of the skeleton, and the "fat eunuchoid," where the disproportion is less marked. In these types there seems to be an analogy to what is observed after castration; as we have mentioned in Chapter II., similar types have been recognised by Tandler in the Skopecs. Lately *Koch* (1921), who very carefully examined the Skopecs, has proposed an even more detailed classification according to four different types. Furno distinguishes the following four different clinical types of eunuchoids:

(*a*) *Pure eunuchoidism* as caused by deficiency of gonad only;

(*b*) *Gerodermic eunuchoidism,* where there is also a pathological state of the thyroid and the hypophysis;

(*c*) *Acromegalic eunuchoidism,* where there is also a pathological state of the hypophysis;

(*d*) *Eunuchoid feminism,* where the effects are possibly produced by heterosexual hormones.

Furno's classification takes account of the fact that probably only a small number of cases of eunuchoidism are of gonadal or monoglandular origin, the majority being of other or pluriglandular origin; in these latter cases the hypogenitalism or underdevelopment of the testicle seems to be caused secondarily by some pathological disturbance in another endocrine gland. It might also be possible that the response of the soma to sexual hormones is changed by some endocrine disturbance without the testicle itself being affected.

As I have no personal clinical experience I do not wish to dwell longer on these problems. But I think that it must be very difficult to discriminate in individual cases whether the underdevelopment of the testicle is a primary or a secondary one. The underdevelopment of the testicle in a "fat eunuchoid," to use the classification of Tandler, may be primary or secondary, since castration may also lead to the development of a similar type, by interfering with the function of the hypophysis.

The histological examination of the reduced testicle of the eunuchoid usually shows a degeneration of the generative part. But in some cases complete spermatogenesis may take place temporarily, as many eunuchoids have had children, and eunuchoidism may be hereditary, as was shown by Furno.

In the development of the interstitial cells there seems to be great variability; they have been described as being present in some cases in normal quantity and in normal condition, whereas in others the interstitial tissue was in a decidedly abnormal condition. The question has lately been studied by *Berblinger* (1921). He described a man of 26 with certain signs of eunuchoidism. Both testicles were reduced in weight. There was a partial underdevelopment of the seminiferous tubules, but highly developed interstitial tissue. The interstitial cells were not only very numerous, forming great masses of cells, but also hypertrophied. Berblinger concludes from this observation that the interstitial cells cannot play the important endocrine rôle ascribed to them, since eunuchoidism was present notwithstanding the great development of the interstitial tissue. I think that this conclusion is unjustified. Berblinger states that some spermatozoa were to be found in the left seminal vesicle in the case described; evidently the left testicle, which was less atrophied than the right one, temporarily produced spermatozoa. So one might conclude that the generative cells have not the endocrine function ascribed to them. And the position might then be summed up in the conclusion that the testicle has no endocrine function at all! Such a case is, indeed, very instructive, showing how discrepancy between experimental and pathological data cannot be used as a proof against a theory built up on an experimental basis. A case like that of Berblinger might be explained in two different ways; first, it is possible that the interstitial cells, though histologically normal, were functionally abnormal, as seems possible in view of some of our experiments (1922 a, 1923); secondly, it is possible that the soma had not the normal capacity for response to sexual hormones owing to some other disturbing factor, possibly of an endocrine nature.

In view of the experimental data as given in Chapter IV, considered in conjunction with the clinical data, I think that eunuchoidism in man can be explained in the following way. Since minimal quantities of testicular substance and also, as we suppose, minimal quantities of sexual hormones are sufficient for a normal masculinization, we must suppose that eunuchoidism depends, as I have emphasized (1921, 1922), not upon variations in the quantities of hormones produced, but upon a complete suppression of the hormonic activity of the sex gland. This suppression might be due to an infantilism or to a retrograde development on the part of the sex gland, as in those cases where eunuchoidism develops in adults previously normal. This infantilism or backward development of the testicle may be primary or secondary; in the latter case some other endocrine disturbance may cause the deficiency of the sex gland. There is evidently no hard and fast line to be drawn between the cases with a primary deficiency of the sex gland and those cases where the deficiency of the sex gland is a secondary one, the interrelations between the sex glands and other organs of internal secretion being very manifold. There are, besides cases of decided eunuchoidism, transitional stages between eunuchoidism and normal sexual activity of the highest

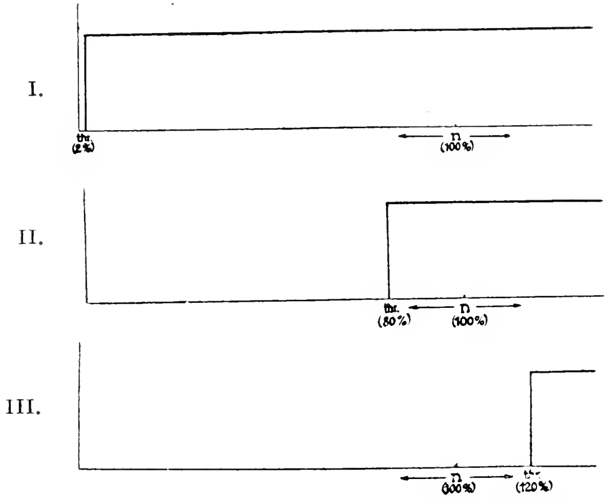


FIG. 134.—*Diagrams to illustrate how a changed capacity on the part of the central nervous system to respond to sex hormones interferes with erotization, without the hormone-production being disturbed.*

Abscissa=quantity of hormones; *n*=normal or average quantity of hormones produced; *thr*=threshold quantity, i.e., the quantity of hormones necessary for erotization when the response of the soma is a normal one. The *thr* may be normally of about 1 to 2 per cent. of *n*. Ordinates=the degree of erotization. The arrows indicate that there is in the normal individual a *physiological variation* in the quantity of hormones produced.

I. *Normal condition.* The erotization is a normal one, notwithstanding the great quantitative variations of hormone-production. The low limit of *thr* will never be attained, however great the variations of hormone production are.

II. *Disturbed erotization.* *thr* is about 80 per cent. of *n*, i.e., the capacity to respond to sex hormones is reduced; normal erotization will take place only when 80 per cent. of the average quantity of hormones is produced. *When the physiological variations of hormone-production surpass this limit downwards there will be a disturbed erotization, whereas these quantitative variations do not harm an individual with a normal capacity to respond* (I.).

III. *Disturbed erotization.* *thr* is about 120 per cent. of *n*, i.e., the capacity to respond is much reduced; normal erotization will take place only when 120 per cent. of the average quantity of hormones is produced. *When the physiological variations surpass this limit upwards there will be a normal erotization, otherwise there will be a disturbed or eunuchoid psycho-sexual behaviour.* Whereas case II. will be *sometimes eunuchoid*, as to the psycho-sexual behaviour, but *mostly normal*, case III. will be *mostly eunuchoid* and only *sometimes normal.* The somatic sex characters may remain quite normal in II. and III. If we could condition in such an individual an exaggerated production of sex hormones in such a manner that say 150 per cent. instead of 100 per cent. hormones are produced, there would be again a normal erotization, the average quantity of hormones then remaining always higher than 80 or 120 per cent.

degree. Now if minimal quantities of sexual hormone are sufficient for a normal erotization, it follows that the differences which occur in regard to the erotization of the individual cannot be really caused by a disfunction of the sex gland.

So, besides cases of eunuchoidism with a primary or secondary suppression of the hormonic activity of the sex gland, there may be recognized a second group in which the response by the soma to sexual hormones is changed; in these cases variations in the quantity of sexual hormones even far beyond the normal threshold quantity might cause eunuchoidism, and especially disturbances of erotization (*Fig.* 134). We must suppose that in erotization also some other factor is involved besides hormones. We must not forget that the psycho-sexual behaviour depends very greatly upon the condition of the nervous system, and only partly on the endocrine organs.

Eunuchoidism in *women* is a question of great practical importance. We find in these cases the following symptoms: a disproportion of the body growth characteristic of the "castrate," i.e., abnormally long extremities, in the gluteal region and in the upper part of the abdominal wall less fat than in the normal woman, a deficiency of hair in the regio pubis, an underdevelopment of the breasts, and, finally, the symptoms which are of such great importance for the gynæcologist, the abnormally small uterus and the irregularity or non-occurrence of menstruation.

There have been many controversies as to eunuchoidism in women from a clinical point of view, as may be seen in *Aschner's* book (1918, p. 169), where this question is examined in great detail. But all authorities agree that the state of "eunuchoidism" is connected with ovarian deficiency. The ovaries are small and difficult to feel. The histological examination reveals an infantile condition, follicular development not having taken place or being very incomplete.

At first thought it might seem that the theory of eunuchoidism in women can be formulated on quantitative lines without great difficulty, as it is generally admitted that all the quantitative variation in sexual development and sexual life in normal women is due to a certain degree to quantitative variation in the endocrine function of the ovary. But there is in regard to the dependence of the hormonic effect upon the quantity of hormones such a striking difference between man and woman that I cannot repress the feeling that we are still very far from a true insight into the quantitative side of the question.

B. SEXUAL PRECOCITY.

Many cases have been described in which such sex characters as the penis and the hair of the regio pubis were developed in boys at a very early age instead of at or shortly after puberty, and similarly with the larynx and the voice. Erotization also can take place very early, and erections and pollutions may occur. Examples are to be found in the extensive paper of *Neurath* (1909). *Krabbe's* case (1917) was a boy of 10 months with a penis five cm. long and of a virile type. The scrotum was voluminous and limp. The skin of the penis and of the scrotum was strongly pigmented. There was a crown of dark short puberal hairs around the radix penis. There was no hair on the face, in the axillae or on the perineum. Definite erections were often observed. No signs of disturbance of the hypophysis are recorded; the child showed various nervous troubles of a spastic character and was imbecile. It should be pointed out, however, that concomitant disturbances are not always present in cases of sexual precocity. The individuals may be harmoniously developed in every somatic respect, there being not only a precocity of sexual development, but at the same time also a precocity of somatic development in general. An interesting case of this kind has been described by Obmann and *Hirschfeld* (1917). A boy of 4 with milk teeth had genitalia like a boy of 16 or 18; the voice was like that of an adult man. The boy had a body height of 121 cm. against 100 cm. for normal children of this age, and weighed 68 gr. against the normal 28. The boy was observed by Hirschfeld doing hard agricultural work. A similar case was recently observed by Professor Masing in Dorpat, and through his kindness I have had the opportunity of seeing this case myself also. This boy of 3 years and 3 weeks was highly developed in every respect. Figure 135 in which a photograph of the patient is shown along with a normal boy of the same age is sufficient to give an idea of the high somatic development attained in this case. The body length was 113 cm. against a normal body length of about 90 cm. at the same age; the real body length was even greater as the boy had highly pronounced bow legs. The circumference of the head was 55 cm., against a normal one of about 49. There were no clinical signs of a cerebral tumour. The penis had a length of 7 to 8 cm. The scrotum was voluminous and the testicles were as big as in a boy after puberty. The hair of the regio pubis was highly developed but the upper limit was sharply marked, the triangle characteristic of the adult being absent. In the axillae only a few hairs were to be seen. An erection was observed when the boy

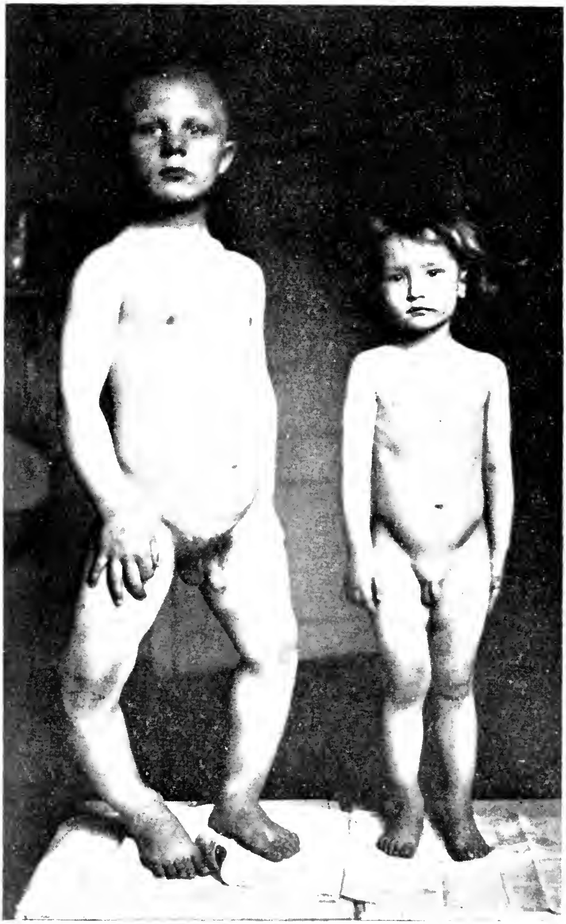


FIG. 135.—*Pubertas praecox in a boy of three.* Patient standing beside normal boy of just same age.—By kind permission of Masing.

was in the hospital. There were no signs of acromegaly. The boy was very strong and helped in the household even in such heavy work as carrying wood. His mental development was far beyond his age. His behaviour towards his surroundings was that of a boy of 7 or 8. He did not care to amuse himself with his elder sister, declaring her to be still "a child." While being photographed with a normal boy, he expressed great astonishment at seeing such a small penis and a regio pubis without any hair.

FIG. 136.—*X-ray picture of the hand of a girl of 13½ with sexual precocity.* Nat. size. The epiphyseal lines have disappeared.—Photo kindly lent by Krabbe.

A local paper described this case anticipating that the boy would become a giant. This prognosis, however, is entirely erroneous, as the body size of individuals showing sexual precocity in general is not beyond the normal. There are cases even in which the precocious individual attains a smaller size than the normal one. This is due to the fact that the growth of the bones stops sooner than in normal individuals. The condition of the skeleton in sexual precocity is the opposite to what we observe in eunuchoidism; in the latter the suppression of the endocrine function of the sex gland causes a more prolonged persistence of the zone of proliferation in the long bones, whereas in sexual precocity an exaggerated hormonic activity of the sex gland causes disappearance of the zone of proliferation sooner, and thereby the growth of the long bones comes to an end precociously.

This may be illustrated by the following case of *Krabbe* (1919), which may also serve as an example of sexual precocity in women. A girl menstruated regularly from her birth, and from the beginning had developed mammary glands. She grew well up to her 7th year, having then attained an abnormal height. Afterwards growth ceased. At 13½ years of age she was 131 cm. in height as compared with 145 cm. in normal individuals. The under extremities were strikingly short in relation to the trunk—just the opposite of what is to be observed in eunuchoidism. The zones of proliferation in the bones of the upper and under extremities had disappeared; the photograph of her hand may serve as an example (*Fig.* 136). In cases of sexual precocity in women there is also precocious development of the hair in the regio pubis and in the axillae. In Krabbe's case the girl was psychically normal, and there was no erotization, though at 13½ she was somatically entirely mature.

The question whether sexual precocity can be interpreted on an hormonic basis is naturally of great interest for us. First, it must be questioned whether sexual precocity can be explained by a precocious development of the sex gland. We do find in such cases a precocious development of the sex gland, as, for instance, in the above-mentioned case of Masing, and presumably also in those cases where precocious menstruation occurs. But there is no reason for assuming that the precocious development of the sex gland is always of primary origin in these cases; it is possibly often only a secondary phenomenon caused by some other endocrine disturbance. But it is probable that if the sex gland has entered into a precocious development, the latter will lead to a precocious development of sex characters. In some cases tumours of the testicle and of the ovary have been factors. Sacchi's case (quoted from *Neurath*, 1909, p. 71) is instructive. Signs of sexual precocity became visible in a boy at an age of 6. The left testicle was enlarged, and attained the size of that of an adult man. At the age of 9 the boy was 143 cm. high, he had hair on the face, and the sexual organs were extremely large. Now the highly enlarged left testicle was removed. Some months after the operation the signs of sexual precocity disappeared. Instead of the beard, only down was present. The penis was shorter and thinner. The sexual libido, pollutions and erections which were previously experienced ceased. The general psychical behaviour of the boy became more childish. The tumour of the testicle is stated to have been a glandular carcinoma. As to women a number of cases have been described in which sexual precocity was associated with ovarian tumours. *Bell* (1920, p. 154) holds the opinion that sexual precocity in girls must always be considered in relation to ovarian neoplasm and hyperplasia. Cases have also been recorded in which symptoms of sexual precocity disappeared after removal of the tumour. The relevant paragraph in Bell's book may be referred to here.

In many other cases tumours of the adrenals have been recorded. The question about the relation between the adrenals and sexual precocity has been lately discussed by *Krabbe* (1921). He assumes that the cells of the adrenal tumour are by no means normal adrenal cortex cells influencing testicular development, and thereby causing indirectly precocity in the development of sex characters, but that these cells have the same hormonic quality as the hormone-producing cells of the testicle, and directly influence the soma, causing sexual precocity in the male sex. Krabbe argues further that the cases described as "sexual precocity" in woman, as caused by adrenal tumours, are not really such. In these cases a development of the pubic hair and beard or a condition of general hypertrichosis, a great hypertrophy of the clitoris and transformation of the voice into a male-like one have been observed, whereas menstruation and precocious development of the uterus is only extremely rare, having been recorded only once in the data collected by Krabbe. According to Krabbe all these symptoms can be taken as evidence not of sexual precocity, but of virility or hermaphroditism in female individuals with adrenal hyperplasia. A similar view is held by Bell. Krabbe has elaborated the hypothesis that the cells of the adrenal tumour originate from "foetal testicular cells which have been absorbed by the adrenal cortex." This assumption is very suggestive, especially if we take into consideration that in the majority of the cases of sexual precocity in women where an adrenal tumour was *not* mentioned, there was a precocious development of the mammae and of the uterus with the occurrence of menstruation. A recent observation of *Pézard* (1922) is in favour of Krabbe's suggestion. Pézard recorded in three incompletely castrated cocks an interpenetration between the testicular fragment and the adrenal on which the small fragment was located. Medullary cells in full activity were found surrounding or even entering into underdeveloped seminal tubules; seminal tubules were found incorporated in the middle of the adrenal. Pézard concludes that the embryological relationship between seminal and cortical tissue is thus corroborated physiologically, both tissues supplying the conditions necessary for the secretory activity of medullary cells. But on the other hand the statement of *Matthias* (1922) that the adrenal tumour may be connected with feminization of the male individual is opposed to Krabbe's assumption. The observation of Matthias is, indeed, quite unique.

It is well known that sexual precocity is sometimes connected with tumours of the pineal gland. Such tumours have been described in boys and girls, the tumour in general being a teratoma, though other forms of tumours also have been observed. Sexual precocity connected with pineal tumours has been recorded only for boys. This latter fact is of great interest in relation to the question of the connection between the pineal tumour and sexual precocity. *Marburg* (1920) suggested that sexual precocity is caused by precocious destruction of the pineal by the tumour, there being a precocious involution of the pineal, which normally undergoes decrease during development. On the contrary, *Askanazy* (1921) holds the opinion that the teratoma developing in the pineal gland is the factor causing sexual precocity. Both these theories seem to be insufficient. That of Marburg does not conform with the fact that sexual precocity as connected with pineal tumours has been observed only in boys, never in girls. On the other hand, the fact that sexual precocity is absent when normal pineal tissue is present besides the tumour seems to support Marburg's theory. The theory of Askanazy is opposed by the fact that sexual precocity has been observed in boys also where the pineal tumour was a sarcoma. But Askanazy's assumption that the tumour of the pineal is the active factor in sexual precocity contains, I think, some truth. One might suppose that the pineal tumour represents, like the hypernephroma, a masculinizing factor. Two observations came to my notice which might give support to such a suggestion. The first is the case described by *Boehm* (1919) of a boy of 9 with very pronounced signs of sexual precocity (external genitalia, pubic hair, male voice). On account of the latter it was assumed *intra vitam* to be a case of a pineal tumour. Necroscopia showed that the diagnosis was a right one. It was a teratoma containing as usual different kinds of tissues. Besides, there were also big cells of an epithelioid character with much protoplasm and a spherical vesicular nucleus. The author insists that these cells had a striking resemblance to the interstitial cells of the testicle. According to him there must be some interrelation between the pineal and the male sex gland. The second observation I should like to mention here is that of *Baar* (1920), who described a girl of 5 with pubic hair and an enlarged clitoris and of a height of 121 cm. There was no menstruation. The symptoms remind one very much of those generally described in cases of adrenal tumours. But Baar insists on the ataxia of the under extremities, which was recorded in this case. There were also temporarily intensified reflexes and a patellar *clonus*. Baar is of the opinion that the described symptoms must have been caused by a pineal tumour. If this really was so, one might suppose that the described symptoms, which are identical with those in girls with adrenal tumours, were caused by a masculinizing factor abnormally present in the pineal. But it must be said that Baar's diagnosis is insufficiently proved.

We see that our knowledge of the factors conditioning sexual precocity as far as it can be based on clinical data is still very incomplete. I find no real basis for a proper explanation of the condition, though various experiments with administration of thyroid or hypophysis and with removal of the pineal gland perhaps give some indication of an hormonic basis for sexual precocity. The paper of *Krabbe* (1923) may be referred to here.

Steinach (1916) claims that sexual precocity may be observed in guinea pigs and rats. According to him the precociously developed male rat can be recognised by the occurrence of a hairiness at a time when the other animals of the litter are still bare. The precocious animal is said to grow quicker than the normal one, and the penis, prostate and seminal vesicles to develop earlier; erection and sexual activity may be observed. According to Steinach in such animals there is also a normal development of the seminal tubules, but an hypertrophy of the interstitial cells. But these observations, in my judgment, are not very convincing.

BIBLIOGRAPHY TO CHAPTER X.

ASCHNER. 1918. *Die Blutdrüsenerkrankungen des Weibes.* Wiesbaden.

ASKANAZY. 1921 (?). Die Zirbel und ihre Tumoren in ihrem funktionellen Einfluss. *Frankf. Zeitschr. f. Pathol.*, 24, p. 58.

BAAR. 1920. Makrogenitosomia praecox—Zirbeltumor. *Zeitschr. f. Kinderheilkunde*, 27, p. 143.

BELL. 1920. *The Sex-Complex.* London.

BERBLINGER. 1921. Über die Zwischenzellen des Hodens. *Verhandl. d. deutschen patholog. Gesellsch.* Jena.

BIEDL. 1913. *Innere Sekretion*, Vol. II., 2nd edition. Berlin-Wien (p. 255).

BOEHM. 1919. *Zirbeldrüsenteratom und genitale Frühreife.* Med. Inaug.-Diss. Heidelberg.

FURNO. 1922. Studio di genetica e di clinica sopra cinque casi di eunucoidismo eredo-familiare. *Rivista di Pathol. nerv. e mentale*, 26, p. 245.

HALBAN. 1921. Keimdrüse und Geschlechtsentwicklung. *Archiv f. Gynäkologie*, 114.

HIRSCHFELD. 1916. Über Geschlechtsdrüsenausfall. *Neurolog. Zentralblatt*, No. 8 and 9.

—— 1917. *Sexualpathologie*, Vol. I. Bonn.

JOSEFSON. 1915. *Om endokrina skelett—och utvecklingsrubbningar.* Stockholm.

KOCH (Walter). 1921. *Über die russisch-rumänische Kastratensekte der Skopzen.* Jena.

KRABBE. 1917. Pubertas praecox. *Hospitalstitende,* No. 48 (Scandinavian literature).

—— 1919. Early synostosis of the epiphyses with dwarfism in pubertas praecox. *Endocrinology,* 3, p. 459.

