direct effect of any hormone used therapeutically.

Moreover, while the hormone control of sebaceous glands has been stressed, it should not be forgotten that other hormonal influences may have considerable bearing on the pathogenesis of acne. Œstrogens have a profound influence upon the epidermal cell in both sexes, causing cell proliferation and increased keratinization; testosterone may have similar effects; surely keratinization of the follicle is an important factor in the etiology of acne. Similarly, both œstrogens and androgens, as well as progesterone, are capable of altering vascular tonicity, capillary permeability, electrolyte balance, and hydration, all factors which profoundly influence the function of sebaceous glands. We have shown that premenstrual activation of acne is partially due to water retention and that these flares can be modified by diuretics. Many apparent contradictions appear to be due to different experimental conditions. The dosage used in experiments is obviously of greatest importance and a biphasic effect has been assumed for several hormones, where small doses may have the opposite effect to a larger one. Significant also is the time relation of hormone administration to the ovulatory cycle, and opposite effects may occur before and after ovulation. Undoubtedly, some of the conclusions of clinical investigations and of animal experiments were due to faulty observations, to lack of adequate control series, and to neglect of variables.

Reference should be made to the classification of acne. MacKenna has pointed out that a number of acneiform eruptions should not be included in the diagnosis of acne vulgaris, and Aron-Brunetiere holds the view that comedo acne (acne punctata juvenilis), acne vulgaris (polymorph acne), and MacLeod's acne of adult females (monomorph acne) should be considered separately since they react differently to therapy and probably differ in mechanism.

It is obvious that the great number of variables of hormone action and the variables of acne patients (age, type) are factors which introduce numerous sources of error and tend to render conclusions indefinite.

While there is agreement on the important role of endocrine factors in the pathogenesis and therapy of acne, no conclusive proof exists that acne is in all cases an expression of an endocrine disease or disorder. While the concept of a disturbed endocrine balance as an etiological factor in acne may be correct, we have also evidence that the receptiveness of the target cell as well as the hormonal stimulus determines the presence or absence of acne in the adolescent. Local factors, lanugo hair, size and keratinization of the ducts of the sebaceous glands as well as the viscosity, the melting point and the chemical composition of the sebum play an important role in the pathogenesis of acne. Many people have an excessively oily skin, have seborrhœa and overactivity of sebaceous glands and yet do not develop acne.

The incidence of adolescent acne has been estimated as from 60 to 70% in both sexes. Fluctuations of the hormone output are physiological in puberty, and the determining factor in adolescent acne may be the genetic predisposition of the sebaceous gland to react to stimuli rather than any differences in the strength of the stimulus.

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Men and Books

PAUL LANGERHANS, 1847-1888

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PAUL LANGERHANS, son of Dr. Paul Langerhans and his first wife, née Keibel, was born in Berlin on July 25, 1847. He may be said to have been born into and nurtured in a medical atmosphere. His father was a well-known physician and minor politician, possessing the honorary freedom of the city, while his mother was a cousin of the distinguished histologist, Franz Keibel. His younger half-brothers both became physicians. Robert became a professor of pathology, author of a popular textbook of pathology, and assistant to Virchow. Richard afterwards bore the honorary title of Sanitätsrat. After graduating from the Gymnasium zum Grauen Kloster at 16, Paul commenced his medical studies in Jena, but transferred after a time to Berlin. Here he came under the influence of Rudolf Virchow and Julius Cohnheim, though he also credits W. Kühne, who later occupied the chair of physiology at Amsterdam, with much advice and friendly assistance. From his tendency to employ Cohnheim's methods, I suspect that he was largely trained technically as a histologist by Cohnheim, but he held for Virchow an intense admiration, and developed with him an enduring friendship.

A year away from home under the eye of his "adored teacher", the renowned Ernest Haeckel,† in Jena was doubtless good for the boy, but an opportunity to develop under two of the most stimulating scientists of the day in Europe was not to be missed, as his father, the doctor-politician, was probably astute enough to realize and doubtless arrange. Even into our own land Boyd has traced a royal succession—Cohnheim to Roy to Adami to Klotz to Duff. Let us not

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†At this time Ernst Haeckel (1834-1919) was writing the first edition of his "Generelle Morphologie der Organismen". This important book was based on the Darwinian theory of Natural Selection, which most German scientists regarded with indifference, or even hostility, even as it was in England in many quarters.

go further at the moment; the future of the succession looks bright.

It is therefore not surprising that under such tutelage he had already published two papers on histological subjects before submitting his graduation thesis for the Doctorate in Medicine, which was to make him forever remembered. The "Beiträge zur Mikroskopischen Anatomie der Bauchspeicheldrüse", Berlin 1869, describes the histology of the pancreas, a organ previously described most inadequately from an anatomical standpoint, in contrast to the considerable accumulation of physiological knowledge regarding it at the time.