—— 1920 (?). L'infantilisme. *Nordiskt Medicinskt Arkiv,* 51, p. 551.

—— 1921. The relation between the adrenal cortex and sexual development. *New York Medical Jl.,* July.

—— 1922. Om forholdet mellem tuberœs hjaernesklerose, hydrocephalus og pubertas praecox. *Bibliotek for Laeger,* 114, p. 1.

—— 1923. The pineal gland, especially in relation to the problem of its supposed significance in sexual development. *Endocrinology,* 7, p. 379.

LIPSCHÜTZ, OTTOW *et* WAGNER. 1921. Sur le ralentissement de la masculinisation dans la castration partielle. *C. R. de la Soc. de Biol.,* 85, p. 630.

—— WAGNER *et* BORMANN. 1922a. Ralentissement expérimental de la masculinisation. *C. R. de la Soc. de Biol.,* 86, p. 238.

—— 1922b. L'ipogenitalismo dal punto di vista sperimentale. *Rassegna di Studi Sessuali,* 2, p. 132.

—— 1923. New experimental data on the question of the seat of the endocrine function of the testicle. *Endocrinology,* 7, p. 1.

MARAÑÓN. 1922. *Problemas actuales de la doctrina de las secreciones internas.* Madrid.

MARBURG. 1920. Neue Studien über die Zirbeldrüse. *Arbeiten des Neurolog. Instit. a. d. Wiener Universität,* 23, p. 1.

MATTHIAS. 1922. Über Geschwülste der Nebennierenrinde mit morphogenetischen Wirkungen. *Virchows Archiv,* 236, p. 446.

NEURATH. 1909. Die vorzeitige Geschlechtsentwicklung. *Ergebnisse der inneren Med. u. Kinderheilkunde,* 4.

PÉZARD *et* CARIDROIT. 1922. Interpénétration surrénalo-testiculaire chez des coqs castrés incomplètement. *C. R. de l'Acad. des Sc.,* 175, p. 784.

STEINACH *und* HOLZKNECHT. 1916. Erhöhte Wirkungen der inneren Sekretion bei Hypertrophie der Pubertätsdrüsen. *Arch. f. Entw.-Mech.,* 42, p. 490.

TANDLER *und* GROSS. 1910. Über den Einfluss der Kastration auf den Organismus. III. Die Eunuchoide. *Arch. f. Entw.-Mech.,* 29, p. 290.

WILDBOLZ. 1917. Ein Fall von kongenitaler Anorchie. *Corr.-Blatt f. Schweizer Aerzte,* No. 39.

CHAPTER XI.

Sexual Hormones and Morphogenesis.

THE important bearings of the morphogenetic influence of the sexual glands on the development of the organism may be again discussed here from a more general point of view.

A. THE ASEXUAL EMBRYONIC SOMA.

The well known facts concerning castration in men and mammals seemed to render it very probable that the organism after removal of the sex gland assumes a type common to both sexes, though this was not always equally clear for all animals. The pelvis of the sheep castrated at an early age, the skull of the ox and of the castrated cow, the plumage and the spurs of the castrated hen and cock, may be recalled in this connection. An "*asexual*" type (*Tandler* and co-workers, 1910, 1913) or a "neutral" form (*Pézard*, 1915, 1918) is the result of the operation in each case.

It has often been said that the mammal becomes transformed into the type of the opposite sex. The accumulation of fat, and loss of beard in the eunuch, and the hair on the chin of the woman at the menopause seemed to prove this. But as Tandler and Gross have pointed out, the accumulation of fat in the eunuch is very different from what is characteristic of the normal woman, the localization of the fat in the former being different from that of the latter. Lately, *Koch* (1921), who again examined the Skopecs in Rumania, came to the same conclusion as Tandler in regard to this question. As to the beard of the old woman, it may be mentioned that the number of individuals having this character is relatively extremely small and absolutely insufficient to admit of such important conclusions being drawn as has been done. Besides this, Tandler and Gross report that a similar growth of hair on the chin may be observed also in the eunuch. Further, assumption of certain characters of the opposite sex does not prove that there is a transformation into the type of the latter.

It is true that the castrated hen assumes the plumage and the spurs of the cock; but the castrated cock-feathered hen does not resemble the normal cock, but the capon. On the other hand the castrated cock does not assume the characters of the hen, and whereas cock-feathering is very often to be found in old hens, hen-feathering in cocks is a very rare phenomenon. So it is clear that there is no mutual transformation of one sex into the other in birds after castration, but only an assumption of a common or neutral form by the male and female; this common form is very like the male one.

Several authors such as *Tandler and Keller* (1910), *Tandler and Gross* (1913, pp. 29 and 133) and *Kammerer* (1912) have discussed the occurrence of the asexual type in relation to phylogenetic questions also. But here we shall confine ourselves to the embryological side of the problem.

Basing his position upon observations on castrated birds, Pézard suggested that in birds there is a "neutral" form also during embryonic development.

In accordance with the view held by Tandler and his co-workers and by Pézard, I suggested (1917, 1918 a) that during embryonic development the soma in mammals and birds is asexual, and that differentiation of male and female sex characters begins only after the differentiation of the hormone-producing sex gland has taken place. Such a suggestion implies that the male and female hormones have a different or, as I said, a sex specific effect. The experiments of Steinach with feminization and masculinization, which have been fully confirmed by the numerous observations of Athias, Brandes, Goodale, Lichtenstern, Lipschütz, Minoura, Moore, Pézard, Sand and Zawadowsky, leave no doubt about this latter point. It cannot be denied that the sex gland also produces hormones which have no sex specific effects; the experiments of Steinach and Meisenheimer on the frog, and certain observations on castrated hens as related in Chapter IX. seem to prove this. But the fact that the sex glands produce hormones which are able to modify the organism in a sex specific manner must be regarded as definitely established

The view I put forward on this question in the first edition of this book has been discussed and much contested by different authors. But on the other hand some authors, who base their position on experimental work, came to conclusions similar to mine.

Zawadowsky (1922), who has performed a great many experiments on fowls, also came to the conclusion that the soma of the male and female is essentially identical, and that sexual differentiation of the soma is caused by the influence of specific sex hormones. He likewise speaks of an asexual type which develops after removal of the sex glands. The term "equipotentiality of the soma," which is also used by Zawadowsky, seems to me more convenient, as it leaves the door open for adopting our view in regard to possible new facts which might not conform wholly with the original and more radical meaning implied by the term "identity." Zawadowsky mentions some facts which are opposed to the idea of an absolute identity of male and female soma; absence of spurs in castrated female pheasants may be taken as an example. But on the other hand in every such case the question must be put as to how far the deviation from the common neutral or asexual type after castration is caused by the removal of the sex glands having been performed late. We shall discuss this question again below.

Zawadowsky has drawn similar conclusions as to the existence of an identical soma from observations made on the results of castration on mammals. In the antelope *Portax pictus* the grey hair of the male is transformed more or less into the brown hair characteristic of the female; the transformation takes place at the first moult after castration. He made similar observations about other species, fully confirming the view developed by Tandler and his fellow workers many years ago.

For amphibians, Aron, as well as Champy, who made detailed investigations as to the dependence of the sex characters on the sex gland, have accepted the hypothesis of the asexuality of the soma. *Aron* (1922) says that the male and female triton are morphologically identical except in the gonads: "Whereas the soma apparently remains for a longer or shorter time asexual, the gonad is differentiated very early and without doubt is fixed from the beginning of development. At a different time, which varies according to the classes and species of vertebrates, the testicle most likely becomes, by intermediation of an endocrine tissue, the starting point of the general influence which leads to the first differentiation of the soma." *Champy* (1922, p. 157) writes: "I accept for the tritons and in a general way for vertebrates the hypothesis of Lipschütz on the asexuality of the embryonic form; this hypothesis is the expression of common sense. As long as I am unable to distinguish the sex in the embryo I regard it as having no sex."

On the other hand certain facts have been related which do not seem to conform with our hypothesis. *Riddle* (1920) finds that there is from the beginning "a metabolic difference between the ova (egg yolks) which give rise to the two sexes in doves"; female-producing eggs appear to have a lower metabolism than male-producing eggs. In accordance with this observation Riddle stated that female-producing eggs are better able to survive a decreased oxygen pressure than male-producing eggs. But I do not find that such a statement is really opposed to our hypothesis, which by no means denies, as will be made clear in the next section, the existence of biochemical differences between male- and female-producing eggs. *Lillie* (1923) says that it is not evident as to whether the hypothesis that the embryonic soma is primarily asexual is to be understood to presuppose the zygotic determination of sex or not. But the position is a clear one: the hypothesis that the soma is primarily asexual refers only to the phenomena of sex differentiation. This means that biochemical differences between male and female eggs, as in Riddle's experiments, may be present from the beginning without there being biochemical differences between male and female somatic cells, the metabolism of which may indeed be influenced by sex hormones before sexual differentiation of the soma takes place. Certain observations of *Minoura* (1921) do not, however, at first thought fully agree with our conceptions in regard to fowls. He describes a transformation of the original female gonad into a male one under the influence of an engrafted testicle, but he records at the same time the remains of the Müllerian ducts. But the graft had to be made in the second week of incubation, when sexual differentiation had already begun, and it is easy to understand that some heterosexual characters such as the Müllerian ducts might persist, though in a rudimentary state.

Goldschmidt (1920) argues that in birds the genetic position is the same as in insects, every cell containing from the beginning the catalyzers regulating the production of the sex hormones in such quantities as are necessary for sexual differentiation. He considers even the cock-feathering of old hens as representing a state of intersexuality caused by the female hormones being unable further to inhibit the action of the male ones. There is no real basis for such an assumption, which is founded only on analogy with insects.

For mammals *Lillie's* objections (1923) are very weighty. "The opportunity for fusion of embryonic membranes from a two-sided twin pregnancy is present from the 10-mm. stage of the embryos, and as to vascular anastomosis from the 19-mm. stage, or slightly earlier. . . . This antedates the beginning of visible sex differentiation . . ." (*Lillie,* 1923, pp. 61–62). So exchange of blood between twin embryos must be possible before the beginning of sex differentiation. Now Lillie examined a case of a freemartin in which fusion of the membranes, according to his reconstruction of the probable history of this case, was possibly complete at least at the 10-mm. stage and a vascular anastomosis must have been established at the same time. Such a case, according to Lillie, would seem to have afforded the maximum opportunity of masculinization by the hormones of the male partner on account of the early time of onset and the long duration of possible action. But, nevertheless, the modification of the freemartin in this case was not particularly extreme. "It is obvious," as Lillie says, "that the male sex hormone is acting against resistance in the female soma; moreover, this resistance is not that of already differentiated parts, for the hormone is introduced before sex differentiation; it is rather a constitutional resistance native to the determined sex. The phenomena can be understood only on the assumption that the zygotic sex-determining factors are also sex-differentiating factors in mammals as in insects" (*Lillie,* 1923, pp. 71–72). "If there were no other factors at work in determining the sex differentiation of embryonic primordia than the specific sex hormone, it is difficult to understand why the freemartin, which receives only male sex hormones, should not become completely male" (p. 71). Besides this, interstitial cells to which the production of male sex hormones is ascribed are found only from the 3-cm. stage of the embryo onwards (*Lillie and Bascom,* 1922), i.e., after sexual differentiation of the soma has been already going on, according to Lillie, for some time.

Keller (1920) has examined the question of differences of sex characters of male and female embryos in cattle at different stages of about 25 to 67 cm. of body length. He finds that in opposite sexed twins with both twins normal the male partner is always longer and heavier than the female. All the measurements relating to the skeleton and the muscles were greater in the male than in the female. The sex differences already begin to appear at the end of the second intrauterine month, and become gradually more and more accentuated; in the fifth or sixth month they are no less developed than in mature foetuses. Keller concludes that a neutral or asexual soma could be held to exist in cattle only for a short period of early embryonic development, but that such an assumption would not imply that somatic sex differences are absent before visible differences appear.

A detailed criticism of our paper has been made by *Kammerer* (1919). He finds that our assumption is opposed by the fact that the sex can be determined already at fertilization; we shall discuss this question in the following section. Further, he insists that our hypothesis is contrary to what we know concerning the heterochromosomes; this question is discussed below. Kammerer holds that the soma is a bisexual one; but I do not see what difference there is between the assumption that the soma, during embryonic development, is an asexual one, and that the soma is a bisexual or an indifferent one, as Kammerer holds. When speaking of an asexual soma I have nothing else in mind than that the soma is an indifferent one in the sense that either male or female sex characters can develop according to the sex of the hormones produced by the gonads. The assumption of Kammerer that our hypothesis implies that sex characters are formed by sex specific hormones "from absolutely undifferentiated plasm, and therefore, so to speak, out of nothing" (*Kammerer*, 1919, p. 382), is incorrect. According to our hypothesis sex characters are simply characters of the neutral, asexual or equipotential form of a given species, partly influenced and partly uninfluenced by sex specific hormones.

Kohn (1920) also has failed to realize that our hypothesis, as already remarked, does not concern sexual determination, but sex differentiation. We find the same misunderstanding in a paper by *de la Vaulx* (1922).

The view taken by *Harms* (1922, p. 212) is a contradictory one. He says: "The fertilized egg is sexually determined only in respect of the gonad, whereas the sex characters have an indifferent bisexual *anlage*. This assumption is widely supported by recent experimental investigation." Now one might suppose that this sentence implies the acceptance in some form of our hypothesis. But on the contrary: "This is why the hypothesis of Lipschütz on the asexual embryonic form held also by Tandler and Gross, Steinach and Biedl must be rejected, at least for the living animals of to-day." But on p. 216 of the same paper Harms is less radical in his rejection of this hypothesis. Here he merely argues that the sex characters may become differentiated to a certain degree even in the absence of the sex glands, though in the presence of the glands all the sex characters are indifferent before a differentiation of the gonad has taken place.

There is, however, another set of facts which might be cited in opposition to our hypothesis; the statements made as to the sex chromosomes. If the number of chromosomes in males and females is different in birds and mammals, the soma of both sexes must be a different one from the beginning. As far as I understand it, the problem of the sex chromosomes is not yet solved for birds (*Goldschmidt*, 1920, p. 57). As to mammals, a recent statement of *Wodsedalek* (1920, quoted from Arch. f. Zellforschung 16, p. 439) may be mentioned. This author examined various embryonic organs such as brain, lung, liver, etc., in cattle, and he records having found in male embryos 37 chromosomes and in females 38. It is possible, according to this author, to state the sex of the embryo by counting the chromosomes before the sex can be recognized morphologically. It is clear that our hypothesis, which postulates an identity of male and female somatic cells before differentiation of sex endocrine cells has taken place, is contrary to the theory of the sex chromosome. If the latter holds for birds and mammals, our theory must fail, at least in its extreme form. But it nevertheless remains true that the male and female soma can be changed in the direction of its development by the influence of an hormonic or some other factor; absence of identity does not exclude "equipotentiality," to use Zawadowsky's expression.

The possibility of feminization and masculinization by heterosexual transplantation in birds and mammals has been placed beyond any doubt. The fact of sex being characterized by an 'X'-chromosome is contrary to our hypothesis of the identity of male and female somatic cells before differentiation; *and thus facts seem to stand against facts!* Since a change in the direction of the somatic development can be induced experimentally by the intermediation of hormones, the question arises as to how this fact can be brought into line with the conception of sex chromosomes. Further, the question arises as to what happens to the chromosomes of the somatic cells when a change of sex characters takes place during extrauterine life in insects, birds and mammals. To these questions no satisfactory answer has as yet been given.

B. DETERMINATION OF SEX.

When discussing in the foregoing section the influence exerted by the sex glands on the morphogenetic processes in the organism, we put aside the questions as to the factors which are responsible for the determination of sex, and the time at which determination takes place.

There are two possibilities: Sex may be determined at or even before fertilization; sex may be determined after fertilization, i.e., during embryonic development following fertilization. Various external factors are able, as has been shown experimentally, to affect the sex-ratio, and it is thought that external factors may normally determine sex. It is of interest to examine the bearing of this question on the hypothesis of an asexual or equipotential embryonic soma, the sexual differentiation of which depends upon sex hormones.

It is clear that our hypothesis is in full accord with the second suggestion. One might suppose that external factors influence the development of the endocrine sex gland, and thereby determine the sex not only of the latter, but of the soma as well. But there are a great many experiments showing that sex in mammals is already determined at or before fertilization. Is it possible to bring our hypothesis on the asexuality of the embryonic soma into line with these facts? I think that this can be done. If the sex of the fertilized egg is already determined, we must assume that biochemical differences exist between a male and a female fertilized egg. If, further, both a male and a female fertilized egg give rise to an asexual or identical soma, which is feminized or masculinized by hormones produced by the sex gland, this might be caused by the biochemical differences between male and female becoming localized during embryonic development in the sex gland when cellular differentiation is proceeding. We must suppose that every inborn abnormality is due to a certain biochemical difference or biochemical abnormality in the fertilized egg, and we must further assume that this abnormality becomes later on localized in a certain group of cells, being really nothing more nor less than a morphological manifestation of such a localization. It suffices to mention the inherited pigmentary spots, double fingers, *retinitis pigmentosa*, etc. In all these cases the whole soma remains normal throughout life, and is not influenced by the biochemical abnormality present in the fertilized egg. In a similar way the soma of the embryo may remain identical in both sexes till the time when the sex gland, which becomes differentiated and is the morphological manifestation of the biochemical difference between a male and female fertilized egg, begins its hormonic action.

We see that the biochemical difference existing between a male and female fertilized egg is so far not opposed, as *Kammerer* (1919, p. 372) thinks, to our hypothesis of the asexuality of the embryonic soma, this biochemical difference becoming localized and causing differentiation of a male or female sex gland, which determines a male or female reaction on the part of the equipotential soma. Here, however, the question again arises whether such an assumption can be brought into line with the theory of the sex chromosome.

C. FIXATION OF SEX CHARACTERS.

That male and female somatic cells are different from the beginning, and that rudimentary sex characters are already present in a latent state during the earliest stages of embryonic development, seem to be proved at first thought by the fact that sex characters persist to a certain degree after removal of the sex gland and after cross-grafting of ovaries or testes. There is never complete atrophy of the uterus in the female, or of the penis, the prostate and seminal vesicles in the male after castration; there is rarely a transformation into a condition which really could be regarded as a neutral one, as with the pelvis and the skull in mammals or the plumage and spurs in birds. Experiments with castration and cross-grafting seem to show that the sex characters are to a certain extent independent of the sexual hormones. But it must not be forgotten that all these experiments were made on animals in which the sexual differentiation had already been going on for a long time. Sexual differentiation begins during embryonic development, and at the time of experimental interference the sex characters are already *fixed* to a certain degree. The different tissues of the organism have a certain *growth intensity* which can be expressed quantitatively by the number of cell divisions in a unit of time. As was shown by *Minot* (1908), this rate of growth generally diminishes in proportion to the time which has elapsed after fecundation, and for some tissues, as, for instance, the nerve cells, the rate of growth is *nil* soon after birth. One might suppose that a tissue, the growth rate of which had already markedly diminished during previous development, would react to the morphogenetic hormones in a less pronounced manner than tissues, the growth rate of which was still at a high level. The experiments of Steinach and my own observations (*Lipschütz*, 1918 b and 1918 c) supply evidence for such an assumption.

As we have seen in Chapters VI. and IX., the rudimentary teats and mammary glands of the male guinea pig become transformed under the influence of the ovarian graft into organs similar to those of a female during pregnancy or even lactation. There is not only a feminization, but as Steinach pointed out, an actual *hyperfeminization* of these organs. On the contrary, the clitoris of the female undergoes beneath the influence of the testicular graft an incomplete masculinization, though other sex characters, such as the psycho-sexual behaviour, may be found markedly changed towards maleness. We have learned that the penis-like organ of the masculinized female is not only shorter than the penis of a normal male, but that there is also a total lack of the corpora cavernosa urethrae. We see that the mammary gland and the clitoris react in a different way, though they are both under the influence of the respective sexual hormones. There is much evidence for the assumption that this difference is caused by variation in growth intensity. The above-mentioned experiments of Steinach were made on animals 2 to 3 weeks old. At this time the mammary gland

and the teats of the male guinea pig are still very similar to those of the female of that age, and it is easy to understand that under these circumstances the reaction of these organs in the feminized male will be similar to that in an ordinary female. On the contrary, the penis in the new-born male guinea pig, and especially in one of 2 to 3 weeks old, is very different from the clitoris of the female of the same age, the corpora cavernosa undergoing sexual differentiation towards maleness or femaleness during embryonic development. Formation of a normal penis in a masculinized guinea pig of this age is not possible, though male sexual hormones are now in process of circulation. The result is the formation of the hypospadic penis, which is shorter than the normal organ.

It is very interesting to note that neither Steinach nor Sand nor Moore could discover any effect produced by the ovarian graft on the development of the mammary glands or teats in *rats* completely feminized in respect of sexual instincts. *J. A. Myers* (1916, 1917 a, 1917 b) stated that the sexual differentiation of the mammary gland in the female rat begins about five weeks after birth. The rudimentary mammary glands in the male and female at ages of about 4 or 5 weeks are already very different from one another; the nipples are wholly absent in the male rat. The young rat, therefore,. is very different from the young guinea pig, in the former there being profound differences between male and female, and in the latter no difference at all. In view of these facts it is possible to explain the different reaction towards the female sexual hormones shown by the two species of rodents in the experiments with cross-grafting of ovaries.[1]

Certain observations of *Goodale* (1916) and *Pézard* (1918) deserve to be mentioned here. In fowls sexual differentiation of the plumage takes place at an age of about two months. At this time the plumage characteristic of the two sexes begins to develop. Evidently the inhibitory influence of the female hormones begins to act at this time in the hen and to fix the plumage in a sex specific manner. If the young hen has been castrated at an age of two months, the male plumage does not appear immediately after castration, but much later. In the

---

[1] Even in fully grown guinea pigs of about 1½ years of age the teats and mammary glands can undergo, after ovarian transplantation, hyperfeminization with milk secretion, as shown by *Lipschütz and Voss* (unpublished experiments, see p. 291).

experiments of Pézard the male plumage did not appear unti about four months after castration at the first moulting. Evidently the female plumage had already been fixed, and a change could only take place when new feathers started growing during the moult. If the castrated hen dies before moulting no change in the plumage is observed after castration (*Pézard*, 1918, p. 139). If castration is done during moulting, as in some experiments of Goodale's, the feathers may show in colour, in pattern, and even in shape a mixture of male and female, "the area occupied by each depending upon the age of the feather germs; the younger the feather the larger the area of male characters" (*Goodale*, 1916, p. 31). Similar observations have been made by *Morgan* (1919) and *Zawadowsky* (1922) and recently by *Pézard* (see p. 408). No better evidence could be given in support of our assumption that reaction to experimental interference depends on age. The castration experiments made by myself and *Bormann* (1922) on guinea pigs and rabbits may also be mentioned here. As already shown in Chapter II., the change observable after castration on the penis and its accessory apparatus depends largely upon the age at which the gland was removed. By varying the time of castration different degrees of development of those sex characters which depend upon sex hormones may be obtained. I have shown the same for the seminal vesicles in the guinea pig (see pp. 20 ff.).

It is even possible that the fixation of the sex characters under the influence of the sexual hormones is a *latent* one, being invisible at the time of the operative interference, but becoming revealed in course of time. This may be the true explanation, for instance, of the sexual instincts so often present in some degree in castrated mammals and birds, and of the growth of the penis in the castrated guinea pig (see Chapter II.).

Lillie's statement (1923), that masculinization of the female partner in twin cattle is never a complete one even when the fusion of the membranes occurs very early, seems contrary to our assumption. In the case of the freemartin it is, indeed, very difficult to explain the resistance of the female somatic cells to masculinization by assuming a fixation of characters caused by the influence of female hormones acting at an earlier stage. But we must not forget that possibly the antagonism between the male and female gonads might be responsible.

D. EVOLVED CHARACTERS OF THE ASEXUAL EMBRYONIC SOMA.

Besides persistence of characters after castration due to former fixation there is still another kind of persistence to which this explanation does not apply. Instances of such a persistence of characters are the plumage and the spurs of the capon. Feminization experiments with castrated cocks supply evidence that these characters can be changed by an ovarian graft; there is a fixation of plumage only up to the next moult. These persistent characters in the cock develop independently of sexual hormones, but they may be considered as *the result of the development of characters of an asexual soma common to both sexes.* The fact that certain sex characters are really independent of sexual hormones is not contrary to our theory of an asexual embryonic soma. *There is no need to explain persistence of certain sex characters by the assumption that they are already present as such in the embryo, for the persistence is due rather to the fact that the characters of the asexual embryonic soma are not influenced during their development by the hormones of one sex, but are changed by those of the opposite sex.*

As already mentioned, Pézard and Goodale were the first to make an assumption of this kind. Later on *Goodale* (1918) changed his original view somewhat after observing certain new facts. He found that the spurs may be well developed in castrated hens even when there is afterwards a regeneration of the ovary, and that in spite of this organ they may even continue to grow. In the feminization experiments spurs developed, though the plumage was a female one. To explain these results *Goodale* (1918, p. 391) assumed that the germinal factors in the various individuals differ from one another; he suggested further that additional germinal factors may be present, owing to which the reaction to sexual hormones or to the removal of the latter may become modified. This assumption is not necessary, for the variability as observed by Goodale can be explained on our theory that the sensitiveness of a given tissue to sex hormones is a function of time.

The question here discussed seems to be of great importance also in connection with the theory of intersexuality in mammals. It seems likely, as I have pointed out already in Chapter IX., that the enormous variability in intersexual types is due to the variability of *time* at which the hormones of one sex cease and those of the opposite sex begin to act, or at which the quantitative relations between the two undergo considerable change. Goldschmidt drew attention to this factor in discussing his experiments on the moth. I think that the question of the *time* at which the soma begins to come under the influence of the sex hormones, and the question of the mutual *quantities* of the hormones, are of the greatest importance in reaching an understanding of the great variation in abnormal sex characters presented by different individuals of the same species.[1]

Lillie (1917, 1923, p. 70) insisted on time "as the principal factor, so far as hormones are concerned, in determining the range of variation within the freemartin series . . . in relation to the early stages of sex differentiation, at which vascular interchange is established." But to supplement this he believes it is necessary to assume that different individuals vary in the state of balance of the zygotic sex factors, and this may influence the quantitative effect of the hormone factor.

In insisting so much on the time factor as influencing the sensitiveness of different somatic cells to sex hormones I should not like to deny that this sensitiveness in a tissue may be different from the beginning in two individuals of the same sex. But for the moment no facts in support of this contention are available.

E. TERMINOLOGICAL.

As a consequence of the assumption that sexual dimorphism in mammals and birds is due simply to the fact that an hormone-producing gland becomes differentiated and influences an asexual embryonic soma in a sex specific manner, the terms feminization and masculinization as introduced by Steinach acquire a new meaning. They are not merely terms for laboratory use, but really indicate the normal morphogenetic sex specific action of the sex hormones on the soma (*Lipschütz,* 1918 c). It seems advisable, on the other hand, to speak of the cross-grafting of Steinach and his followers as an *experimental* feminization and masculinization.

In the last few years there has been much discussion not only as to the question of the seat of hormone-production in the

---

[1] A similar point of view is held by *Crew* (1923).

sexual glands, but also about the term by which the hormone-producing cells are to be designated, and this has to a large extent centred around the term "puberty gland" introduced by Steinach and adopted by myself in the first edition of this book. The term was introduced by *Steinach* (1912) to emphasize the function of the interstitial cells, this function consisting of the promotion of full sexual maturity or puberty. The idea implied by this term was based by Steinach on two assumptions; first, that the hormones are produced not in the generative part but in other cells of the sex gland, and, secondly, that puberty is the essence of sexual maturation.

In regard to the former assumption we have seen, especially in Chapters IV. and V., that the matter is not yet decided. But I think that this is no argument against using a special term in referring to the whole problem under discussion. In this connection the term "puberty gland" still seems to me very useful. Bouin and Ancel introduced the term "interstitial gland," an expression of a morphological order; whereas the term "puberty gland" leaves the question of the seat of hormone-production open, the term "interstitial gland" tacitly presumes that the question is already settled. As applied to the ovary, the term "interstitial gland" is anatomically inappropriate, even on the view that hormones are not produced by the generative part. In the endocrine function of the ovary various cells are involved, cells originating from different tissues. It is not possible to designate the endocrine apparatus of the ovary under a single term of anatomical or histological order without causing repeated misunderstanding. This is best shown by the endless discussions about the "interstitial gland" of the ovary. Misunderstandings may be avoided if we use a term of a physiological order, since all the different parts of the ovary involved in hormone-production are united by a common function. Further, it seems advisable to use a term convenient also for the hormone-producing testicle; it may be useful to emphasize as far as possible also in our terminology that there is, or must be, some parallelism in the mechanism of hormone-production in both sexes. In view of these considerations I think that the term "puberty gland" is very convenient in connection with the problem of the seat of hormone-production in the sexual glands. The term was introduced by Steinach on the assumption that the question of the seat of formation was already determined, in the sense that there is a special hormone-producing tissue in the sex glands; but this need not necessarily prevent one from using this term in a somewhat different sense.

As to the second assumption that puberty is the essence of sexual maturation, it should be clear that from this standpoint the term "puberty gland" is convenient. *Tandler and Gross* (1913, p. 751) objected that sexual hormones begin to act long before puberty and continue to act long after it. Under these circumstances they find it inconvenient to designate the hormone-producing sex glands by a term which relates only to a certain period of its activity. But *Tandler and Gross* (1913, p. 72) themselves pointed out that puberty is in reality not a process *sui generis*, the period of puberty not being a time of new creations, but only a period when morphogenetic processes already in existence are accelerated. But on the view that puberty is not a process *sui generis*, the term "puberty gland" seems to be the most suitable one. For "puberty" is really the symbol of full sexual maturity in regard to somatic and psychical characters, and at the same time the symbol of an intense endocrine activity on the part of the sex gland and the other organs of internal secretion. The term "puberty gland" emphasizes that all the processes leading to sexual maturity both during embryonic development and at the time of actual puberty and after, have something in common, all of them representing stages in the development of the sex characters, and being correlated with different degrees of hormone production.

F. ASEXUAL EMBRYONIC SOMA AND HEREDITY.

It has been suggested by Darwin that the male "secondary" sex characters are present, though in a latent condition, in every female, and that female "secondary" sex characters are present in every male; and, further, that the latent characters under certain circumstances are able to develop. This suggestion will now be discussed from the point of view of our hypothesis of the asexuality of the embryonic soma.

There are many observations which seem to favour Darwin's suggestion.

(1) It is known that in mammals rudiments of the genital

organs of the opposite sex are to be found in every individual (*Fig.* 137). Rudiments of the Müllerian duct, which develops in the female into the uterus and oviduct, are represented also in the male individual by the appendix testis and the utriculus prostaticus; rudiments of the Wolffian duct from which the vas deferens in the male originates are represented in the female by the appendix vesiculosa and the longitudinal part of the epoophoron.

(2) Many cases of intersexuality, where a change into the opposite sex took place during extrauterine life, seem also to support this suggestion, more especially the cock-feathering of old hens.

(3) A further proof seemed to be supplied by the fact that female sex characters present only in the stock of the father

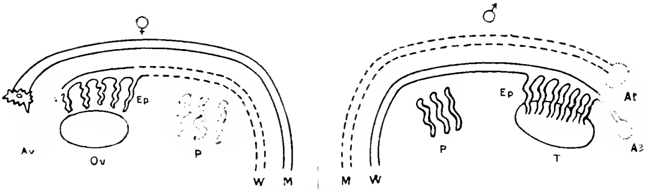


FIG. 137.—*Diagram: Origin of the different parts of the male and female sex apparatus.* ——— parts normally always present in extrauterine life; …….. parts not always present in normal individuals; - - - - - parts present only during intrauterine life. Ov=ovary; T=testis; M=Müllerian duct; W=Wolffian duct; Ep=epoophoron or epididymis; P=paroophoron or paradidymis; Av=appendix vesiculosa; Ae=appendix epididymidis; At=appendix testis.—Combination from Bromann and Toldt.

can be transmitted by the male, and *vice versâ* male characters can be transmitted by the female. An example may be given from an experiment of Mrs. *Haig Thomas* (1912). A female Formosan pheasant (*P. formosus*) was mated with a male of the Japanese species (*P. versicolor*). "The first-cross offspring already showed that each sex can transmit the secondary sexual characters of the other, for the males had some of the characters of the male *formosus*, the females some of those of the female *versicolor*. The transference of the female characters by the male was still more clearly proved in the second generation; one of the hybrid females was mated back with the *versicolor* male, and all the female young produced (five) had all the typical characters of pure *versicolor* females. In this case there was no *versicolor* female in the ancestry, the crosses being made thus:

formosus ♀ × *versicolor* ♂

|

hybrid ♀ × *versicolor* ♂

versicolor ♀ (5) hybrid ♂ (2)

The female offspring of the second cross were nevertheless pure *versicolor* in their secondary sexual characters. Their two brothers still showed considerable traces of their hybrid ancestry. Similar results were obtained by the same investigator with crosses between the Swinhoe and Silver Pheasants, in which it was shown that the Swinhoe male transmits the plumage-characters of the Swinhoe female" (*Doncaster*, 1914, p. 109). The examples could be multiplied. Further, the existence of *sex-limited* inheritance must be mentioned here. Many cases of this kind are known. One of the best examples is the result first obtained by Pearl and Surface when mating Plymouth Rocks and Cornish Indian Game. The Plymouth Rocks are good winter egg producers, Cornish Game mediocre ones. Females from a cross between Plymouth Rock and Cornish Game always inherit capacity of egg production *only* from the father, and not from the mother. If we wish to obtain good winter egg producers we must cross male Plymouth Rocks and female Cornish Game, and not *vice versâ,* as one might think at first sight. The Plymouth Rock cock transmits a marked female character (egg production) to female offspring. This fact is also of practical importance; it is of no use to select for crossing hens with high egg production, as only cocks of the respective strain transmit this special female character. We see, then, that each sex can transmit the sex characters proper to the opposite sex, at least in many cases, and "possibly always," as *Doncaster* (1914, p. 110) says.

Darwin has made no attempt to give any further explanation of this latency of characters of the opposite sex. His method of thought is really dynamical or physiological. This is what he says: "In every female all the secondary male characters, and in every male all the secondary female characters, apparently exist in a latent state, ready to be evolved under certain conditions." This mode of reasoning is not contrary to the hypothesis of an asexual embryonic soma. Unlike what we find in Darwin, in the study of modern heredity a mere statical or morphological way of thinking sometimes prevails. We meet with a tendency to speak of male and female genetic factors, corresponding to sex characters, and being present simultaneously in male and female individuals; the individual is phenotypically monosexual because the genetic factors of the opposite sex are recessive or latent. If we assume the hypothesis of an asexual embryonic soma there is no further need to postulate special genetic factors for male and female sex characters in mammals and birds, maleness and femaleness being represented in the fertilized egg only by the single genetic factor for the hormone-producing sex gland.

It is easy to show that the three above-mentioned groups of facts which at first sight seem to prove the presence of genetic factors of both sexes in every individual can be explained also on our hypothesis.

(1) Tandler (*Tandler and Gross*, 1913, pp. 80, 81, 137) pointed out that the rudiments of the Müllerian and Wolffian ducts as present in both sexes prove the great phylogenetic importance of these organs, but not the bisexuality of the soma. According to *Oscar Hertwig* (1902, p. 413), the ductus Wolffii is regarded as an excretory duct which probably served simultaneously for the expulsion of the products of excretion of the Wolffian body and of the generative cells of both sexes. As Hertwig points out, similar conditions are to be found in invertebrates, as for instance, in certain worms, where through nephridia perforating the body wall not only various execretions but also generative cells are expelled. Hertwig claims that in vertebrates these two functions were taken up by two different ducts, the ductus Wolffii and the ductus Mülleri. And, according to Tandler, it is easy to understand how the ductus Wolffii, being the excretory duct of the primary urinary apparatus, is present in individuals of both sexes, though later on losing its importance in the female. A similar line of argument seems to be true also for the ductus Mülleri, which evidently lost its significance in the male after the ductus Wolffii had again taken up its original function of expelling the excretions and with these the male generative cells. The position may be expressed as follows: It is probable that the ductus Wolffii and the ductus Mülleri originally served both for the expulsion of the different excretions and of the

generative cells, and they still persist in the embryonic soma as long as sexual differentiation has not yet take place. Rudiments of these parts persist also in the sexually differentiated individuals. One may assume, therefore, that *the asexual embryonic soma in mammals and birds recapitulates a phylogenetic phase in which sexual differentiation related only to the generative cells.* The rudimentary organs which seem to be signs of an intersexual soma (the appendix vesiculosa, the appendix epididymidis, the ductus longitudinalis of the epoophoron) may be rudiments of an excretory apparatus common to both sexes, like the ductuli transversi of the epoophoron and paroophoron, and the ductuli transversi of the epididymis and paradidymis (*Fig.* 137).

(2) With reference to the second group of facts mentioned above we know that the manifestation of characters of the opposite sex may be brought about by a change in the dynamics of the hormonic apparatus. In some cases such as the cock-feathering of old hens, the appearance of characters of the opposite sex may be regarded as due to a suppression of hormone-production, which previously inhibited the development of the characters of the asexual type. No special genetic factors seem to be necessary to account for these facts.

(3) Let us now consider the third group of observations relating to the transmission of female characters by the father and of male characters by the mother. This phenomenon can be easily explained if we assume that *the parent transmits to its offspring the characters of the asexual type,* i.e., *the capacity to react to sexual hormones in a manner characteristic of a given species. The parent always transmits the capacity to react both in a male and in a female manner.* In crossing experiments the *male* generative cell transmits characters of the asexual soma of the strain of the father, and the capacity to react to female sexual hormones in a manner characteristic of the *female* of the *father's* strain is thereby inherited. On the other hand, the *female* generative cell in a crossing experiment transmits the characters of the asexual soma of the mother's strain, and the capacity to react to male sexual hormones in a manner characteristic of the *male* of the *mother's* strain is thereby inherited. It depends upon the sex specific hormones of the offspring whether the reaction of its soma will be a male or a female one. I find my view, as expressed in the first edition of this book,

fully confirmed by experiments recently performed by *Zawadowsky* (1922). It has long been known from certain experiments by *Morgan and Goodale* (1912), that a cross of a black male Langshan and a female barred Plymouth Rock gives in the first generation barred cocks and plain black hens. If my view is correct, castration of a black hen of the first generation will cause the appearance of the male plumage of a Langshan and not that of a Plymouth Rock cock. This actually happened in an experiment by Zawadowsky who castrated hens of the first generation. The females of the first generation inherit the characters of the neutral form of the strain to which the male parent belongs. Zawadowsky writes that he expected to obtain by castration of cocks and hens of the first generation a form common to both sexes. But his expectation was not justified.

A passage in Darwin's book on "Variation" may be quoted here: "We can in this way understand how, for instance, it is possible for a good milking cow to transmit her good qualities through her male progeny to future generations, for we can confidently believe that these qualities are present, though latent, in the males of each generation." The mechanism of such a transmission of a female character by the male is easy to explain; the male transmits a certain character of the asexual soma, i.e., the capacity to react to the female sexual hormones in a manner characteristic of his strain.

Recently *Pézard and Caridroit* (1922 b) have adopted the idea of a neutral form influenced by sex hormones into the genetic analysis of sheep of the cross Dorset × Suffolk. They have shown that the interpretation of the facts here observed becomes perfectly clear if this principle is made use of. The distinguished French author *Cuénot* (1923), who gave an analysis of the theory of Pézard and Caridroit from the point of view of one studying heredity, has also come to the conclusion that the theory is completely in accord with the known experimental results.

If we accept the explanation given above of the transmission of sex characters in mammals and birds by the opposite sex, it seems necessary to assume that the sex specific hormones are the same in different species. Certain experiments of Bouin and Ancel on guinea pigs and of Pézard on fowls described in foregoing chapters (see pp. 94, 95), show that a *species* specifity of sexual hormones is not very probable. Zawadowsky confirmed the observations of Pézard. He brought about the manifestation of male sexual instincts in a castrated cock by implantation of the testicle of a pheasant (*P. versicolor*); there was some evidence also of a feminization of a castrated cock after implantation of an ovary of a pheasant. The experiments of Steinach, who obtained an erotization of castrated *Rana temporaria* by introducing a pulp of testicle from *R. esculenta* may also be mentioned here. The successful transplantation of apes' testicles on man as made by *Voronoff* (1923) and by *Thorek* (1922) is further evidence. I had the opportunity of personally observing a man in whom the testicle of a goat was transplanted in the muscular wall of the abdomen, and in whom a marked erotization took place. Various anthropological facts also are evidence of the non-existence of a species specifity of the sex hormones. There are in men and women of most races certain sex differences which, though absent at time of birth, develop during extrauterine life. These sex differences are very pronounced in all human races, and they are invariably *of the same order* (*Martin*, 1914, p. 331). The body height of the female is in all races less than that of the male. And so with the length of the extremities and those of the hands and feet. On the contrary, in all human races the pelvis in the female is broader than in the male. Many of these sex differences have nothing to do with propagation. As certain of them depend upon the sex specific hormones it must be assumed that the latter are similar in the different human races.

The above assumption does not imply, however, that there can be no differences at all between the sex specific hormones in various species. The question needs further experimental investigation, being of great importance in studying heredity. *Pézard and Caridroit* (1922 a) assumed that the hormones of the ovary, besides their general action on the plumage of the neutral form, may also possess an inhibitory action on characters of a given race. They performed the following experiments:—

	EXPERIMENT A.	EXPERIMENT B.
P	Male Leghorn × Female Dorking.	Male Dorking × Female Leghorn.
F_1	♂—mixed plumage with characters of Leghorn and Dorking. ♀—plumage of *pure Leghorn*	♂—mixed plumage with characters of Leghorn and Dorking. ♀—plumage of *pure Dorking*

We see that the males of the first generation are similar in both experiments, whereas the females have the plumage of the male parent (sex-limited inheritance). To explain this result the authors assume that the ovary in the F_1 generation of A checks the development of the plumage of the neutral Dorking form, and changes the plumage of the neutral Leghorn form into a female one; the result is pure Leghorn plumage in the F_1 hens in A and *vice versâ* a plumage of pure Dorking in the F_1 hens in B. The acceptance of this theory of Pézard and Caridroit that the ovary is able to exercise a special influence besides its general sex specific influence might be controlled by castration experiments. If Pézard and Caridroit are right, castration of a hen of the generation F_1 in A and B should give the same result: a plumage presenting a mixture of characters of Leghorn and Dorking; if such a castration experiment were to result in the plumage of a capon of a pure Leghorn male in A and the plumage of a capon of a pure Dorking male in B, it would be necessary to reject the theory. Cuénot points out that certain experimental facts are in harmony with the presumption that the result of the indicated castration experiments would be pure Leghorn and pure Dorking plumage; he mentions an experiment of *Davenport* (1912), in which a male golden Leghorn was mated with a female dark Brahma. In the F_1 generation there were cocks with characters of both parents, whereas the hens were of the type of golden Leghorn. In the F_2 generation there were cocks with mixed characters as well as male birds of the pure Leghorn type.

That the sex hormones, however, may differ according to the species is not improbable, and this may be the explanation of many facts. We shall return to this question in Section H. In Chapter II. we have already touched on its importance in relation to phylogenetic problems. *Pézard* (1918, p. 173) pointed out that a factor responsible for evolution might have acted primarily on an endocrine gland which had a morphogenetic influence on the *whole* organism. *Morgan's* experiments (1919) may be especially referred to in this connection. We know that a peculiarity so characteristic of a given race as the hen-feathering in the Sebright is probably caused by an hormonic factor. Here the introduction of a single factor seems to produce manifold changes, or, as Morgan says, "a single factorial difference may be at the root of exceedingly great differences in the individual." Morgan proceeds as follows: "Such results, while they admittedly do not *in most cases* tell us that the differences involved have arisen at a single progressive step, show us nevertheless that such differences may depend on very simple initial differences, and if so, the entire problem becomes enormously simplified. To Darwin the excessive development of colour and ornamentation appeared due to a long, slow process of evolution laboriously brought about by the female through selection of those males a little more ornamented than their fellows. To-day we have found out that in many cases the genetic composition of a male with such ornamentation and of a female without it may be almost identical, except that the genes in one chromosome are duplex in one sex and simplex in the other. Owing to this initial difference, the female in birds produces an internal secretion that suppresses in her the ornamentation shown by the male, and in the mammal an internal secretion produced by the testes causes the full development in the male of the secondary sexual characters. If, as seems probable, these secretions are some particular kind of substance, the condition that led to their appearance historically need not have been very complex; and if not, the problem appears simplified" (*Morgan*, p. 98). But I should like to add that the problem as expressed by Darwin becomes not only simplified, but possibly reversed. According to Darwin the modest plumage of the female bird is phylogenetically older than the brilliant male one, and Darwin asks how the brilliant male plumage developed from the female one. But it is possible, or even very probable, that the brilliant male plumage is phylogenetically older than the female one. There is at least no better evidence for the older assumption of Darwin than for the assumption expressed here. Under the first alternative, phylogenetic transformation of the modest plumage into the brilliant one would be caused by cessation, in males, of the production of a hormone inhibiting the plumage of the neutral form of the given race; under the second alternative, there would be phylogenetic transformation of the brilliant plumage into a modest one by the production, in females, of a hormone inhibiting the neutral form of the given race.

To sum up our argument: *There is no need to assume special genetic sex factors for the male and female sex characters in mammals and birds. Transmission of male sex characters by the* *female, and of female characters by the male can be explained on the assumption of a transmission of the characters of an asexual soma, which has the capacity to react in a male, or female manner according to the sex specific hormones, the latter being possibly not peculiar to the species.*

In the six years which have elapsed since I wrote the above passage in the first edition, the papers of Morgan, Zawadowsky, Pézard and Caridroit, and that of Cuénot, as reviewed above, have come to my knowledge. In these we see that the view here expressed has proved, quite independently of mine, to be a useful working hypothesis.

Though I am not trained in the study of genetics, I may be permitted to point out that the number of genetic factors which during the last few years has been multiplied so enormously, may be brought within much more reasonable limits, when a fuller knowledge has been gained concerning the mutual relations between the various groups of cells or organs during the progress of embryonic development.

G. CLASSIFICATION OF SEX CHARACTERS.

We shall now attempt to classify the sex characters on the basis of our theory of the sex specifity of the hormones, and the asexuality of an embryonic soma feminized or masculinized thereby (*Lipschütz*, 1918 a). The principles of the classification I propose here have been recognized by *Pézard* (1915) in discussing his experiments on fowls.