Notwithstanding the prolix and involved German sentence structure common to this period, the inaugural dissertation is a simple straightforward account of his investigations, modestly and perhaps a little too deprecatingly set forth. But, naturally, one would not tempt fate when defending the thesis before the august Medicinische Fakultät der Friedrich-Wilhelms-Universität zu Berlin! In my belief, it might well be recommended to medical students for their encouragement in learning the language. It is available in the *Bulletin of the Institute of the History of Medicine*, 1937, V, No. 3, with an excellent English translation (almost literal) and an introductory essay by H. Morrison, who has collated most of the available information (and from which these notes have largely been abstracted) about Langerhans.

Among other structures described in the dissertation were "Kleine Zellen von meist ganz homogenen Inhalt and polygonaler Form mit runden Kern ohne Kernkörperchen, meist zu zweien oder zu kleinen Gruppen beisammen liegend". These cells were further described in scarcely more than a page. Size and shape of cells and nuclei and their clear cytoplasm, devoid of granules, gathered together in small masses (Häuflein) of various sizes 0.1-0.25 mm. in diameter and widely distributed throughout the gland, are noted. The compact pancreas of most animals is somewhat difficult to fix, harden and stain, but above all is subject to rapid postmortem change. I can remember that my earlier attempts resembled more a map of North America A.D. 1608 than a modern topographical survey. While Langerhans did sufficient work on other animals to satisfy him that the picture was essentially the same, he found in the rabbit a pancreas scattered in small particles through the mesentery which lent itself to observation more readily. In this animal, as well as in the salamander, not only could histological sections be examined but the tissue could be observed in the living state. Injections of the blood vessels and pancreatic duct could also be made and portions of the tissue could be teased apart to observe more clearly the interrelationship. By hardening particles of the pancreas for two or three days in Müller's fluid, he saw bright yellow specks scattered through the gland, which on microscopic examination were seen to consist exclusively of these cell masses. By these methods he must have indeed gained an impression of the relative importance of these structures in the pancreas, not matched by later observers using only histological sections of the gland, until Lane, Bensley and other investigators examined the pancreas by newer and different methods. He mentions nothing about the blood vessels of the "Häuflein" specifically, though he had noted the very rich vascular network demonstrated by injection of the arterial tree in the gland as a whole. Though he made the first injections of the pancreatic ducts and studied their distribution, he does not mention their relationship to these small cell masses. This was later to become a subject of much controversy for many years. By advances in histological techniques, it has now been established that these cells arise from duct epithelium though blocked off by solid cords of epithelial cells from contact with the lumen of the ductules, and it is from the duct epithelium that all regeneration of these cells takes place. (Under some conditions considerable regeneration of islet cell tissue does take place but is insufficient to cure an established diabetes.) Nerve fibres were seen running over the cell groups but not actually connected with the cells, though in some instances the cells were in intimate contact with the ganglia, which indeed were found to be exceedingly numerous throughout the gland. The cytoplasm of the cells is described as brilliantly clear and free of granules, and so it is until special histological techniques developed after his time revealed granules of two types—the alpha granule, probably the glucagon precursor, and the beta granule, surely the precursor of insulin. He concludes the reference to these cells with the remark that he must refrain from any hypothesis as to their nature and significance. To them 24 years later, indeed five years after his death, the eminent French histologist Laguesse (1893) gave the name of "îlots de Langerhans". Laguesse, Diamare and Sharpey Schafer at about the same time suggested that these islets were the source of the antidiabetic hormone of the pancreas. Von Mering and Minkowski, who first proved the origin of diabetes in animals in 1889 by pancreatectomy, were apparently unaware of these structures.

Langerhans worked for a short time in the Near East, returned to serve in the Army Medical Service and in 1871 became a Privat Docent in Pathology in the University of Freiburg. After four years in Freiburg, working as prosector of pathology and publishing several papers, he became Prof. Extr., but tragically was compelled to resign his post because of phthisis of some duration. Seeking a cure, he emigrated to Madeira. Here, feeling improved in health, he commenced the practice of medicine and published occasional papers.

It is interesting that during his convalescence he should return to zoological investigations as well as to subjects more purely medical in nature. He had, it is true, published a paper on Petromyzon during the Freiburg period. Perhaps his return to zoology was in the nature of occupational therapy but one may also surmise that his earlier studies under Haeckel directed his choice of an avocation.

He married in 1885 and lived three happy years, during which a daughter was born, before a severe infection brought on renal disease which caused his death. He was buried in Madeira and was mourned as a typical genial, fun-loving child of Berlin, but one who, had the Fates been kinder, would have achieved a greater fame.

From such small beginnings, long unnoticed, but gradually increased by the work of many investigators in many lands and of many different disciplines, has grown that knowledge which has proved such an inestimable boon to more than one per cent of the world's population and their families. There is thus good reason to remember the medical student Paul Langerhans.