Two groups of sex characters can be distinguished:—

(1) Sex characters not dependent upon sex specific hormones.

(2) Sex characters dependent upon sex specific hormones.

In regard to the characters not dependent on sex specific hormones, it may be recalled that they can be considered as evolved characters of the asexual soma, which become sex characters only in the sense that they are changed by sex specific hormones in the *opposite* sex.

The second group deserves further consideration in detail. The influence of one organ on another is always a quantitative one; there is a change in the intensity of the metabolism or at some link in the metabolic chain; there is an increase or a decrease in the growth intensity of the cells. So one might assume that the sex specific hormones will act on the characters of the asexual embryonic soma in a double sense: they may either *stimulate* or *inhibit* growth. *Herbst* (1901) was the first to point out many years ago that there may be inhibition of somatic development by sex hormones, and the experiments of Steinach, and especially those of Goodale, Pézard and Zawadowsky on fowls, have shown that such an inhibitory influence on the part of the sex hormones actually occurs.

In the following scheme the experimental results relating to the dependence of the sex characters upon sex hormones as recorded in Chapters II., III. and VI. are summarised.

THE BEARING OF THE SEX HORMONES ON THE SEX CHARACTERS.

+ promotion of development or furtherance; — inhibition; ± promotion or furtherance and inhibition of different parts of an organ; o no influence.

Sex characters.	Ovary.	Testicle.
1. *Mammals.*		
Body weight	–	+ (?)
Skeleton	±	±
Larynx	– or o	+
Hairiness	+	+
Deposition of fat	±	±
Body temperature	o	o
Mammary gland	+	– or o
Corpora cavernosa (clitoris and penis) ..	–	+
Müllerian duct	+	–
Wolffian duct	–	+
2. *Birds.*		
Plumage	–	o
Spurs	–	o
Head apparel	o or +	+
Larynx	–	+
Deposition of fat	–	–

In reality the relation between sex characters and sex hormones is a much more complicated one than can be expressed by the terms "furtherance" or "inhibition." But as we have not yet sufficient knowledge of the whole complex of relations, it is necessary to restrict ourselves somewhat so as to simplify the facts. Anyway we must never forget that "furtherance" and "inhibition" may be the result of very varied changes in the cellular metabolism; further, it must be taken into consideration that the different organs or systems upon which the sex hormones act, such as the skeleton, the fat, the condition of hairiness, and so on, are not uniform, and every part of an organ or of a system may have its special relations to the sex gland which are different from those of the others; it suffices to recall how varied are the reactions of the individual parts of the skeleton to the sex hormones. This is why it is impossible to draw really hard and fast lines between "furtherance" and "inhibition" and lack of influence, as demanded by the scheme which must be regarded as no more than a working classification.

It is quite probable, as indicated in the scheme, that some characters furthered by male hormones are inhibited by female hormones and *vice versâ*. This seems to be true especially for the ductus Mülleri and ductus Wolffii, and possibly also for the corpora cavernosa of the penis and of the clitoris, for the body weight and for the mammary gland; we have as yet no detailed knowledge on these matters. There is, however, in this instance an evident *antagonism* between the male and female sex hormones. According to Steinach the development of heterologous sex characters is inhibited by the hormones of a given sex. This contention of Steinach is not, indeed, of general validity, as sex differences (or sex characters) may be the result of very different physiological conditions. For instance, the growth of the long bones is inhibited both by male and female hormones, and the sex specific effect which the hormones have on the growth of the long bones is due clearly to the fact that the female hormones inhibit growth in a more marked manner, or begin their inhibitory action sooner. In opposition to the assumption that there is an antagonism between male and female sex hormones *Moore* (1921, p. 168) has objected that "hormone action is not characterized by an inhibition, but by a stimulation." This objection is not entirely correct, as *Lillie* also recognises (1923, p. 71).

The existence of furtherance and inhibition as well as antagonism of sex hormones appears to exist also in birds. Thus inhibition of spurs by female hormones obviously occurs. The influence of the female hormones on the plumage is a more complicated one; though the existence of an inhibitory action of the female sexual hormones on the plumage cannot be denied, the opposite effect also seems to occur, for some of the dorsal feathers in the hen are even better developed than in the cock (*Goodale*; personal communication). The larynx seems to be influenced in an antagonistic manner. As to the head apparel it is probable that both the ovary and the testicle act in the same direction, but "furtherance" by male hormones is much more pronounced than by female ones.

Notwithstanding lack of detailed knowledge as to the dependence of the various sex characters upon the hormones, it seems clear that there is no sex character which can be regarded simply as a furthered or inhibited character of the asexual type, the problem being always a more complicated one. But leaving aside details we may assume that *in mammals and birds the sexually differentiated type originates from an asexual embryonic soma, the characters of which underwent "furtherance" and inhibition by sex hormones or developed independently.* In the *Genetic System* shown opposite I have tried to represent this hypothesis schematically.

The objection might be made that this genetic system based on a critical consideration of the results of experimental castration, feminization and masculinization relates only to *quantitative* differences between the sexes. There is no place in this system for the differences in psycho-sexual behaviour. But this defect is merely occasioned by lack of knowledge; further investigations on the psycho-sexual reflexes should reveal that in this field also sex differences are of a quantitative order.

There are certain facts which seem to show the dependence of the *generative cells* also upon sex specific hormones. *Ancel and Bouin* (1904, p. 1041) were the first to lay stress on such a dependence. These authors pointed out that male interstitial cells are present in the gonad during embryonic development even before there is a sexual differentiation of the generative cells. Further, *Tandler and Gross* (1912) concluded from their observations on the seasonal dimorphism of the mole that the ripening of the generative cells depends upon the interstitial cells. We have seen, especially in Chapter IV., that the question as to the seat of endocrine function in the testicle is not yet solved, and is even more complicated than formerly appeared. The observations of Ancel and Bouin, and of

GENETIC SYSTEM OF SEX CHARACTERS.

	Examples.	
	Mammals.	Birds.
1. Sex characters *independent of the sex specific hormones = evolved characters of the asexual embryonic soma.*	Body temperature Mammary gland of the male (?)	Plumage of the cock Spurs of the cock Head apparel of the hen (?)
2. Sex characters *dependent upon the sex specific hormones*		
(*a*) by *furtherance*	Corp. cavern. penis Prostate Seminal vesicles Body growth (?) Uterus Nipples Mammary glands	Head apparel of the cock Larynx Wolffian duct of the cock Oviduct of the hen
(*b*) by *inhibition*	Clitoris (?) Body growth Müllerian duct in the male Wolffian duct in the female	Plumage of the hen Lack of spurs in the hen

Tandler and Gross, do not supply definite proof of a dependence of the generative cells upon sex hormones. *Herrmann* (1915, p. 36 and 44) found that follicular development can be stimulated in young rabbits when extract of corpus luteum is injected. In the freemartin, where hormones of the opposite sex are supposed to circulate in the organism of a female, there is also an influence on the sex gland, in this case an influence of male hormones on the generative part of the ovary (*Keller and Tandler*, 1916, footnote on pp. 513–14; *Chapin*, 1917) The observations of *Willier* (1921) on the sex gland of the freemartin made it probable that there is in this animal an actual masculinization of a gonad which began originally to develop in the female direction. Finally, the experiments of *Minoura* (1921) have shown that by cross-grafting the sex of the gonad can be changed in the direction of the sex of the graft. In view of these results it is not impossible that there are hormonic factors in the sex gland which may influence the generative part of the gonad in a sex specific manner. We know of similar influences arising from other endocrine glands such as the thyroid and the hypophysis, which in a general way are connected with metabolic changes in the gonad. These latter influences are, indeed, not sex specific like those of the hormones produced by the ovary and the testicle. But it is not impossible, however, that the adrenals may exert a sex specific influence on the gonad. One cannot say how far these hormones really interfere with the normal development of the gonad, neither can we draw from the experiments of Minoura any conclusions as to what normally goes on in the gonad, or whether there is really a causal dependence on the part of the generative portion of the gonad upon sex specific hormones. But the question deserves further consideration. Originally I thought it advisable to speak of an asexual embryonic *form* instead of an asexual embryonic soma, leaving the question open as to whether the generative cells also may be of the nature of sex characters dependent upon sex specific hormones. But to avoid misunderstanding, I prefer to speak of an asexual embryonic *soma*.

Kammerer (1919, pp. 343 and 344) has adopted the above genetic system, but proposes to replace the expression "evolved characters of the asexual form" by "characters of the neutral form of the species."

A similar genetic system has been adopted by *Zawadowsky* (1922, p. 207). Later on, however, this author (1923, p. 103) has somewhat modified the system in question, and added certain other terms such as "sex-limited" and "somatosexual" characters. By "sex-limited" characters he means certain characters of the neutral form occurring in hybrids which are absent in the neutral form of the opposite sex, the soma of the males and females in such cases not being equipotential (see p. 461). By "somatosexual" characters Zawadowsky understands those which are present from the beginning in the soma, and do not depend upon sex hormones, but yet do not belong to the first group in our genetic system. Zawadowsky refers here to the sex characters of insects, and perhaps some characters in birds which are present in the male but do not appear in the castrated female, such as possibly the spurs and the red ring around the eye of the male pheasant.

When we consider what we learned about the dependence of the sex characters upon the sex glands it becomes clear that the classification into primary and secondary sex characters must be abolished as causing endless misunderstanding, since the term *secondary* often implies *genetic* dependence. Whether any sex character is genetically dependent upon the sex gland can be shown only by thorough analysis, as in the case of the plumage in birds. Further, the term "sex gland" may include diverse tissues, and the question is still open as to which part of the sex gland is involved in internal secretion and to what extent. All parts of the sex gland are not to be considered as genetically primary sex characters, ripe spermatozoa and ripe ova not being necessary for the performance of the endocrine function of the gonad. Though different phases in the development of the generative cells may be involved in the processes of internal secretion (see "follicular theory," p. 176), the generative cells, as we have seen, may be influenced by hormones produced by the sex gland, i.e., the generative cells may become genetically dependent upon sex specific hormones. In view of these considerations it seems inadvisable to preserve a classification which is capable of giving rise to so much misunderstanding.

For practical use we need a system similar to the old classification into primary and secondary sex characters, but such as at the same time will not cause the old confusion.

Poll (1909, p. 347) was the first to make a step in this direction. He classified the sex characters in the following way:—

DIFFERENTIAE SEXUALES:

1. *Essentiales* s. germinales
2 *Accidentales*.
    - (*a*) Genitales subsidiariae.
        - Internae.
        - Externae.
    - (*b*) Extragenitales.
        - Internae.
        - Externae.

This classification met with much approval as being of great practical use. But it is not without certain disadvantages. The terms "essential" and "accidental" may give rise to misunderstanding Poll says, that the sex gland is an "essential" sex character as being of "prominent importance" (von "überragender Wichtigkeit"). But what importance is here meant? Importance in relation to propagation, or to inheritance, or to the formation of "accidental" sex characters? If "essential" means most important for the formation of the accidental sex characters Poll's classification is nothing more nor less than a classification into primary and secondary sex characters on a genetic basis. Further, "extragenitales" may mean: (1) sex characters, which functionally have nothing to to with the genital apparatus, and (2) sex characters which, being localized far from the genetic apparatus, nevertheless are functionally related to the latter, i.e., to the "genitales subsidiariae," like the plumage, the larynx, the pads of the frog, etc.

For practical use I propose the following classification of sex characters:—

1. Endocrine sex apparatus.
2. Generative cells.
3. Somatic sex characters.
    - (*a*) Characters of the copulatory and genital apparatus.
    - (*b*) Characters of the sexual auxiliary apparatus.
    - (*c*) Characters of other organs.
4. Functional sex characters.
5. Neuro-psychical sex characters.

The first two groups comprise the characters of the sex glands. It is necessary, especially in the case of mammals, to make two groups; even in attributing hormone-production to the generative part of the sex gland we must admit that the process depends not only upon the generative cells, but also upon other parts of the organ. The group "sexual auxiliary apparatus" includes all somatic characters, which, without relating to the copulatory or internal genital apparatus, take part in some manner in the performance of the sexual function; the plumage and larynx in birds, certain glands in various species and the pads in the frog are examples. There are, however, no sharp boundary lines between (*a*) and (*b*) or between (*b*) and (*c*). To the group of "functional sex characters" there belong all the differences between the sexes which are not morphological, such as differences in the body temperature or in the intensity of the metabolism. Sex differences relating to nervous and psychical reactions are included in the fifth group.

Such a classification does not collide with the genetic system given above. It is intended to serve only for practical ends.

Various authors such as *J. S. Huxley* (1912), *Champy* (1922, p. 121), *de la Vaulx* (1922) and *Marañon* (1922), recognizing the drawbacks of the old classification of the sex characters into primary and secondary ones, have proposed others for practical use. *Champy* (pp. 65, 123) speaks of *permanent* and *temporary* sex characters in amphibians; *Marañon* (p. 90) groups the sex characters as somatic and functional ones, including in each group primary and secondary characters according to their importance for propagation. Other classifications might very well be made to satisfy special practical requirements.

It is desirable to define closely the terms *sex gland* and *gonad* for mammals especially. I propose to restrict the term gonad to the generative part of the ovary or testicle. The hormone-producing part, even though generative elements may be involved in it, might be called "puberty gland," as proposed by Steinach, or, as Sand suggested, "sex hormonic gland"; but *sex-endocrine gland* is the better term. The "*gonad*" and '*sex-endocrine gland*" together form the "*sex gland.*"

H. THE HORMONIC ACTIVITY OF THE SEX GLANDS WHICH IS NOT SEX SPECIFIC.

We have already mentioned that there is evidence that the secretions of the testicle and the ovary may in certain circumstances produce similar effects. The growth of the pad in the frog and that of the comb in the fowl is promoted not only by the testicle, but to a certain degree also by the ovary (see p. 285). Other observations also have been made on the fowl (see p. 396). These can be explained by assuming that the ovary may produce male hormones. But, on the other hand, one might suppose that both sex glands may produce identical substances or hormones *which do not act in a sex specific manner*

Fichera (1905, quoted from Biedl) observed in various mammals that the hypophysis increases in volume and weight after castration. According to the same author an increase of the eosinophile cells both in number and size takes place in the castrated cock and in certain castrated mammals (rabbit, guinea pig, ox, buffalo). Similar statements have been made by others who have investigated the question, but not, indeed, by all. The problem has been dealt with by *Schönberg and Sakaguchi* (1917) and by *Bell* (1920, p. 42). Schönberg and Sakaguchi examined a great number of bulls, oxen and cows, and stated that the hypophysis is on the average much increased after castration, but the increase is not constant. They found also an hyperplasia of the eosinophiles, but they point out that it is very difficult to make any certain statements about their quantity, as the number of cells coloured with eosin depends greatly on the technique employed. Very similar are the statements of Bell who experimented on female cats. Removal of the ovaries appeared to cause some increase in the secretory activity of the anterior lobe; but the change was slight, and not quite constant. "There was (about eight months after castration) a large preponderance of brightly stained eosinophile cells in the anterior lobe—a condition indicating increased activity, but not the great activity seen after the thyroidectomy." In one experiment seven months after castration no divergence from the normal could be recognized histologically. The observations of Schönberg and of Bell seem to indicate that the changes occurring in the hypophysis after castration are identical in both sexes. Further, *Schleidt* (1914), in Steinach's laboratory, found that the hypophysis remains normal in feminized and masculinized animals. The influence exerted by the testicle on the hypophysis appears to be identical with that of the ovary. This influence is therefore apparently not sex specific. The question is of great theoretical interest, and should be dealt with more fully experimentally.

There is still another aspect of this question. We learned that there is in the "castrate" of both sexes a disproportion between body length and the length of the extremities, due to the fact that in the "castrate" the zone of proliferation persists for a longer time. Evidently both male and female sexual hormones influence the long bones in the same way, at a certain time inhibiting further growth. It might seem at first sight that here we have an hormonic effect which is a non-sex-specific one, like that on the hypophysis. But the condition is really somewhat different. Though there are differences between the male and female hypophysis in weight and histological structure, it seems that they are induced only by pregnancy. On the other hand, the length of the long bones is a very pronounced sex character; whenever measurements have been made the differences between male and female were found to be very marked, both for the upper and lower extremities (see the data in *Martin*, 1914, pp. 983, 992, 1016, 1017, 1040). One must suppose that male and female sexual hormones influence the growth of the bones in a quantitatively different way; possibly the quantity of the respective hormones entering the circulation and the rhythm of their secretion are different in male and female. Owing to this there is brought about a quantitatively different condition which is a sex specific effect.

But the dependence of morphogenetic processes and that of the metabolism upon sex hormones is in reality much more complicated than can be indicated under the expressions sex-specific or non-sex-specific activity. First of all, it must never be forgotten that the other organs producing internal secretions, which have such an enormous influence on all the processes going on in the organism, especially during growth, are also influenced by the internal secretions of the sex gland. It would be very difficult to say how far the hormonic effects of the sex glands are direct or indirect. Further, the sexual gland may influence the metabolism in a very complicated manner. This may be illustrated by examples. It has long been known that fat tends to accumulate in the castrated animal. One might suppose that this is due to the absence of sex hormones as with the other results of castration. But new experiments of *Heymans* (1921) in Gley's laboratory show that a different explanation is possible. Heymans measured the gaseous exchange of cocks and capons, and, like other investigators, found that the exchange in the capon is about 20 to 30 per cent. lower than that of the cock. Heymans found further that the gaseous exchange of normally developed cocks in which only small fragments of testicular grafts were present is about 10 to 20 per cent. lower than that of the ordinary cock. Since the accumulation of fat must be explained by the diminution of the gaseous exchange, and since the latter is also diminished in a bird with normal hormonic activity, it appears that the accumulation of fat and the changes occurring in the metabolism after castration cannot be due to lack of those sex hormones upon which the development of other sex characters depends. Whereas a small testicular fragment suffices for normal masculinization in the copulatory and genital apparatus and the neuropsychical sex characters, the state of the metabolism seems to depend upon the quantity of testicular tissue present in the body. Evidently the metabolism is affected by the quantitative level of the spermatogenetic processes. Is this influence an hormonic one? Or is this influence due to absorption by the testicle of different substances necessary for spermatogenesis? The latter explanation seems to me more likely.

The following is another example showing how complicated the relations between the sex gland and other parts of the organism may be. It was stated by Owen that the retractor muscles of the penis of the gelding become transformed into sclerotic tissue. The question has been examined histologically by *Retterer* (1915), who came to the conclusion that this transformation of the muscles is due simply to atrophy by inactivity, since the gelding, unlike the stallion, does not expel the penis when urinating. It seems possible that other castration effects might be explained similarly; for instance, the diminution of the corpora cavernosa penis (see p. 6), since sexual desire and erection diminish or disappear after castration. On this view one might understand why the corpora cavernosa penis and the corpus cavernosum urethrae behave differently after castration, the function of the latter being independent of sexual activity. The following observation is also not without interest (*Lipschütz*, 1923). In our experiments when there was operative interference with one testicle, such as removal of the greater part of it and retention only of a fragment above the cauda epididymidis, no testicular secretion could enter the latter. Now we found in these experiments that the cauda was much diminished, though there was a normal hormonic activity of the testicular fragment, and though, as in some experiments in which the second testicle was left intact, the cauda was normally developed on that side. There can be no doubt that in these experiments the underdevelopment of the cauda epididymidis was caused not by absence of hormones, but by decreased distension or by atrophy due to the fact that no more testicular secretion entered the epididymis.

The seminal vesicles of the guinea pig in my experiments (1923) were always normally developed on both sides, although a testicular fragment was present only on one side. It seems clear that the dependence of the seminal vesicles upon the testicle is an hormonic one; it may be recalled that no testicular secretion normally enters the seminal vesicles of the guinea pig. Now contrary to what was the general rule, I twice saw underdevelopment of the seminal vesicle on the side on which the testicle was removed, once in a guinea pig (*Fig.* 138) and once in a mouse after unilateral castration. I am unable to explain this phenomenon. There were no adhesions which could explain the underdevelopment.

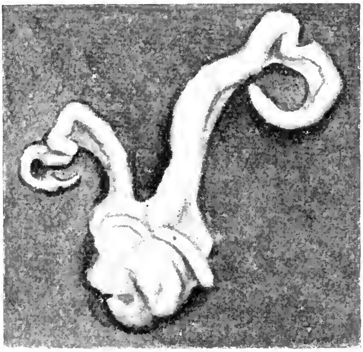


FIG. 138.—*Unilateral underdevelopment of seminal vesicles in case of unilateral castration in guinea pig 6½ months old* (Phot. Nr. 63). Nat. size. The right testicle has been removed at an age of 2 weeks; an upper fragment of the left testicle has been left in the body. The left vesicle is normal, the right one underdeveloped.

In view of all these observations I should like to emphasize the fact that the influence of the sex gland on the organism is evidently not merely hormonic, but is of a much more manifold nature (cf. Cramer in Marshall's *The Physiology of Reproduction,* 2nd edition, 1922). The greater the knowledge we possess concerning the dependence of morphogenetic processes on the sex gland, the more complicated the whole problem becomes, and the greater are the difficulties to be surmounted. Many apparently contradictory facts are probably due to the practice, which is perhaps inevitable, of attempting to simplify our problems arbitrarily, in considering the function of an endocrine gland or of a system of such glands as something acting *per se*; in reality there are mutual relations existing between all the internally secretory organs on the one hand, and between the whole endocrine apparatus and the other parts of the organism on the other. In physiology we are often compelled to think too morphologically, and we attempt to localize functions in a way which does not correspond with reality.

It seems to me also that the desire to replace an endocrine gland by the injection of an extract from the respective organ arises from a too purely morphological attitude. *In reality it will never be possible to accomplish such a substitution until we are able to imitate quantitatively the rate and rhythm of the secretory action of the gland.*

We mentioned above that sex hormones do not act in a way that is specific for each separate species. But nevertheless it seems possible that the endocrine action of the sex gland may sometimes be responsible for differences between species. It suffices to refer again to Morgan's experiments on hen-feathering in breeds of fowls. Probably certain qualitative differences between the testicle of the Sebright breed and that in other breeds are the cause of the special distinguishing characters of the Sebright. But possibly also different time and quantitative factors in the endocrine function of the sex gland may determine the distinguishing characters of the breeds. When considering the great differences between human races in regard to the relation between the length of the upper part of the body and the lower extremities one cannot but think that the sex gland or some other organ of internal secretion is a factor here. There are races with relatively long extremities such as certain natives of Australia and certain negroes; and those with relatively short extremities like the Eskimos and various Mongoloid races. Possibly also differences in the distribution of the hair on the body are due to variation in endocrine activity. The idea that racial differences in regard to body growth may be dependent on differences in the development of the endocrine glands, and especially the sex glands, has been already expressed in general terms by *Friedenthal* (1914, p. 140). *Keith* (1919, 1922) also has attempted to elaborate a more detailed theory on similar lines.

BIBLIOGRAPHY TO CHAPTER XI.

[* *Not seen in the original.*]

Ancel *et* Bouin. 1904. De la glande interstitielle du testicule des mammifères. *Journ. de Physiol. et Pathol. Génér.*, 6.

Aron. 1922. Sur le developpement des caractères sexuels primaires cehz les Urodèles. Hypothèse sur son déterminisme. *C. R. de l'Acad. d. Sc.*, 174, p. 1568.

Bell. 1920. *The Sex-Complex.* 2nd ed. London.

Biedl. 1913. *Innere Sekretion*, 2nd ed. Berlin–Wien.

Bormann. 1922. Über die Folgen der Kastration in ihren zeitlichen Beziehungen. *Skandin. Archiv für Physiologie*, 42, p. 240.

Champy. 1922. Etude expérimentale sur les différences sexuelles chez les tritons. *Arch. de Morphol. Génér. et Expérim.*, Fasc. 8.

*Chapin. 1917. A microscopic study of the reproductive system of foetal freemartins. *Jl. of Experim. Zool.*, 23, p. 453.

Crew. 1923. Studies in Intersexuality. I. A peculiar type of developmental intersexuality in the male of the domesticated mammal. *Proceed. Roy. Soc.*, B., 95, p. 90.

Cuénot. 1923. Hormones et hérédité. *Revue Française d'Endocrinologie*, 1, p. 41.

*Davenport. 1912. Sex-limited inheritance in poultry. *Journ. of Exp. Zool.*, 13, p. 1 (quoted from Cuénot, 1923).

Doncaster. 1914. *The Determination of Sex.* Cambridge.

Friedenthal. 1914. *Allgemeine und spezielle Physiologie des Menschenwachstums.* Berlin.

Goldschmidt. 1920. *Mechanismus und Physiologie der Geschlechtsbestimmung.* Berlin. English Edition, 1923. London.

Goodale. 1916. *Gonadectomy.* Carnegie Institution of Washington, Publication No. 243.

—— 1918. Feminized male birds. *Genetics*, 3.

Harms. 1922. Keimdrüsen und Alterszustand. *Fortschr. d. Naturwissensch. Forsch.*, 11, p. 189.

Herbst. 1901. *Formative Reize in der tierischen Ontogenese.* Leipzig (Arthur Georgi).

Herrmann. 1915. Über eine wirksame Substanz im Eierstocke und in der Plazenta. *Monatsschrift f. Geb. u. Gynäkol.*, 41.

Hertwig (Oskar). 1902. *Lehrbuch der Entwicklungsgeschichte*, 7th ed. Jena.

Heymans. 1921. Influence de la castration sur les échanges respiratoires, la nutrition et le jeûne. *Journ. de Physiol. et de Pathol. Génér.*, 19, p. 323.

HUXLEY (J. S.) 1912. The great crested grebe and the idea of secondary sexual characters. *Science*, N.S. 36, p. 601.

KAMMERER. 1912. Ursprung der Geschlechtsunterschiede. *Fortschritte d. naturwissenschaftl. Forschung*, 5, p. 1.

—— 1919. Steinachs Forschungen über Entwicklung, Beherrschung und Wandlung der Pubertät. *Ergebnisse d. inn. Med. u. Kinderheilkunde*, 17, p. 295.

*KEITH. 1919. On the differentiation of mankind into racial types. *Lancet*, No. 5013 (quoted from Biedl, 1922, *Innere Sekretion*, 4th ed., p. 28).

*—— 1922 a. The evolution of human races in the light of the hormone theory. *Bull. of the Johns Hopkins Hosp.*, 33, p. 155 (quoted from *Ber. über d. ges. Physiol.*, 15, p. 530).

*——1922 b. The evolution of human races in the light of the hormone theory. Racial status and form of body. *Bull. of the Johns Hopkins Hosp.*, 33, p. 195 (quoted from *Ber. über d. ges. Physiol.*, 15, p. 104).

KELLER *and* TANDLER. 1916. Über das Verhalten der Eihäute bei der Zwillingsträchtigkeit des Rindes. *Wiener tierärztl. Monatsschr.*, 3.

—— 1920. Zur Frage der sterilen Zwillingskälber. *Wiener tierärztl. Monatsschr.*, 7, p. 146.

KOCH (Walter). 1921. *Über die russisch-rumänische Kastratensekte der Skopzen.* Jena.

KOHN (Alfred). 1920. Der Bauplan der Keimdrüsen. *Arch. f. Entw.-Mech.*, 47, p. 95.

LILLIE *and* BASCOM. 1922. An early stage of the Free-martin and the parallel history of the interstitial cells. *Science*, N. S. 55, No. 1432 (quoted from Lillie, 1923).

—— 1923. Supplementary notes on twins in cattle. *Biolog. Bull.*, 44, p. 47.

(See also Chapin, Minoura and Willier.)

LIPSCHUTZ. 1917. Die Gestaltung der Geschlechtsmerkmale durch die Pubertätsdrüsen. *Anz. d. Akad. d. Wissensch.* Wien.

—— 1918a. Die Gestaltung der Geschlechtsmerkmale durch die Pubertätsdrüse. *Arch. f. Entw.-Mech.*, 44.

—— 1918b. Umwandlung der Clitoris in ein penisartiges Organ bei der experimentellen Maskulierung. *Arch. f. Entw.-Mech.*, 44.

—— 1918c. Prinzipielles sur Lehre von der Pubertätsdrüse. *Arch. f. Entw.-Mech.*, 44.

—— 1923. Beobachtungen zur Frage einseitiger Kastrationserscheinungen. *Arch. f. Entw.-Mech.*, 52, p. 395.

(See also Bormann.)

MARAÑÓN. 1922. *Problemas actuales de la doctrina de las secreciones internas.* Madrid.

MARTIN. 1914. *Lehrbuch der Anthropologie.* Jena.

MINOT. 1908. *The problem of age, growth and death.* London.

MINOURA. 1921. A study of testis and ovary grafts on the hen's egg and their effects on the embryo. *Jl. of Experim. Zool.*, 33, p. 1.

MOORE. 1921. On the physiological properties of the gonads as controllers of somatic and psychical characteristics. III. Artificial hermaphroditism in rats. *Jl. of Experim. Zool.*, 33, p. 365.

*MORGAN *and* GOODALE. 1912. Sex-linked inheritance in poultry. *Annals of the New York Acad. of Sc.*, 22, p. 113 (quoted from Plate, 1913. Vererbungslehre. Leipzig, W. Engelmann).

—— 1919. *The genetic and the operative evidence relating to secondary sexual characters.* Carnegie Institution of Washington Public. 285.

MYERS (J. A.). 1916. The Growth and distribution of the milk-ducts and the development of the nipple in the albino rat from birth to ten weeks of age. *Americ. Jl. of Anatomy*, 19.

—— 1917 a. The fetal development of the mammary gland in the female albino rat. *Americ. Jl. of Anatomy*, 22.

—— 1917 b. A comparison of the developing mammary glands in male and female albino rats from the late fetal stages to ten weeks of age. *Anatom. Record*, 13.

*PEARL. 1912. The mode of inheritance of fecundity in the domestic fowl. *Jl. of Experim. Zool.*, 13, p. 153 (quoted from Plate, 1913. Vererbungslehre. Leipzig, W. Engelmann).

PÉZARD. 1915. Transformation experiment. des caractères sex. sec. chez les Gallinacées. *C. R. de l'Acad. des Sc.*, 160, p. 260.

—— 1918. Le conditionnement physiologique des caractères sexuels secondaires chez les oiseaux. *Bull. Biol. de la France et de la Belgique.* (Thèse de Paris.)

—— *et* CARIDROIT. 1922a. L'hérédité sex-linked chez les Gallinacés. Interprétation fondée sur l'existence de la forme neutre et sur les propriétés de l'hormone ovarienne. *C. R. de l'Acad. des Sc.*, 175, p. 910.

—— *et* CARIDROIT. 1922b. L'action de l'hormone testiculaire sur la valence relative des facteurs allélomorphes chez les ovins (Dorset × Suffolk). *C. R. de l'Acad. d. Sc.*, 175, p. 1099.

POLL. 1909. Zur Lehre von den sekundären Geschlechtscharakteren. *Sitzungsberichte d. Gesellsch. naturforsch. Freunde zu Berlin.*

PUNNETT *and* BAILEY. 1921. Genetic studies in poultry. III. Hen-feathered cocks. *Journ. of Genet.*, 11, p. 37.

RETTERER. 1915. Influence de la castration sur la structure des cordons rétracteurs du pénis. *C. R. de la Soc. de Biol.*, 78, p. 192.

RIDDLE. 1920. Differential survival of male and female dove embryos in increased and decreased pressures of oxygen; a test of the metabolic theory of sex. *Proceed. Soc. f. Exp. Biol. a. Med.*, 17, p. 88.

STEINACH. 1912. Willkürliche Umwandlung von Säugetier-Männchen, etc. *Pflügers Archiv*, 144.

—— 1916. Pubertätsdrüsen und Zwitterbildung. *Arch. f. Entw.-Mech.*, 42 (Ch. II.), p. 307.

SCHLEIDT. 1917. Über die Hypophyse bei feminierten Männchen und maskulierten Weibchen. *Anz. d. Akad. d. Wissensch.*, Wien. (Also *Zentralbl. f. Physiol.*, 27.)

SCHÖNBERG *und* SAKAGUCHI. 1917. Der Einfluss d. Kastration auf die Hypophyse des Rindes. *Frankf. Ztschr. f. Pathologie*, 20.

TANDLER *und* KELLER. 1910. Über den Einfluss der Kastration auf den Organismus. IV. Die Körperform des weiblichen Frühkastraten des Rindes. *Arch. f. Entw.-Mech.*, 31, p. 289.

—— *und* GROSS. 1912. Über den Saisondimorphismus des Maulwurfshodens. *Arch. f. Entw.-Mech.*, 33, p. 297.

—— *und* GROSS. 1913. *Die biologischen Grundlagen der sekundären Geschlechtscharaktere.* Berlin, Springer.

*THOMAS (R. Haig). 1912. Experimental pheasant-breeding. *Proc. Zool. Soc.*, 3, p. 539 (quoted from Doncaster, 1914).

THOREK. 1922. The present position of testicle transplantation in surgical practice: a preliminary report of a new method. *Endocrinology*, 6, p. 177.

DE LA VAULX. 1922. Les caractères sexuels et le problème de leur groupement. *Revue génér. des Sciences*, June 15.

VORONOFF. 1923. *Greffes testiculaires.* Paris.

WILLIER. 1921. Structures and homologies of freemartin gonads. *Jl. of Experim. Zool.*, 33, p. 63.

*WODSEDALEK. 1920. Studies on the cells of cattle with special reference to spermatogenesis, oögonia, and sex-determination. *Biol. Bull.*, 37, p. 290 (quoted from *Arch. f. Zellforschung*, 16, p. 439).

ZAWADOWSKY. 1922. *Das Geschlecht und die Entwicklung der Geschlechtsmerkmale.* (Russian with German summary.) Moscow.

—— 1923. *The sex of animals and its transformation* (Russian). Moscow–Petrograd.

Chapter XII.

Some Practical Aspects. The Problem of Rejuvenation.

We have discussed in the foregoing chapters the manifold influences which the sex hormones exert on the organism. We have seen how far morphogenesis during embryonic and extrauterine development depends upon sexual hormones, and, moreover, how somatic and psychical puberty, if once reached, is further maintained and developed during the whole sexual life by the intermediation of sex hormones. The endocrine sex gland is in very close relation to other organs of internal secretion, and variation in the function of the sex gland necessarily interferes with the activity of the whole system of endocrine glands. On the other hand the production of sex hormones and its influence on the body depends greatly on the simultaneous activity of the other parts of the endocrine system.

We have seen further that various abnormal or pathological conditions such as *intersexuality, eunuchoidism, sexual precocity* and possibly, it may here be added, certain other pathological conditions in women depend to a certain degree, directly or indirectly, upon abnormal or pathological conditions of the endocrine sex gland. The abnormal condition may be either *inborn* or *acquired.* Many *infectious diseases,* especially those of a chronic character, as, for instance, tuberculosis, can injure either the sex gland or the other organs of internal secretion. Poisons such as *alcohol* may act similarly. The question of castration also has its practical interest in connection with many diseases in women and tuberculosis of the testicle in men. In view of these considerations one can assuredly say that the study of the sex hormones must be one of great interest to those concerned with medical science.

It is none the less of great importance also in relation to *eugenics.* It is one of the main objects of eugenics to regulate mating in such a way that healthy progeny is produced. Now it is probable that this can be attained only when a normal erotization occurs in both parents; first, because an individual who is normal in this respect, will have a better chance of choosing for a mate another individual who is sexually normal in every respect; secondly, because an individual who is normal in this way is likely to produce normal generative cells, and to have a somatic constitution such as is necessary for normal uterine development, normal parturition and normal nutrition of the progeny. But the occurrence of normal erotization, sex characters, and possibly generative cells, depends on a normal production of sex hormones.

There is still another aspect of our problem which bears on the science of eugenics. The question has often been discussed as to how temporary or permanent *sterilization* can best be practized from a social standpoint; ligature of the vasa deferentia has been done upon men for this purpose in Switzerland and in America; for the women irradiation with X-rays has been suggested. *Pearl's* paper (1919) may be referred to in this connection.

The question of sex hormones is of interest also in relation to *veterinary medicine* and "*zootechnics.*" Many of those pathological conditions referred to in man in connection with the sex hormones may be observed also in the domestic animals.

Another matter of great practical interest is that of the possible utility of *ovarian and testicular transplantation* in man in cases of hormonic deficiency. Much depends on whether it will be possible in future to use glands of other species of mammals for transplantation. Since sex hormones probably do not have a "species specifity," it is a question not of theory but of practice. The papers of *Voronoff* (1923) and *Thorek* (1922) on transplantation of apes' testicles in man seem to indicate that a practical solution to the question is on its way. *Voronoff* (1924) lastly gave an account of 43 cases of heterotransplantation in man, *Thorek* (1923) of 97 cases. As to autotransplantation of testicle and ovary there is, I think, no surgical practitioner in this field to-day who does not appreciate its utility.

The practice of *irradiation of the sex gland* in men and women is also one of practical interest. So also are the questions relating to the *injection of extracts*, though, as already remarked in Chapter VII., we are still a long way from their solution.

In recent years there has been much discussion concerning the relation between sex hormones and *senility*. The question seemed to have been lost sight of for about thirty years after the first experiments of *Brown-Séquard* in 1889. But *Harms* in 1914 described an experiment in which a senile male guinea pig had implanted into it the testicle of its six weeks old son. Renewal of sexual activity was noticed subsequently for several weeks or somewhat longer. *Harms* (1922) performed similar experiments on old dogs, both male and female. Hairless places on the skin became covered with hair again after testicular transplantation, and the hair was thick and shiny. The teeth which had been loose became firm again. In one case a senile cataract disappeared almost entirely. *Voronoff* (1923) transplanted testicles of young animals into senile rams ten or twelve years of age. Various indications of senility, such as thin wool, cachexia, apathy, tremor in the legs, and incontinentia urinae, partly disappeared. The animals became more lively about two months after the operation; the wool became shiny, sexual activity reappeared, and one animal which was said to be sterile for two years once more bred. Voronoff says that the animals looked so well that one would suppose them to be 6 to 8 years of age if the horns and teeth had not indicated an age of 12 to 14. He observed his animals for more than four years. Removal of the graft causes reappearance of the signs of senility, which disappear again when a second transplantation is made. Voronoff fixed the testicular fragments on the testicle *in situ* with catgut. Spermatozoa could be detected fourteen months after transplantation; they were present even when the graft did not originally contain ripe spermatozoa.

Great interest has been aroused by *Steinach's* experiments (1920) in which, to bring about *rejuvenation*, another method was used. Since Bouin and Ancel performed their original experiments it has been known that *ligature of the vasa deferentia* causes profound changes in the testicle. Several investigators some time after the operation have observed an increased sexual activity which has been ascribed to greater hormonic activity on the part of the testicle. Now Steinach conceived the idea of using this method to increase the hormonic activity of the testicle in animals with symptoms of senility. In the experiments which Steinach performed on rats, there were unmistakable signs of improvement. The hairless spots on the skin disappeared and the hair of the whole body became thick; it was the same with the scrotal skin. The bent position of the aged animal changed to that characteristic of a vigorous youthful one. The weight increased. The seminal vesicles and the prostate, which were in a state of atrophy, regenerated. The animals which were hitherto apathetic became more active, and they took an interest in individuals of the other sex and generally regained sexual activity. These results could be attained even if only *one* vas deferens was ligatured. To bring about this effect it is necessary to avoid injury to the blood vessels accompanying the vas deferens. Since it is not always possible to do this, Steinach, in his later experiments, effected a ligature of the efferent ducts between the testicle and the cauda epididymidis. He observed operated senile animals for about eight months after the operation. In regard

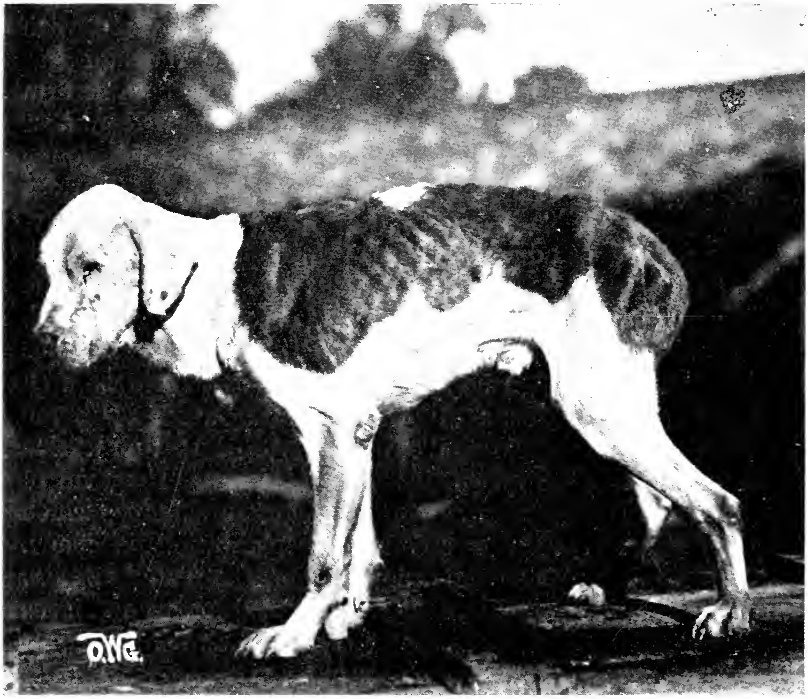


FIG. 139.—''*Rejuvenation*'' *of senile dog*, 18 *years old.* Before operation, after having been seven months under observation. Weight 33 kgr.; only small changes in weight during the whole time of observation notwithstanding best alimentation.—From Wilhelm.

to the question whether besides a general improvement and a regeneration of sex characters there is also a prolongation of life, the experiments do not provide data.

If a unilateral operation only is made, the regenerated animal can fecundate. According to Steinach, regeneration of the generative part also in the testicle may take place in the senile animal. Similar statements as to the generative part have been made, as already mentioned, by Harms and Voronoff about the results of testicular transplantation in senile animals.

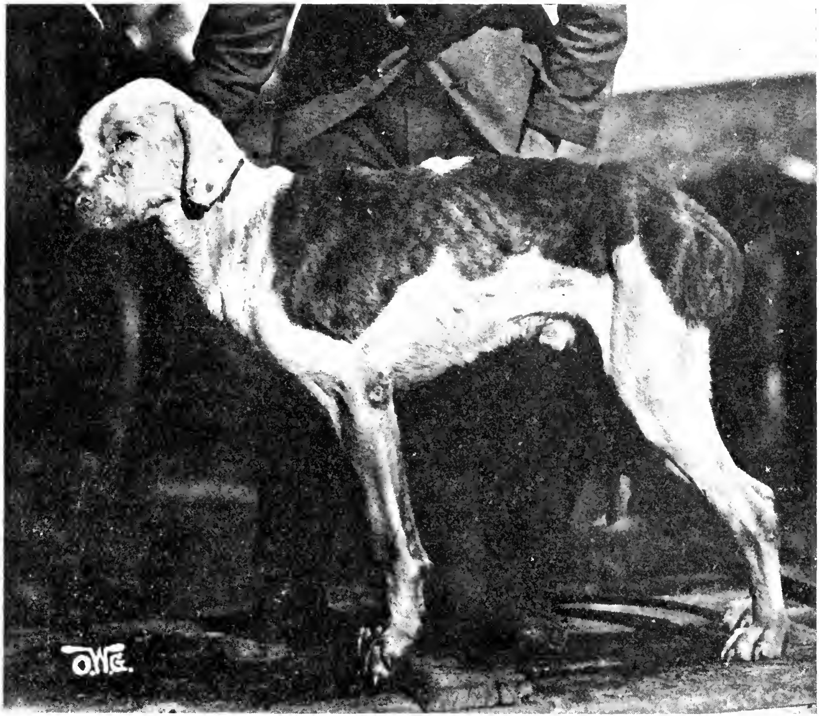


FIG. 140.—"*Rejuvenation*" *of senile dog, 18 years old.*—Same as 139. The animal is only able to stand for a short time, and has to be supported.—From Wilhelm.

Steinach states that he succeeded in regenerating female rats by ovarian transplantation. An example may be given. A female rat 26 months old, which was sterile for 10 months, and showed no signs of heat and revealed hairless patches on the skin and atrophic teats, and was thin and generally apathetic, had implanted into it both ovaries of a pregnant four months old female. Four weeks after the operation heat occurred, and about two weeks later the teats grew in size. Later on the hair began to grow. Subsequently 2½ months after the operation the animal became pregnant and gave birth to five young, which she suckled.

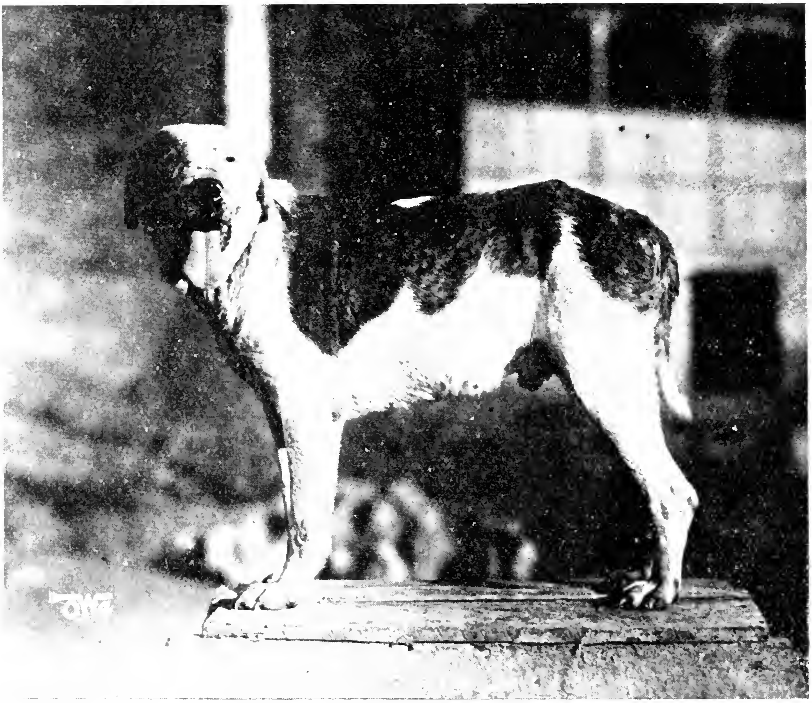


FIG. 141.—"*Rejuvenation*" *of senile dog*, 18 *years old.* Three months after operation (unilateral resection of the epididymis). Weight 40 kgr.—From Wilhelm.

Steinach's experiments, in which he ligatured the vas, have been confirmed by *Sand* (1921) and *Wilhelm* (1922, 1923) on the dog. In Sand's experiment the animal was more than 12 years old, and in those of Wilhelm as much as 18 years old. Both authors made a resectio epididymidis. There was an extraordinary general improvement and recuperation of sexual activity. The body weight increased greatly. The results of the numerous successful experiments of Wilhelm were extremely striking (*Figs.* 139–142). Wilhelm has performed six similar experiments out of which five gave the same positive result. The improvement lasted in one case about 10 months.

Romeis (1921) made a unilateral ligature of the vas deferens on *one* old rat, while the second testicle was removed. He states that there was an increase of weight and the animal

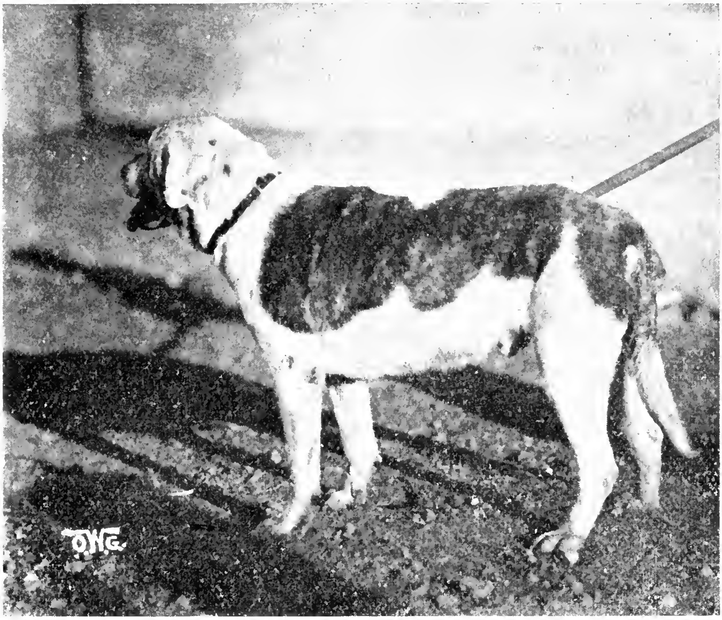


FIG. 142.—"*Rejuvenation*" *of senile dog, 18 years old.* Six months after operation. Weight 48 kgr.—From Wilhelm.

became livelier, but there was no recuperation of sexual activity. The hair became less rough, but the hairless patches remained as they were. There was an increase of the prostate, but Romeis claims that this was due to a distention of the prostatic gland by its secretion and that the glandular cells were atrophic. A single partly negative experiment, however, can hardly be made the basis for a discussion of the whole problem in the way the author attempts to do, especially in view of the numerous experiments of Steinach on rats published previously and of the positive experiments of Sand

and Wilhelm on dogs published afterwards. Further *Wilhelm* (1923) has recently published a series of six experiments on rats which fully confirm, without any exception, the experiments of Steinach. The improvement lasted sometimes several months.

Steinach's observations on female rats were confirmed by *Kolb* (1922, 1923), who experimented on a goat of 14, weighing 36 kgr. There were pronounced signs of senility, lack of fat, flabby muscles, general debility to such a degree that it was necessary to raise the animal on its feet to feed it; there was an almost total hairlessness, a flabby udder with no milk. The animal was sterile for three years. Kolb engrafted ovarian fragments under the skin into the muscles and into the abdominal cavity. Some weeks subsequently the animal became livelier and more robust; it could get up on its legs without help. In the second month after the operation the udder increased in size. Two and a half months afterwards a growth of hair began, and there was finally a thick coat of hair. In October, about four and a half months after the operation, the animal weighed 41 kgr., and it was then in a state of pronounced heat for two weeks. It became pregnant, and in March gave birth to a healthy kid. The animal had to be killed soon after the birth of its kid on account of a gangrenous mastitis.

Steinach and Lichtenstern have employed ligature of the vasa deferentia also as a method of regeneration or rejuvenation in man. It is impossible here to discuss the whole question from a clinical point of view. The papers of *Peter Schmidt* (1922), *Benjamin* (1922) and *Sand* (1922 a) may be referred to. Notwithstanding the differences of opinion expressed about the usefulness of the operation, it seems clear that in some cases of precocious senility a general improvement and a recuperation of sexual potency may be induced by vasoligature.

I have had the opportunity of seeing certain patients operated on by Steinach and Peter Schmidt, and I cannot but say that in some cases the effect of the operation seems to be very striking and beneficial. It is probable that the method will reveal its practical utility more especially in cases of precocious senility (*Lipschütz*, 1921).

Various doctors have employed testicular transplantation in man as a remedy against senility. The papers of *Stanley* *and Kelker* (1920) and of *Voronoff* (1923) may be mentioned in this connection. Voronoff claims to have had excellent results in many cases of transplantation of apes' testicles. Two of his cases, men of 61 and 74 years of age, were observed for about two years after the operation. Recuperation of sexual potency and a very remarkable general improvement are recorded. In other cases there was no success at all or only a temporary or partial one. Voronoff is of the opinion that testicular transplantation is indicated only in those cases where the symptoms are conditioned by an hormonic insufficiency of the testicle, and that no success will be attained when insufficiency of other organs is involved. *Thorek* (1922) removed a heterograft 7 months after the operation, and he stated that the graft was histologically in a condition assuring normal endocrine activity. Stanley and Kelker report that, according to the statement of the oculist, a very marked improvement of eyesight was obtained in a man of 54 after testicular homoiotransplantation. *Stanley* (1922) claims also to have treated senility successfully by implantation of testicular substance obtained from various mammals. In the latter cases there could only have been an effect from the resorbed hormones, as the testicular substance was introduced by pressing it out of a syringe.

In women, Bumm and *Sippel* (1923) obtained good results in certain cases of precocious menopause and senility by ovarian homoiotransplantation.

There has been much discussion on the question whether "rejuvenation" really occurs after ligature or transplantation. Since the changes characteristic of old age take place throughout all the organs, and since senility is caused not merely by the disfunction of one organ or of a certain group of organs (*Lipschütz*, 1915), it is clear at the outset that in as far as rejuvenation might be induced by an improvement in the functional capacity of a certain organ, this rejuvenation could be only a partial or a restricted one. Further, it must be taken into consideration that the changes which the cells undergo owing to age are in general irreversible ones, pigmentation and cellular atrophy, and finally sclerosis taking place. But on the other hand, the experiments on animals with transplantation and ligature of the vasa deferentia leave no doubt that symptoms of senility may be checked to a certain degree, and regeneration may take place under the influence of sex hormones, the effects lasting for some time. According to *Růžička* (1922), who examined the experimental animals of Steinach, the tissues of ligatured rats show some change even in their state of aggregation in the direction of being rejuvenated. But it would evidently be better not to speak of a *rejuvenation,* but of a *regeneration,* as Sand does, since as yet we have no certain data concerning the changes induced in the organism in the above-mentioned experiments. The first functions to be affected in the rejuvenation process are apparently those which depend upon sex hormones. *Loewy and Zondek* (1921) stated that the output of CO_2 in old men increases after ligature of the vasa deferentia, at any rate temporarily. The increase may be 17 to 30 per cent.; this corresponds to the difference between a normal and a castrated individual. But I should like to point out that a similar statement does not imply that normally senility depends on a disfunction of the sex gland. On the other hand, it cannot be denied that the impression produced is that the operation leads to a general regeneration besides re-erotization. The statements of Steinach and Peter Schmidt to the effect that there is a new growth of hair after the operation is evidence of this.

The question has also been heatedly discussed as to whether the effect of ligaturing the vasa deferentia is caused by an intensified hormone-production of the interstitial cells, as Steinach supposes, or by a resorption of the products of decomposition of the seminal cells, as has been claimed by several authors. This question also is not without some interest from the standpoint of practical medicine. *Kohn* (1921), who is of the opinion that the beneficial effects of the ligature are due to resorption of substances derived from the generative cells, remarks that it may be necessary to return to the older method of Brown-Séquard, who injected testicular extracts. Heterotransplantation, and even homoiotransplantation, if the graft does not "take," may often act merely by resorption.

It is still difficult to understand why the discussion upon the seat of production of the sex hormone became so heated, especially in Germany. "Unfortunately," as *Sand* says (1922 b), "the discussion reveals a certain tendency; certain publications, showing evidence of complete misunderstanding and full of false quotations, are without any scientific value.

It is curious to note, for instance, how the theory of the interstitial gland put forward originally by French men of science has subsequently acquired a new nationality, and is attacked as the 'theory of the puberty gland' of Steinach, who, as is well known, has made some of the best contributions in this field, but who was not very fortunate in the choice of his term." The question of the seat of hormone-production in the testicle is not yet definitely solved, as we have seen especially in Chapter IV.; why complicate the question of the effects of transplantation or ligature in senile or precociously senile individuals, or in other pathological conditions, a question which is essentially practical, by confusing it with the former question as to the seat of hormone-production? Such confusion is the more to be avoided in view of the possibility that some of the effects of ligature are not necessarily of an hormonic order at all. However these problems may finally be solved, there is one conclusion which stands beyond the reach of controversy, and that is that the testicle and the ovary are organs of internal secretion, and that *their hormones are sex specific.*

BIBLIOGRAPHY TO CHAPTER XII.

[* *Not seen in the original.*]

BENJAMIN. 1922. The Steinach operation; report of 22 cases with endocrine interpretation. *Endocrinology*, 6, p. 776.

*BROWN-SÉQUARD. 1889. Expériences démontrant la puissance dynamogénique chez l'homme d'un liquide extrait de testicules d'animaux. *Arch. de Physiol.*, 1, p. 651.

*—— 1889. Du rôle physiologique et thérapeutique d'un suc extrait de testicules d'animaux d'après nombre de faits observés chez l'homme. *Ibidem*, 1, p. 738.

*—— 1890. Nouveaux faits relatifs à l'injection souscoutanée chez l'homme d'un liquide extrait de testicules mammifères. *Ibidem*, 2, p. 204.

GLEY. 1922. Sénescence et endocrinologie. *Bull. de l'Acad. de Médec.*

HARMS. 1914. *Experimentelle Untersuchungen über die innere Sekretion der Keimdrüsen.* Jena.

—— 1922. Keimdrüsen und Alterzustand. *Fortschr. d. naturwissensch. Forsch.*, 11, p. 189.

HOSKINS. 1921. Some current trends in endocrinology. *Jl. of the Amer. Med. Ass.*, 77, p. 1459.

KOHN. 1921. "Verjüngung und Pubertätsdrüse." *Medizin. Klinik*, 17, p. 804.

KOLB. 1922. Über einen Verjüngungversuch bei der Ziege. *Verhandl. d. schweizer. naturforsch. Gesellsch.*, 103, p. 311.

KOLB. 1923. Mitteilung über einen Verjüngungsversuch bei der Ziege durch Ovarientransplantation. *Wiener Med. Wochenschr.*, Nr. 45.

LIPSCHÜTZ. 1915. *Allgemeine Physiologie des Todes.* Braunschweig, Vieweg u. Sohn.

—— 1921. Die innere Sekretion der Geschlechtsdrüsen und ihre Bedeutung für die Sexualität des Menschen. An address delivered at the I. Internat. Tag. f. Sexualreform (etc.), Berlin, 1921. (In *Sexualreform und Sexualwissenschaft*, herausgegeb. von Weil, Stuttgart, 1922.)

LOEWY *und* ZONDEK. 1921. Der Einfluss der Samenstrangunterbindung (Steinach) auf den Stoffwechsel. *Deutsche mediz. Wochenschr.*, No. 13.

PEARL. 1919. Sterilization of degenerates and criminals considered from the standpoint of genetics. *The Eugenics Review*, April.

ROMEIS. 1921. Untersuchungen zur Verjüngungshypothese Steinachs. *Münch. medizin. Wochenschr.*, p. 600.

RŮŽIČKA. 1922a. Über Protoplasmahysteresis und eine Methode zur direkten Bestimmung derselben. *Pflügers Archiv*, 194, p. 135.

—— 1922b. Die Protoplasmahysteresis und das Verjüngungsproblem. *Deutsche medizin. Wochenschrift*, No. 28.

SAND. 1921. "Vasectomi" hos Hund som Regenerationseksperiment. *Ugeskrift for Laeger* 83, No. 46 (also in German, 1922. *Zeitschrift für Sexualwissenschaft*, 8, No. 12).

—— 1922a. Vasoligature (Epididymectomy) employed ad mod. Steinach with a view to restitution in cases of senium and other states (impotency, depression). Operation on man. *Acta Chirurg. Scandinav.*, 55, p. 387.

—— 1922b. L'hermaphrodisme expérimental. *Jl. de Physiol. et de Pathol. Génér.*, 20, p. 472.

SCHMIDT (Peter). 1922. *Theorie und Praxis der Steinachschen Operation.* Wien,

SIPPEL. 1923. Die Ovarientransplantation bei herabgesetzter und fehlender Genitalfunktion. *Arch. f. Gynäkol.*, 118, p. 445.

*STANLEY *and* KELKER. 1920. Testicle transplantation. *J. Am. M. Ass.*, 75, p. 1501 (quoted *Ber. ges. Physiol.*, 2, 1920, p. 575).

—— 1922. An analysis of one thousand testicular substance implantations. *Endocrinology*, 6, p. 787.

STEINACH. 1920. *Verjüngung durch experimentelle Neubelebung der alternden Pubertätsdrüse.* Berlin.

THOREK. 1922. The present position of testicle transplantation in surgical practice; a preliminary report of a new method. *Endocrinology*, 6, p. 771.

—— 1923. Über eine neue Methode der Hodenverpflanzung und verwandte Probleme. *Wiener Med. Wochenschr.*, Nr. 50.

VORONOFF. 1923. *Greffes testiculaires.* Paris, Octave Doin.

—— 1924. *Quarante-trois greffes du signe à l'homme.* Paris.

WILHELM. 1922 and 1923. Contribución al estudio histiofisiologico de los llamados fenómenos de rejuvenecimiento. *Revista Médica de Chile*, 50 and 51.

Index of Authors.

Adler 178, 399
Aimé 211
Albers-Schönberg 153
Albertoni 99, 100
Amantea 24, 337
Ancel 380, *see also* Bouin
Aristotle v.
Aron 52, 122, 126, 189–90, 443
Asch 372
Aschner 211, 213–7, 220, 221, 230, 248–9, 256, 258–9, 263–4, 266, 269, 430
Askanazy 436–7
Athias 28, 88, 217–9, 256–7, 262, 265, 269, 288, 291–4, 331, 442
Aunap 114–5

Baar 437
Bab 377
Baglioni 99–101, 337
Bailey 394
Bamber 390
Barnabo 322
Bascom 389
Bayliss 80
Beard 251
van Beek 270, 388
Bell, W. Blair 15, 16, 33, 90, 227, 239, 249, 323, 373–7, 397, 407, 435–6, 474
Benda 111, 148, 368, 377
Benjamin 490
Benoit 191, 193, 197, 199, 345, 396
Berberich 183
Berblinger 128, 177, 376, 427–8
Bergonié 153
Bernard v
Berman v.
Berthold v., 81
Bertholet 178
Biedl 5, 25, 64, 82, 88, 233, 255–6, 320, 335, 339, 350, 447, 474
Bierens de Haan 298
Bloch 351
Boehm 437
Bogoslavski and Korenčevski 339
Bolognesi 142, 377
Bond 409
Bond and Horsley 243
Bordeu v.
Boring, *see* Pearl
Bormann 22, 290, 452
Bormann, Brunnow and Savary 299
Born 251
Böttcher 345
Bouin 109, 224, 331
Bouin and Ancel 94, 109, 111, 118, 122, 127–131, 133, 143, 145–7, 152, 154, 166, 170, 174, 178–9, 183, 188, 194–7, 252–5, 258–260, 320, 322, 455, 461, 469, 485
Bouin, Ancel and Villemin 230–31, 234
Bouin and Garnier 178
Brack 133, 183
Brandes 288, 293, 442
Brehm 48–9
Bresca 52, 286
Bromann 457
Brown-Séquard v., 93, 319, 485, 492
Bucura 36, 88, 239, 265, 287
Bujard 380
Bumm 90, 491
Busquet 13, 35, 99–100, 335

Camus and Gley 336–7
Caridroit 358
Carmichael and Marshall 25, 29, 243
Caullery 58, 79, 287
Çeni 142, 195, 199
Čejka 183
Champy 187–90, 199, 399, 400, 443–4, 473
Chapin 388, 469
des Cilleuls 191–2
Clowes and Bachman 345
Cohn 249
Cordes 178
Corner 246
Courrier 58, 64–6, 172–3, 186–7, 191, 199, 344–5
Cramer 477
Crew 143, 381–2, 392, 398–9, 454
Crew and Huxley 397
Cuénot 461, 463, 465

Darwin 50, 456, 458, 461, 464
Davenport 463
Dittler 331
Donaldson 294
Doncaster 390, 409–10, 458
Dragoiu 68

Els 86, 92
Exner 34, 160, 335

Falcone 88
Faure 34
Fauré-Fremiet 68

Fell 381, 392–3
Fellner 320, 323–4, 327, 329–30
Fichera 474
Fisher 355, 362
Fitzsimons 44
Foges 36, 39–41, 82, 166, 195, 287, 309, 323, 363
Forel 409
Forster 86
Fraenkel 211–14, 220, 249, 251, 255, 260, 267, 322–3
Franz 30–2
Friedenthal 478
Friedmann 189
Fürbringer 335, 343
Furno 424, 426–7

Ganfini 170
Gerlinger 249, 261
Giacomini 249
Giard 59, 66
Gley 79, 109, 319–21
Gley and Pézard 23
Goddard 125
Goette 183
Goldschmidt 58–9, 63, 65, 350, 369, 400–3, 412, 444–5, 447, 454
Goltz 53, 98–9
Goodale 36, 38–47, 63, 198–9, 273–5, 288, 307–9, 312, 352, 357–8, 394–6, 410, 442, 451–3, 466, 468
Goormaghtigh 227, 250
Goto 359, 390
Gorki 7
Gould 69
de Graaf, Regnier 338
Griffith and Duckworth 425
Gross, *see* Tandler and Gross
Guggisberg 234–5
Guthrie 43
Gurney 390
Guyénot and Ponse 92, 188, 272, 399
Guyer 195

Haberern 338
Haberlandt 90, 243, 257
Halban 18, 29, 56, 351, 403, 426
Hammond 259
Hammond and Marshall 253, 255
Hansemann 170, 178
Harms 51–3, 58, 68, 96, 186–7, 272, 285–7, 291, 297, 303, 322, 330, 399, 447, 485, 487
Hartmann and Hamilton 392
Heape 255, 263
Hedinger 180–1
Henry 263
Herbst 56, 58, 466
Herlitzka 286
Herrmann 320, 323–9, 469
Herrmann and Stein 257, 323, 327, 329, 330
Hertwig 459
Hewer 230
Heymans 235, 475
Hill 249
Hirokava 335, 343
Hirschfeld 5, 7, 12, 13, 351, 368, 371, 403, 408, 424, 431
Hitschmann and Adler 260
Hofstätter 5, 178, 255
Holzknecht, *see* Steinach and Holzknecht
Houssay 167
Houssay and Hug 142
Houssay and Wallart, 230
Hunter 81, 287
Humphrey 188–9
Huxley 401–3, 473

Iscavesco 323
Itagaki 330–1
Iwanoff 341, 344

Jaffe 183
Josefson 424

Kammerer 5, 25, 29, 54, 57, 286, 442, 446, 449, 470
Kasai 125–6, 178–9
Keith 478
Kelker 87–8, 490–1
Keller 386, 388, 446
Keller and Tandler 383–4, 387, 469
Kellog 55
Kitahara 183
Koch 5, 12, 16, 426, 441
Kohn, Alfred 120, 163, 174, 181, 446, 492
Kolb 490
Kölliker 335, 343–4
Kolmer and Koppányi 190
Kolmer and Scheminzky 186
Kon 12
Kopeć 54–5, 57, 312–13
Kornhauser 66
Kostich 178
Krabbe 372, 431, 434–6, 438
Kraepelin 371
Krause 88, 291, 352, 356, 360–1
Krediet 270, 381
Kreuter 370
Kropman 129, 160
Krzyśkowsky 344
Kull 111–2, 123–4, 139–40, 158–9, 162, 182, 215, 217–9, 221, 223–4, 240–1, 244–5, 252
Kuntz 128, 133

Kyrle 143, 152, 154, 160, 174, 179–80
Kyrle and Schopper 178

Labhardt 266
Lacassagne 36, 133, 163, 166, 227–8, 269
Lane-Claypon 250
Langhans 100–1
Lauche 161, 190, 273, 276
Lecaillon 171–3
Lehbert 27, 114–6, 151, 156–7, 164–5, 212, 216, 247
Lespinasse 84
Leuckart 337
Leydig 110, 111
Lichtenstern 12, 19, 34, 85–6, 92, 148, 288, 335, 338, 341–2, 369–70, 442, 490
Lillie 270, 359, 383–9, 444–5, 452, 454, 467
Lillie and Bascom 389, 445–6
Limon 211–12, 222–4, 227
Lipschütz vi., 17, 28, 79, 84, 102, 145, 150, 160, 162–3, 243–4, 246, 262, 287–8, 291, 299, 301, 352, 388, 428, 442, 444, 447, 450, 454, 465, 476, 490–1
Lipschütz and Ibrus 161
Lipschütz and Krause 359, 363
Lipschütz and Voss 246, 291, 352, 356–7, 362–3, 451
Lipschütz and Wagner 131
Lipschütz, Krause and Voss 352, 356, 362
Lipschütz, Lange and Tiitso 357
Lipschütz, Ottow and Wagner 87, 157
Lipschütz, Wagner and Bormann 145
Loeb, J. 345
Loeb, L. 252, 255, 257, 382
Loewy 93
Loewy and Zondek 492
Loisel 196
Lucas and Adrian 168

Macht 339–40
Macht and Bloom 342
Macht and Ulrich 342
Magnusson 387–8
Marañon 320, 473
Marburg 436–7
Marey 168
Marshall 25, 36, 170, 172, 196, 246, 248–50, 253, 255, 263, 335, 341, 394, 477
Marshall and Halnan 261
Marshall and Jolly 89–90, 235–6, 239, 242, 356
Marshall and Runciman 263–4
Marshall and Wood 264, 266
Marshall, *see also* Carmichael
Martin 8, 9, 11, 17, 462, 475
Masing 431–2, 434
Massaglia 191, 194–5
Matsumoto 340
Matsuyama 358–9, 390
Matthias 373, 436
Mattill and Carman 184
Mauclaire 84, 86
Mayer 389
Mazzetti 189, 192
Meisenheimer 51, 55, 57, 96, 285–7, 312–3, 403, 409, 412, 442
Meyer, Robert 15, 222, 249, 260
Michon and Porte 142
Mingazzini 249
Minot 450
Minoura 270, 310–11, 352, 358, 388, 390, 404, 442, 444, 470
Mittasch 376
Moore 29, 33, 239, 262, 288, 291–3, 295, 299, 303–6, 352, 354, 359, 362, 442, 451, 467
Morgan 47–50, 65–6, 191, 313, 393–4, 452, 463–5, 478
Morgan and Goodale 461
Mühsam 86, 370
Møller-Sørensen 353
Murisier 391
Myers 128, 133, 294, 451

Nemenov 154
Neugebauer 371, 379, 403
Neurath 431, 435
Niskoubina 253
Nothnagel 160
Nussbaum 51, 53, 90, 92, 95, 97, 335
Nonidez 191, 198–9, 275, 394

Oberholzer 13
Obmann 431
Ocaranza 33, 299
Ochoterena and Ramirez 226, 250
O'Donoghue 249
van Oordt 50, 187
Ottow 87
Oudemans 55, 58
Owen 476

Parès 342–3
Patzelt 191
Pearl and Boring 111, 191–3, 195, 274–5, 391–2, 484
Pearl and Schoppe 275
Pearl and Surface 257, 382, 458
Pease 191, 394
Pérez 66
Peters 255
Peyron 375, 377

Pézard 37–44, 47, 63, 82, 95, 167–70, 191–4, 196–7, 274, 288, 307, 309, 312, 320–22, 352, 358, 363, 388, 390–1, 395–6, 410, 436, 441–2, 451–3, 461, 463, 465–6
Pézard and Caridroit 461–3, 465
Pézard, Sand and Caridroit 358, 408, 410
Pfeiffer 370
Pflüger 97, 98
Pick 375, 377, 379–81
Plato 174
Plaut 234
Polano 376
Poll 36, 42, 46, 195, 409, 471–2
Pollitzer 344
Ponse 287
Posner 129
Potts 59, 64–5
Prénant 251
Priesel 376
Przibram 298
Punnett 191, 394

Rasmussen 170, 171, 189, 226
Rauther 341
Reeves 192
Regaud 171–3
Regaud and Policard 143
Regen 57
Reinke 115
Retterer 129, 476
Ribbert 157, 235
Richon and Jeandelize 23
Riddle 444
Romeis 390, 489
Rössle 12
Rubaschkin 118–9, 197, 396
Ruge II., Carl 260
Růžička 492

Sacchi 435
Sainmont 211, 218, 227, 249–50
Salazar 225, 257
Salen and Pick 375
Sand 83, 129–30, 133, 143, 145, 150, 152, 158, 163, 166, 170, 238–9, 256, 262, 265, 288–9, 291–2, 295, 298–9, 303–5, 351–6, 358–9, 360–6, 375, 388, 442, 451, 473, 488–9, 490, 492
Sauerbeck 376, 378–9, 403
Schaeffer 211–13, 220
Schafer 330
Schickelé 263
Schleidt 474
Schmidt, Peter 490, 492
Schmincke and Romeis 377
Schönberg and Sakaguchi 33, 474
Schrader 99–101
Schultz 148, 236, 287, 354–5
Seitz 211, 220, 222, 226, 250
Sellheim 28, 36, 39, 40
Serralach 342–3
Sexton 401–3
Shattock and Seligmann 41
Simmonds 153, 178
Sippel 90, 491
Smith, Geoffrey 59–65
Sobotta 249
Sollas 67–8
Spallanzani 98, 335
Stabel 88, 370
Starling vi., 80
Stanley 87–80, 93–4, 490–1
Steinach vi., 17, 19, 20, 29, 34, 51, 53, 63–4, 82–4, 93, 95–6, 99–101, 109, 128, 133, 148–52, 162, 166, 170, 233, 237–9, 262, 267, 285, 287–300, 303–5, 330, 335, 340–1, 343, 350–2, 354–5, 359, 362–4, 366–70, 375, 378, 381, 386, 388, 403, 408, 438, 447, 450–1, 454–5, 462, 466–7, 473, 485–90, 492–3
Steinach and Holzknecht 230–34, 241, 262
Steinach and Kammerer 183
Sternberg 368, 377
Stigler 335, 344
Stocker 86, 88
Stotsenburg 303
Stricht, van der 249
Surface, *see* Pearl

Takahashi 96, 142
Tandler 6, 16, 17, 153, 426, 441–2, 443
Tandler and Gross 5–8, 10, 12, 13, 16–7, 25, 32–3, 128–9, 171–3, 350, 424–7, 441–2, 447, 456, 459, 469
Tandler and Keller 29, 32–4, 42, *see also* Keller
Tarchanoff 98–100, 335
Thaler 178
Thomas 457
Thorek 88, 148, 154, 462, 484, 491
Tiedje 128–9
Tigerstedt 298
Toldt 7, 425, 457
Torrey and Horning 397
Tribondeau 153
Tsuji 183–4

Unterberger 88, 90

Vandel 68–70
de la Vaulx 401, 447, 473
Verworn 168
Vešnjakov 360–1

Vészi 168
Villemin 153
Voinov 183
Völker 249
Voronoff 88, 462, 484–5, 487, 491
Voss 356

Wagner 27, 52–3, 87, 93, 111–14, 116–18, 121–4, 126, 131, 134–8, 140, 151, 156–60, 164–5, 182, 189, 212, 215–7, 221, 223–4, 244–5, 247, 252, 287, 399
Wagner and Loeper 131, 139, 141
Waldeyer 111
Wallace 249
Wallart 211, 220–1
Watson 197
Weber 409
Weichselbaum 178
Weil 331, 346, 370–2
Welti 92
Werner, Paul 229
Wertheimer and Dubois 329, 338
Whitehead 116
Wildbolz 86, 424, 426
Wilhelm 486–90
Willier 388–9, 404, 469
Winiwarter 174, 211–2, 218, 220, 226, 249–50
Wischnewsky 335
Witschi 174, 398–9
Wodsedalek 447
Wolf 344

Yocum 394

Zawadowsky, M. M. 32, 46, 274, 288, 307, 310, 312, 352, 358, 363–5, 395–6, 410–12, 442–3, 447, 452, 461, 465–6, 470–1
Zawadowsky, B. M. 397
Zietschmann 249, 270, 387

General Index.

Adam's apple 293, 305
Adrenals 3, 80, 104, 211, 321, 372, 375, 377, 391, 395–6, 412, 435–6, 470
— functional relation to sexual glands 3
Albuginea 289
Alcohol, effect on interstitial cells 178 ff., 483
"All or Nothing," law of 166 ff.
— — for ovary 243
Alytes, experiments in castration of 54
Amenorrhoea 267
Amphelopus 66
Amphibia 52, 54, 187, 285, 397
— asexuality of soma in 443
— intersexuality in 397
— corpus luteum in 249
Anorchism 426
Andrena 66
Antagonism between sex glands 352 ff.
— between sex hormones 467
— between testis and ovary 352
Antennae after castration 56
Apes, testicular homoiotransplantation 155
— — irradiation with X-rays 155
— testicles grafted on man 88, 462, 491
— interstitial tissue of ovary 214
— ovulation in 253
Appendix vesiculosa, etc. 460
— testis 460
Arthropoda, experiments on 55, 312, 358, 401
— condition after crossed transplantation 358
— parasitic castration 59 ff.
— results of castration 55
Ascaris megalocephala 68
Asexual embryonic soma 50–1, 71, 441 ff., 456 ff., 460, 465, 469–70
— — — and heredity 456
— — — evolved characters 453 ff.
— stage in development of soma 17, 175
Aspects, some practical 483
Atretic follicle and corpus luteum 249–50
— — and interstitial tissue 249
Autotransplantation 82, 235, 238, 242, 305, 484
Autotransplantation, definition of 81
— in fowls 82
— in guinea pigs 83
— in rabbits 235
— in rats 82–3, 235
— of ovary in woman 88, 90, 235 ff., 451
— of testicle in man 86
Averting reflex 297–8
Azoospermia 178, 342

"Backward development" 148
Bat, cyclic changes 172
— corpus luteum in 249
— heat in 263
— interstitial tissue in 213, 269
— ovulation in 263
— spermatozoa in 344–5
Bidder's organ 187–8, 272, 286
Birds, intersexuality in 390 ff.
— results of castration in 18, 36–51, 194, 307
— (*see also* cock, hen, fowls, etc.)
Bisexual behaviour 365
Bleeding of uterus after ovariotomy 263
Body temperature of male and female 298
— weight after castration 94–5
Bombyx mori, castration of 55
Bones, condition in castrate after injection of testicular substance 94
"Bouchon vaginal" 337, 341
Brahma fowls 39
Breasts after castration, in man 16
— — in woman 14
Buffalo, hypophysis after castration 33
Bufo vulgaris 187, 272, 286
— pads in 287
— (*see also* toad)
Bull, castration of 5, 18, 28
— hypophysis after castration 32

Calves, mammae after castration 28
Campines 393
— results of castration 47
Cancer and interstitial cells 178
Capon 81–2
— after prepuberal castration 40
— feeding with sexual gland 93
— psycho-sexual behaviour 40

Capon, spurs after castration 39
Carbonic acid 79, 331, 492
— in blood 79
Carcinus maenas, parasitic castration of 64
Cardualis caniceps 48
Castrates, types of 8, 16
Castration, counteraction of results in cocks 41
— effect on sexual characters 16, 17, 306
— heat after 28–9
— in cases of criminal behaviour 13
— in disease 5
— influence on skeleton 8, 16, 474
— morphological signs of 18
— partial 168, 181, 243 ff., 273
— physiological 5, 14
— psycho-sexual behaviour after 40
— results in animals 5, 18
— — in amphibia 52, 54
— — in arthropoda 55
— — in birds 18, 36–51, 194, 307
— — in bulls 5, 18
— — in cocks 36–42
— — in cows 18
— — in crabs 59
— — in dog 24, 82
— — in drake 44, 47, 307
— — in duck 44, 195, 274, 312
— — in fishes 51, 54
— — in frog 51, 190
— — in guinea pig 20–24, 34
— — in hedgehog 18, 29, 36
— — in the horse 18
— — in invertebrata 67, 459
— — in mammals 18, 25, 82
— — in man 5 ff.
— — in rabbit 23, 82
— — in rat 19, 20, 34, 36, 82
— — in triton 190
— — in woman 13–15
— senile atrophy 5, 14
— tendency to common type after 17, 18, 32, 46
— therapeutic reasons for 5
— unilateral, hypertrophy in 157–8, 160–1
— — of ovary 243
— (*see also* prepuberal, postpuberal)
Cat, interstitial cells in ovary 213
— section through ovary 247
— testicle of 113
Cattle, hypophysis after castration 32
— interstitial tissue of ovary
— ovulation 253
— twin pregnancy in 383 ff.
— results of castration 5, 18
Cauterization 190, 251, 253, 264
Central nervous system 92, 97–8
— connection with clasp reflex 99, 101
Cerebellum in clasp reflex 99
Cheiroptera 217
Cholesterine 325
Chondriosoma 116
Chorion condition in twin pregnancy of cattle 386
Chorio-allantoic membrane graft 310
Chorion-epithelioma of testicle 180
Chromosomes, sex 446–8, 464
Circulation in twin pregnancy of cattle 384
Clasp reflex 51, 53, 95, 98 ff., 273, 285, 297, 335, 399
— connection with internal secretions 98
— physiology of 98
— skin in 101
Claws after castration (Inachus) 59
Climacteric in women 13, 14, 220
— after castration 13, 14
Clitellum in Lumbricus 67
Clitoris, atrophy of 231
— hypertrophy in masculinization 300 ff.
— influence of testicular transplantation on 300 ff.
— in the freemartin 383
Cock, feminized 308
— hypophysis after castration 40
— injection experiments 94–5
— results of castration on 36–42, 307
— testicular transplantation 81–2
— unilateral castration 357
— (*see also* hen, fowl, capon, etc.)
Cock-feathering in birds 274, 390, 393, 442, 445, 457, 460
Colour alteration in wings after castration 57
Colostrum, after castration 28
— in feminized male 293
Comb of cock after castration 37–8
— hen after castration 43
Compensatory hypertrophy in testicle 155 ff.
Copulation, after castration 53
Cornish Indian game 458
Cortex of cerebral hemispheres 104
Corpora bigemina and clasp reflex 99, 100
Corpora lutea 190, 212, 215, 235, 237–8
— and atretic follicle 249–50
— and interstitial tissue 251 ff.
— cauterization of 251
— endocrine function of 255

Corpora lutea, function of 252
— graviditatis 259, 260, 268, 271
— histogenesis of 248 ff.
— hormonic function 256
— in testicle 190
— in twin pregnancy 383
— in virgin guinea pigs and rabbits 259
— injection of 322, 325, 330–1, 469
— internal secretion of 246 ff., 263 ff.
— menstruationis 269
— objections against theory of internal secretion of 263 ff.
— "partial" 249
Corpora cavernosa, *see* penis
Cow, castrated, skeleton 29
— — corpora lutera in 384
— — skull in 32
— (*see also* cattle, bull, freemartin)
Crabs, parasitic castration 59, 66
Crepidula plana 69
"Crossed transplantation" 287, 352, 410, 449, 470
Crossoptilum auritum 48
Crustacea 65
Cryptorchism 186, 305
Crystaloids in testicle of man 115
Cynocephalus, testicular homoiotransplantation 155
Cystic degeneration of ovarian graft 238
Cyclic changes of the testicle 53, 170
— — in development of interstitial tissue 170
— — in female sexual life 251

Daphnia atkinsoni 402
Darwinian theory 50, 456, 458, 461, 464
Deciduoma 252
Determination of sex 448
"Development, backward" 148
Dimorphism, sexual 1, 454
Disease, interstitial cells in 178–184
Dog, castration of 82
— interstitial cells in ovary 213
— lesion of infundibulum 142
— ligature of vas deferens 127
— relation between testicle and prostate gland 24
— retention of testicle 142
— senile, rejuvenation of 485 ff.
— X-ray experiments 154
Dorking fowl 462
Dorset x Suffolk sheep, cross 461
Drake, results of castration 44, 47, 307
Drake, feminization of 309
— implantation in 309
Duck, castration of 44, 195, 274, 312
Duodenum 80
Ductus epididymidis 128, 129, 163

Earthworm 67–8, 186
— sexual characters in 67
Endocrine action, sex specific, in birds 310
— cells 177, 233, 266, 269, 271–2
— function 126–30, 133, 143, 157, 158, 161, 175, 185, 188, 194, 197–9, 231, 234–5, 239, 243, 271, 322, 371, 396, 469, 471
— glands 33, 104, 219, 233, 269, 312, 321, 448, 463, 478, 483
— organs 80
Endocrinology 80
Engrafted testicle 81, 148 ff., 369
Eosinophile cells 198, 375, 474
Epididymis 86, 128–9, 163, 172, 337, 341, 344, 369, 476
Epididymitis 129
Epithelial cells 120, 122, 177, 226, 227, 248, 267, 373
Epithelioid cells 119, 121, 195, 211, 218–9, 220, 221, 223, 225, 236, 239, 250, 255, 258, 269
Epithelium 23, 28, 118, 121, 122, 233, 249, 250, 285, 305, 323, 345
Equipotentiality of soma 443, 446–8, 470
Erection, in castrated male 12, 13
— in castrated rat
Erotization 36, 88, 97, 183, 297–8, 336, 364, 423, 429, 431, 435, 462, 484, 492
Erotizing effect of sexual hormones 297
Eugenics 483
Eunuch 85, 441
Eunuchoidism 86, 104, 142, 145, 152, 155, 163, 176, 185–6, 369–70, 423, 424 ff., 483
— four types of 426–7
— in woman 430
Exchange, gaseous, in fowls 475
Experimental hermaphrodite, somatic characters 359 ff.
— — psycho-sexual behaviour 364 ff.
Extirpation of lumbosacral part of sympathetic nerve in guinea pigs 142
Extracts of whole sex glands 319 ff.
— of parts of sex glands 322 ff.
Eyesight, after homoiotransplantation 491

Fat in castration of animals 33
— in castration of birds 40
— in eunuchoids 426, 430
— in feminized male 295
— in interstitial cells 115, 116, 163
— in prepuberal castration 7
— in postpuberal castration 12–14, 85
Feeding with sexual gland 92
— with testicular substance 93
Female and male, transition between 4
— phases of puberty in 267
Feminization 64, 287 ff., 393, 396, 408, 442, 448, 450, 453–4, 462
— change in body growth and proportions 294–6
— condition of hypophysis in 474
— rudimentary male organs in 290
Fertilization 252, 261, 267, 344, 401–2, 446, 448
Fetishism, sexual 36
Fiddler crab 313
Fishes, castration of 54
— corpus luteum in 249
— interstitial cells in 186
Fixation of sex characters 449 ff.
Foetus, condition of, in freemartins 384–8
— extracts of 321
Follicle, an endocrine apparatus 177, 234
— and corpus luteum 249–50
— internal secretions of 265
— obliterated by X-rays 230, 239, 255
— puncture of ripe 253
Follicular atresia in ovary 223, 231, 233, 236, 238, 255, 269, 270
— development 245
— — accelerated 241–2, 269
— theory of hormone-production 176–7, 185, 187, 272, 471
Fowls, comb in 396, 473
— experiments on 169, 307 ff.
— plumage, 307
— results of castration in 46
Freemartin 359, 383–90, 445, 452, 454, 469
Frogs, clasp reflex in, 51, 53, 95, 98-101, 273, 285
— difference from mammals in reaction of testicular fragment 161
— heat in 51
— hypertrophy of testicular fragment 161
— oestral sound in 52
— pad in 51, 53, 97, 285–6, 473
— partial castration 273
Frogs, results of castration 51
— vesiculae seminales 51
— testicular injection experiments 95
— testicular transplantation 90
"Furtherance" 467, 469

Galvanocauterization 55, 190
Gammarus chevreuxi 402–3
Gasterosteus aculeatus 187, 199
Generative cells 1, 3, 63, 120. 121, 126, 396, 460, 469
Genes 464
Genetic factors 47, 459–60, 464–5
— system of sexual characters 2–4, 411, 468, 470
Genital passages, secretion of, and vitality of spermatozoa 343 ff.
Gipsy moth, *see* Moth
Glandular cells 116, 188, 193
Glands of internal secretion, changes after castration 33
"Glande interstitielle" 109
Goat's testicle 88, 462
— interstitial tissue of ovary 214
Goldfinch 48
Gonads 15, 64, 103–4, 350, 424
— bisexual 411
— definition of 473
— not factor in intersexuality 402
— not necessary for development of secondary sexual characters 15
Graft, puncture of, in transplantation 83
Granules of protein nature in testicle of man 115
— in interstitial cells 116
Graafian follicles 263–4
— — rupture of 253
Graviditatis, corpus luteum of 259–60, 268, 271
Gravidity, interstitial tissue during 222, 226–7
Growth, body, after castration 37
— — under testicular graft 303
— curve of, in interstitial tissue 188
— intensity 65, 368, 404, 450
Guinea pig, auto- and homoiotransplantation 83
— castration results 20–24, 34, 83
— experimental hermaphrodite 363 ff.
— extirpation of lumbosacral part of sympathetic nerve 142
— feminization 288
— horny styles in 22, 24, 129, 302
— hypophysis after castration 32
— interstitial tissue in 122
— irradiation effect 154
— ligature of vas deferens 127, 133

Guinea pig, mammae in 28
— mammary gland in 327
— masculinization 299
— ovarian transplantation 88–9
— ovulation 257
— penis in 20, 23
— psycho-sexual condition after castration 34
— puberal development 123
— retention of testicle 142
— seminal vesicles in 21, 23
— sexual activity in 163
— testicle of 112
— unilateral castration 130
— uterus in 28, 88

Hair in normal and castrated man 6, 9–10, 12, 85
— in castrated woman 13, 14
— in eunuchoid state 85
— in sexual precocity 373, 345
Hair-growth, influence by sex hormones 15, 466 ff.
— in feminized male 295
— in masculinized female 304
Hares, heat after castration 36
Head apparel of cock after castration 38, 41, 192
— — — in experimental hermaphoditism 364, 391, 395
Heat 99–101, 162, 172, 188, 195, 197, 261, 263–4, 268, 336
— in prepuberally castrated animal 28
— clasp reflex in heat 99
— corpus luteum in 255
Hedgehog 18, 29, 36
— after postpuberal castration 29
— changes in interstitial tissue 170–1
Hen, masculinization 309
— plumage 42–3, 207
— results of castration 42, 312
— (*see also* cock)
Hen-feathering 393–4, 442, 463, 478
— dependence upon sexual glands 50
Hens' eggs. transplantation on 310, 378, 390
Heredity 456 ff.
— sex-limited 458
Hermaphrodite birds 275, 309
— experimental, somatic characters 359 ff.
— gland 63, 367
— puberty gland 366
Hermaphroditism 349 ff., 436
— experimental 351 ff., 436
— psycho-sexual behaviour 364 ff.
Heterotransplantation 64, 352, 484, 492
— definition of 81
— in man 88
— in rabbits and guinea pigs on hares 89
— in tritons 286
Hibernating mammals, change in interstitial tissue 171
Hibernation 344–5
— interstitial tissue during 171
Hilum ovarii, extract of 330
Holzknecht-units 230–34
Homoiotransplantation 238, 242, 305, 491–2
— definition of 81
— in fowls 82
— in rabbits' ovaries 90
— in rats and guinea pigs 83, 235
— in woman 491
Homosexuality 86, 351, 367 ff.
— in moths 369
Hormones 80, 96, 99, 193–4, 198, 235, 262, 266, 269, 342, 405, 441 ff., 443, 445, 448, 450, 453, 461, 463
— antagonism of 357
— bearing on sex characters 466
— different action of male and female 293
— excess of, in organism 165
— experiments in isolation 323
— isolation of 319 ff.
— sex specific action of 285 ff., 306, 320, 446, 461–2, 465, 493
Hormone-production, 103, 199, 237, 256–7, 273–5, 322, 367–8, 396, 399, 429, 454, 459–60, 483, 492
— follicular theory of 176–7, 185, 187, 272, 471
Hormonic action, increased 162–3
— — of spermatogenetic cells 196
— — specific 287
— activity of sex glands, non-sex-specific 473
— effect 155, 181–2, 241–2
— — dependence upon quantity of testicular hormones 167
— — proportional 166
Horny styles in guinea pig 22, 129
— — in masculinized female guinea pig 302
Horse, castration of 18
— interstitial cells 122
— ovulation 253
— sexual activity after castration 35
— with retained testicle 142
Hyaline degeneration 251

Hyperfeminization 293, 295, 305, 450–1
Hypermasculinization 303, 305
Hypernephroma 372, 375
Hypertrophy, compensatory in testicle 155 ff.
— of interstitial cells 155, 162, 169, 178 ff., 237 ff.
— of ovarian tissue 244
— of testicle in unilateral castration 161
Hypophysis 3, 8, 12, 32, 40, 80, 104, 431, 438, 474
— changes after castration 32, 40, 474
— in castrated woman 12
— increased volume and weight 33
Hypospadia 378
— a sympton of intersexuality? 378
— peniscrotalis 379
— frequency of 379

Impotent frogs 95, 97
Inactivity, atrophy by 476
Implantation of ovaries 262 ff., 352 ff.
— of testicle 299 ff., 352 ff., 369 ff.
Inachus, parasitic castration of 59 ff.
Increased hormonic action under hypertrophy 162–3
— — — with ligature of the vas deferens 162–3
Influenza, Spanish, effect on interstitial cells 181
Infundibulum, lesion of, in dog 142
"Inhibition" 467, 469
Injection experiments 93, 319 ff.
— — on cocks 94–5
— — on frogs 95–7
— — on guinea pigs 94
— of entire sex glands 319 ff.
— of ovarian substance 93, 484
— of partial sex glands 322 ff.
— of testicular substance 93, 484
Insects, intersexuality in 400
— parasitic castration of 66
— (*see also* Arthropoda)
Intermediate phase of puberty 175
Internal secretions, accumulation of 97
— — meaning defined 79, 493
— — of follicle 265
— — of gonads 319
— — of nervous system 97
— — of ovary 211 ff., 239, 270
— — of sex glands 79 ff., 97, 103–4, 319, 330
— — of testicle 82, 97, 100, 109 ff.
— — what are 493
Intersexuality 58, 65, 275, 303, 312, 347 ff., 445, 453, 457, 483
— classification 403 ff.
— gonadal 375
— hormonic 376–8, 393, 402–3, 408, 410
— in amphibians 397
— in birds 390
— in insects 400
— mammals 379
— in man 367
— latent 411
— lateral 409–10
— morphogenetic 403
— partial 407
— zygotic 402
Interstitial cells 109, 111–13, 118–23, 125–7, 130, 147, 150–5, 163, 239, 345, 368, 380, 396, 399, 427, 445, 455, 469, 492
— — as chemical transformers 183
— — always present in testicle 125
— — climaxes in development of 126
— — conditions at different ages 125–6
— — — in intoxication and disease 178–184
— — effect of higher temperature 183
— — hypertrophy of 130, 133, 146, 150, 155–7, 179
— — in amphibians 109, 187
— — in birds 109, 189, 191
— — in fishes 109, 186
— — in guinea pigs 118–120
— — in invertebrates 186
— — in mammals 110
— — in unilateral castration 157–8, 160–1
— — necessary part of endocrine apparatus 185
— — of ovary in mammals 211 ff.
— — of testicle 110 ff.
"Interstial gland" 109, 154, 222, 224, 226, 455
Interstitial tissue and corpus luteum 251 ff.
— — and hormonic effect 155 ff.
— — cyclic changes in 170–5
— — during foetal life 269
— — hypertrophy of 234, 241
— — in intoxication 178–184
— — of ovary in man 220, 222, 227, 237, 242, 324
— — of testicle 120–2, 125–6, 131, 146, 150, 163, 166, 330, 343
— — time of development 172
Intoxication, interstitial cells in 178, 184

Intrarenal grafts 356
Intratesticular transplantation 353, 355 363
Invertebrata, results of castration 67, 459
— internal secretions of ovary in 272
Iodine, effect in interstitial cells 179
Irradiation of sex glands 484
— (*see also* X-rays)
Isolation of the sexual hormones 319 ff.

KATABOLIC substance 79–80

LANGSHAN fowl 461
Larynx in castrated man 8, 12
Law of "All or Nothing" 166 ff.
— — for ovary 243
Leghorn fowl 38, 40, 42, 307, 394, 462
Leydig cells 109, 110, 150, 179, 195
Ligature of vas deferens 127
Limicola 50
Lipoids 323–4, 329
Lizard 344
Lumbricus herculeus 67
Luteal (lutear) cells 268, 274–5, 367–8, 392–4
Lutein cells 226, 233, 236–7, 242, 249, 324
— pigment in ovary 212, 250
Lymantria dispar 55, 57, 312, 369
Lymphocytes 198

MACACUS (ape) testicular homoiotransplantation in 155
Male and female, transition between 4
— phases of puberty in 175
Maleness, change to, in castrated hens 43
— complete, factors in 104
Mammals, castration in 18, 25
— feminization in 287
— — morphological signs 18
— internal secretions of ovary in 211 ff.
— intersexuality in 379 ff.
— masculinization in 290
— psycho-sexual behaviour of 33
— seminal vesicles in 336 ff.
Mammae, hypertrophy after castration in man 12
— — — woman 14
— — — animals 28
Mammary gland 253, 325–6
— after castration in animals 28
— after X-ray irradiation 262
Mammary gland, condition during menstruation 253
— hypertrophy of 324
— in experimental hermaphroditism 363
— in feminized guinea pig 290
— in feminized rats 294
— in mammals after castration 32
Man, homosexuality 367
— intersexuality in 367
— interstitial cells of testicle 112–125
— ligature of vas deferens in 490
— postpuberal castration 12
— prepuberal castration 6
— psychosexual behaviour in 102
— results of castration in 5 ff.
— retained testicle in 147
— testicular transplantation 81, 84–7, 90, 92, 399
Marmot 171
Marsupials, corpus luteum in 249
Masculinization 287 ff., 356, 372, 375, 378, 386–8, 393, 395–6, 408, 412, 442, 445, 448, 450, 452, 454, 470, 476
— effect on coat 304
— psycho-sexual behaviour after 304, 305
Maximum in the building up of the male internal organs of secretion 126
Medulla oblongata 79
— importance of, in clasp reflex 99, 100
Menstruation 268, 430
— after castration 13, 28
— after cauterization of corpus luteum 251
— after X-ray treatment 230
— and corpus luteum 251, 258, 260, 263, 266, 268
— and interstitial cells 258
— and pregnancy—time relation 253
— in monkeys 263
— in pubertas praecox 434, 436–7
— significance of the bleeding 266
Mesenchyme cells 118–19, 122, 197–9
Mesothorium 154
Milk diet, effect on testicle 184
— secretion, after castration 28
— — after X-ray treatment 231
— — in experimental hermaphroditism 363
— — in feminized animals 291
Mitosis 126, 154, 172, 180, 271
Mole 171
Molge cristata 189, 286
Mollusca 69

Monotremes 249
Morphogenesis 441 ff., 454, 475, 477, 483
Moths, castration of 55 ff., 312
— Goldschmidt's experiments 63 ff., 369, 400 ff.
— wings after castration 55 ff.
Mouse, castration results 20
— testicle of 113, 150, 160
Moulting time 46
Mucosa 6, 25, 80, 325, 337
Müllerian ducts 311, 384, 398, 444, 457, 459, 467
— — phylogenetic origin 459

Nephridia 459
Nerve cells 122
Nervous system, internal secretions of 97
Neuroglia cells 121
"Neutral" form 59, 62, 70, 442, 461–2, 470
Nicotine, effect on interstitial cells 178
Non-sex-specific hormonic activity of sex glands 473 ff.
Nuptial apparel 55, 189, 195, 197

Oestrus, *see* Heat
Oöcytes 243, 275–6, 286, 310
Olfactory stimuli 36
Ostrich, hen, after castration 44
Ova, metabolic difference 444
Ovarian hormones, sex specific action of 285 ff.
— tissue changes 261, 395
— — hypertrophy 244
— transplantation 88, 290–1, 299, 450–1
Ovariotestis 353, 373–4, 376, 380–381, 391–2
Ovary and testis, antagonism between 352
— auto- and homoiotransplantation of 88
— crossed transplantation 352
— extracts of 321–4, 326, 331
— feeding with 93
— histology and histogenesis 211
— implantation of 262, 288
— in arthropoda 58
— in partial castration 243
— in pubertas praecox 435
— in twin pregnancy of cattle 383
— injection of corpus luteum 322
— internal secretions of 104, 211 ff. 270
— lipoids in 221
— transplantation of 88, 235 ff., 451
Ovary transplantation of, in mammals 88
— — in rabbits 90
— — in women 15, 88, 90
— X-ray irradiation of 228
Ovulation, inhibited by corpus luteum 257
— in mammals 253
— in rabbits 253
— spontaneous 253, 256

Pachygrapsus marmoratus, parasitic castration 62
Pancreas 80–1
Parabiosis 358, 390
Parasitic castration of crabs 59
— — earthworm 67
— — insects 66
Partial castration 131, 168, 181, 243 ff., 273
Partridge, castration in 48
Pelvis in castrated man 8, 16, 17, 32
— in sheep 32
Penis, castration effect 476
— condition after castration 18
— condition after transplantation of testicle 85
— condition in castrate after injection of testicular substance 94
— in castrated guinea pig 20 ff.
— in castrated rabbit 131
— in castrated rat 19
— in eunuchoid 425
— in experimental hermaphroditism 363
— in feminization 289–90
— in feminized rat 289
— in gelding 476
— in insects after parasitic castration 66
— in masculinization 450–1
— in normal guinea pig 20
— in retarded development 145
— in sexual precocity 432
— (*see also* vesiculae seminales, etc.)
Penis-like organ in masculinized guinea pig 300
— — — rat 303
Persistence of sex characters 2, 64, 453
Phalaropus 49, 394
Phascolomys 214
Phases of female puberty 126–7, 267 ff.
— of male puberty 175–6, 185, 269
Pheasants, castration results 44, 46
— crossing of 457, 462, 471
Phoxinus laevis, nuptial colouring 45

Phylogenetic phase 58, 442, 459–60, 463
Physiology of the clasp reflex 98
— of the prostate gland 338 ff.
— of the seminal vesicles 335 ff.
Pigs, hermaphroditism in 390
— interstitial tissue in 122, 215
— ovulation 253
— retained testicle in 143, 145
Pineal body, functional relation to sexual glands 437
— gland 33, 436–7
— — in pubertas praecox 436
Placenta 255, 262, 267
— extracts of 321, 323–5
Planaria, castration of 68–9
Plasticity of the organs 404
Pleurodeles waltli 190
Plumage of fowls 37, 39, 43, 47, 49, 71, 451, 463
— of ducks 44
— in experimental hermaphroditism 364, 391, 395–6
— in castrated cock 37
— in castrated hen 43
— in castrated duck 44
— persistence of 453
Plymouth rocks 38, 458–61
Poisons, effect on interstitial cells 178
Portax pictus 443
Postpuberal castration 12, 15
— — in animals 35
— — in the cock 40
— — in man 12
— — in woman 13, 14
— — observation of effect 12
— — persistence of sex characters after 18
— — psychical disturbance in man and woman 14
— — sexual libido in 12
Practical aspects 483 ff.
— classification system of sex characters 472
Precocity, sexual 167, 372, 423, 431 ff., 483
— — hormonic basis 438
Pregnancy 268–9
— and menstruation 260
— and puberty 267
— puncture of ripe follicles 253
Prepuberal castration, in animals 35
— — in cock (capon) 40
— — in man 6
— — in mammals 25
Prepuberally castrated man 6
— — effect on general intelligence 14
Prepuberally castrated man, development after castration 18
— — erection in 12, 14
— — genital organs in 6
— — prolonged prepuberal stage 17
— — psycho-sexual behaviour 12
— — psychical disturbance in 12
Prepuberally castrated rat, in feminization 289
Preputial secretion, in castrated guinea pig 22–3
— — in masculinized female 302
Primary sexual characters 1, 471
Problem of rejuvenation 483
Pro-oestrum 264, 265
Prostate gland 172, 425
— in castrated rat 20
— in feminization 289
— in transplantation of testicle 83
— influence of X-rays on 154
— influence on sex characters 335 ff.
— injection of 339
— physiology of 338
— removal of 340–1
Prostatectomy 338, 342
Prostate tissue, dried 342
Prostatic injections, effect of 339
Proteins, introduction in organism in excess 164–5, 320
"Protrahierte Unreife" 17
Pseudo - hermaphroditism 15, 349 ff., 377
Pseudo-pregnancy 253
Psycho-sexual behaviour 33, 351, 367, 424, 430, 450, 469
— — after castration 33, 35, 40, 84, 129
— — and sex glands, relation between 103. 335, 342–3, 368
— — in experimental hermaphroditism 358, 364 ff.
— — in fowls 40
— — in guinea pigs 129, 298
— — in man and mammals 35, 102–4
— — — external factors 102
— — in pubertas praecox 435
— — in rat 84, 298
— — influence of ovary 297
— — of feminized cock 308
— — quantitative laws 166
Puberal development of uterus 231
Pubertas praecox 167, 372, 432
— skeleton in 434
Puberty, phases of, in female 126, 267 ff.
— — in male 175–6, 185, 269
Puberty gland 109, 152, 154, 268, 454, 493
— — hermaphrodite 366

Puberty gland, isolated 150
— (*see also* interstitial cells)
Puncture method of transplantation 83

QUANTITATIVE factors 143–5, 155 ff., 321, 356–7, 362, 364, 368, 389, 392, 402–3, 407–8, 411–12, 423, 428–30, 450, 454, 465, 469, 476, 478
— changes in female 269
— laws of hormonic effect 166, 170
— statements about sexual activity 163

RABBITS, castration results 23, 82
— development of interstitial tissue in ovary 212
— hypophysis after castration 32
— interstitial cells of ovary 212
— interstitial tissue in 122
— ligature of vas deferens 127, 131, 133
— mammary glands 28
— ovulation 253
— penis in 23, 24
— puberal development in 123
— retention of testicle 143
— sexual activity in 35, 163
— testicle of 112
— unilateral castration 130
— uterus in 26–8
Race distinction, dependence on hormones 478
Rams' testicles grafted on man 88
Rana esculenta 188, 462
— temporaria 335, 462
(*see also* Frog)
Rats, autotransplantation in 82–3
— castration results 19, 20
— condition in transplantation of testicle 133, 148
— development of interstitial tissue 222
— feeding with testicular substance 93
— feminization 288
— heat 34
— hypophysis after castration 32
— interstitial cells of ovary 222
— ligature of vas deferens in 128
— mammary glands 294, 299
— masculinization 299
— olfactory stimuli 36
— ovariotestis 354
— psycho-sexual behaviour after castration 34
— retention of testicle 142
— seminal vesicles 19
Rats, sexual activity in 34, 163
— testicle of 150
— transplantation 152
— unilateral castration 130
Regeneration 492
— of implanted testicle after X-ray irradiation 153
Rejuvenation 483 ff.
— in man 490
Reptiles, corpus luteum in 249
Results of castration in frogs 51
— — fishes 51
— — mammals 18
— — morphological signs 18
— — psycho-sexual behaviour 33
— — summary 70
Retained testicle 142 ff.
Retarded development of testicle and sex characters 163, 169
Rhythm in sexual life of female 269
Rhode island reds 394
Roedeer, after castration 129
— antlers in 129, 153
— ligature of vas deferens 129
— after X-ray irradiation 153
Rostratula capensis 49
Rudimentary organs 457, 460

SACCULINA, parasitic castration by 59 ff.
Sandpiper 50
Sclerotic tissue 476
Sclerotization of ovary 233
Sea urchin 346
Seat of production of internal secretions of testicle 109 ff.
— — — — of ovary 211 ff.
Sebright fowls 47, 393, 463, 478
— — castration results 47 ff.
Secondary sexual characters 1 ff., 456–8, 471
Secretion of the genital passages and vitality of the spermatozoa 343 ff.
Sella turcica after castration 12
Seminal vesicles 297, 425, 477
— — condition after castration 19
— — function of 337
— — in earthworm after parasitic castration 67
— — in experimental hermaphroditism 359
— — in eunuchoids 425
— — in frog after testicular transplantation 91
— — in freemartin 384
— — in postpuberally castrated rat 20
— — in rat after testicular transplantation 83

Seminal vesicles, influence on sex characters 335 ff.
— — physiology of 335
— — removal of 340
— — (*see also* vesiculae seminales)
Seminiferous tubules 110, 124–5, 128–30, 133, 148, 158–9, 172–3, 180, 183, 193–4, 196, 427
— — "backward development" 148, 174
— — degeneration of 133, 142–3, 148, 153–5, 178 ff., 305
Senile dog, experiments on 486 ff.
Senility and rejuvenation 485 ff.
Sertoli cells 126–7, 130–1, 143, 145–6, 148, 150, 152, 153–5, 173, 176, 185, 189, 196, 345
Sex apparatus in moth after castration 55 ff.
— characters (*see* sexual characters)
— determination of 448
— differentiation 445–6, 450–1, 467
— endocrine glands 473
— glands (*see* sexual glands)
"Sex-limited" characters 470
Sex specific endocrine action in birds 310
— specifity 68, 104, 322, 327, 331, 397–8, 410, 442, 475
Sexual activity in man after castration 12, 13, 16, 18, 35, 36, 85
— — in woman after castration 14
— — in duck after castration 46
— — in mammals after castration 35
— — after ligature of vas deferens 133
— — [sex] characters 450
— — bearing of hormones on 466
— — classification of 465 ff., 471–472
— — definition of 3
— — development of female, induced by ovary 296
— — development of male, inhibited by ovary 296
— — differentiation 270
— — full development possible without spermatogenesis and spermatozoa 143
— — full development possible without increase of interstitial cells 156
— — fixation of 449 ff.
— — genetic system 2, 3, 405–6, 468
— — influence of testicle in 84
— — normal development 159, 160
Sexual [sex] characters, permanent 473
— — persistence of 453
— — persistence after postpuberal castration 18
— — puberal development of 123–4, 152
— — retarded development 163, 169
— — somatic 63, 168, 297, 335, 341, 343, 349, 367, 398, 401
— — temporary 473
— — what we mean by 3, 446
— dimorphism 1, 454
— fetishism 36
— [sex] glands 2, 3, 15, 51, 80–1, 92, 102, 108, 150, 375, 397, 437, 442, 475
— — and heat 51
— — and psycho-sexual behaviour 103
— — antagonism 352 ff.
— — basis of genetic system 3
— — definition of 471, 473
— — dependence of man on 15
— — experiments with capons 93
— — — with rats 93
— — effect on sexual characters 98, 103–4
— — extracts of whole 319 ff.
— — extracts of parts 322 ff.
— — feeding with 92 ff.
— — how they act 50
— — influence on organism 477–8
— — influence on sexual organs 15
— — influence on other sexual characters 15, 79, 109
— — injection of 319
— — internal secretions of 79 ff., 97
— — morphogenetic influence 441
— — non-sex-specific hormonci activity 473 ff.
— — responsible for psycho-sexual behaviour 35
— — questions on 2
— hormones, isolation of 319 ff.
— — and morphogenesis 441
— precocity 167 372, 423, 431 ff., 483
Sheep, influence of castration on skeleton 32
— interstitial tissue in 122
— interstitial tissue of ovary
Silk moth, castration of 55
Skeleton, influence of castration on, in animals 29, 32, 33, 446, 462
— — — in man 8, 14–17
— — — in birds 40
— — — in eunuchoids 426

Skeleton influence of sex glands in 15–16
— — in sexual precocity 434
Skopecs 6–8, 12–13, 16, 426, 441
Skull of castrated mammal 29, 32
Snipe 49
Soma, asexual embryonic 441
— — — evolved characters 453
— — — and heredity 456
— equipotentiality of 443
— identical 47, 443
— intersexual 460
— neutral form 59
Somatic characters in experimental hermaphrodite 359 ff.
"Somato-sexual" characters 470
Special organ controlling sex characters 65
Sperm, injection of 331
Spermatocytes 176, 187
Spermatogenesis 127–8, 130, 133, 142–3, 150, 163, 170–1, 173, 176–8, 181, 188, 327, 342–4, 353, 394, 427
Spermatogonia 131, 153–5, 176, 187, 345, 349, 373
Spermatozoa 63, 81, 129, 130, 143, 147, 148, 150, 153, 187, 336–8, 342 ff., 349, 428
— vitality of, and secretion of genital passages 343
Spherical nucleus 112–3, 119
Spinal cord and clasp reflex 99–101
Spurs of cocks after castration 37, 39
— — after feminization 308
— hens after castration 43
— in experimental hermaphroditism 364 396
Stag, feminized 293
— masculinized 305
Sterility in man, effect of intoxication on 184
— — effect of X-rays 153
Sterilization 484
Stylops 66
Suprenal tumour 393
Suprarenals after castration 33
Syphilis and interstitial cells 178

Tadpole, experiments on 93, 287, 339, 399
Tail reflex 297
Temperature, body, of female and male 298
Tertiary sexual characters 1
Testes, extracts of 321, 323, 331
Testicle 104, 122, 336
— and ovary, antagonism between 352
Testicle, Berthold's experiments 81
— compensatory hypertrophy 155ff
— crystalloids in 115
— cryptorchid 322
— endocrine function of 127, 196
— engrafted 81, 148–152, 369
— feeding with 92
— Foges' experiments 81
— grafts from apes to men 88
— in amphibians 187
— in birds 191
— in disease 178 ff.
— in eunuchoid 426
— in fishes 186
— in frogs 90–1
— in invertebrates 186
— in the new-born 180
— in toads 91
— influence of X-rays on 153–5
— internal secretions of 109, 154, 195
— poles of 156–7, 159
— puncture of 129
— retained 142, 148, 155, 163
— retarded development 163
— transplantation of, in man 81, 84–7, 90, 92, 399
— tuberculosis, removal in 86
— unilateral castration 157–8, 160–1
— unilaterally retained 142
— undescended 372
Testicular fragment compared with ovarian 245–6
— hormones, sex specific action of 285 ff.
— — implantation 395
— — section, incomplete 181
— — substance. injection of 85, 87, 92, 93
— — transplantation 299
— — — red corpuscles after 33
— — — influence on clitoris 300–1
Theca-lutein cells 226, 249, 366
Thelia bimaculata 66
Thistle-finch 48
Threshold quantity of hormones 167 ff., 195, 410, 423–4, 428–9
Thymus, after castration 33
— extracts of 323
Thyroid gland 3, 8, 80, 92, 104, 183, 319, 399
— after castration 33
— feeding with 397, 438
— functional relation to sexual glands 3
— in Skopecs 8
Time factor 65, 364, 389, 402–3, 407–8, 423, 454
Time relations 124, 177, 253, 264, 321

Toad, clasp reflex in 99–101
— transplantation in 91
Tortoise-shell cat, case of 390
Transmission of characters 460, 465
81 ff.
Transplantation 81 ff., 104, 155, 166, 289, 305, 484
— failure 87
— forms of 81
— heterosexual 448
— ovarian 88–90, 92, 235 ff., 267, 284
— — more successful than testicular 89
— sexual glands 79, 81–2, 195, 330
— testicular 85, 92, 166, 484–5, 490
— — in man 85, 86
Tree hopper 66
Triton 52, 188–9, 399, 443
Tuberculosis and interstitial cells 178 ff.
— of testes 86
Turnicidae 49
Twin pregnancy in cattle 383 ff.
Typhlocyba hippocastani 66

Underdevelopment after castration 84
Ungulata, interstitial tissue of ovary 215
Unilateral castration 381, 394, 477
— — hypertrophy in 157–8, 160–1
— — in frogs 190
Urodele 189
Uterine mucosa 267–8
— changes 271
Uterus after auto- or homoiotransplantation 88
— after castration 13, 28
— after injection of corpus luteum 323-4
— after prepuberal castration in mammals 25
— after transplantation in feminized male 290
— — in masculinized female 300
— after X-ray irradiation 231
— atrophy of, in woman, prevented by ovarian transplantation 89
— in castrated rat 90
— in eunuchoidism 430
Uterus masculinus 287, 297, 329, 338, 343

"Vagina, artificial" 338
Vas deferens 6, 67, 172, 338, 345
— — in castrated fowl 40
— — in earthworm 67
— — in rabbits 131
— — ligature of 127 ff., 163, 194, 253, 484–5, 488 ff.
— — rabbits four years after ligature 130
Vesiculae seminales 67, 297, 327, 329, 335 ff.
— — (*see also* seminal vesicles)
"Vesiculase" 337
Veterinary medicine 484
Voice in castrated man 15, 16

Weight, in feminization 294
— in masculinization 303-4
— increase of, after unilateral castration 161
Wolffian ducts 398, 457, 459, 467
Woman, castration in 13
— cessation of function 14
— changes in metabolism 14
— condition of theca cells 236
— corpus luteum in 268
— ovary after X-ray irradiation 267
— ovulation in 268
— postpuberal effect of castration 13, 14
— results of castration not so marked 15
Woodchuck, changes in interstitial tissue 170–1

X-rays, influence on mammary gland 262
— — on ovary 227 ff., 255, 265, 267, 293, 484
— — on seminiferous tubules 153
— — on sexual activity 153
— — on testicle 153 ff.
— observation of castrate by 8

Zootechnics 484
Zygotic determination of sex 444, 454
— intersexuality 402

Printed by
W. Heffer & Sons Ltd.,
Cambridge, England.