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RESPONSE OF ACHONDROPLASTIC DWARFS TO INSULIN

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The problem of dwarfism is of intriguing interest to the zoologist because of the wide range of problems it presents in every subordinate field. The condition probably appears with relatively minor variations in every vertebrate form from fowls to man. Its understanding involves the solution of complex problems in morphology, physiology, phylogeny, embryology and genetics. There is a definite likelihood that observations on the behavior of dwarfism in one species will be largely valid for other vertebrate species, thus throwing light on many fundamental biological principles.

Studies initiated in our laboratory some two years ago were concerned originally with dwarfism in beef-cattle. An earlier report of these findings deals with anatomical and physiological studies on twelve "short-headed" or "snorter" animals of the Hereford breed (Downs et al., 1959). Our findings agree in large part with the excellent studies of Gregory (1956) and his associates (Julian et al., 1957, Mead et al., 1946) at the University of California, of Brandt (1941), the comprehensive reports of Fransen and Andrews from Purdue (1954, 1955) and Marlow and Chambers (1954), Burruss and Priode (1956) and many others. Our results are in close agreement with the blood-chemistry and blood-cell studies of Massey and other associates of Lasley at the University of Missouri (1957), although we did not attempt to study "carriers" as did they.

Comparisons of findings on achondroplastic dwarfs in cattle with those reported in other forms have impressed us with the many similarities, and the relatively slight differences. Stockard's (1941) definitive work on dogs presents convincing evidence that dwarfism as seen in the Belgian Griffon and the Pekingese is essentially the same condition as has been studied widely in cattle.

In the reports of Brown and Pearce (1945) on rabbits, in which, although the gene is lethal in its effects, there are morphological features which are very similar to those found in other forms. Crary and Sawin (1952) have also described a type of dwarfism in rabbits and related it to that found in other forms.

Landauer's (1930) well-known studies on fowls also reveal many very similar skeletal and endocrine features.

Dwarfism in mice has been described by many workers, including Bates and his associates (1942), Boettiger and Osborn (1938), Gruenberg (1956), DeBeer and Gruenberg (1940), Smith and McDowell (1931) and Snell (1956). While many hereditary types have been described under various names, especially "pituitary" dwarfism, and the condition is occasionally lethally-linked, many of the more constant morphological features are similar to achondroplastic dwarfism in other forms. Dwarfism of apparently similar type has been reported in rats, guinea-pigs and humans (Mortimer 1938).

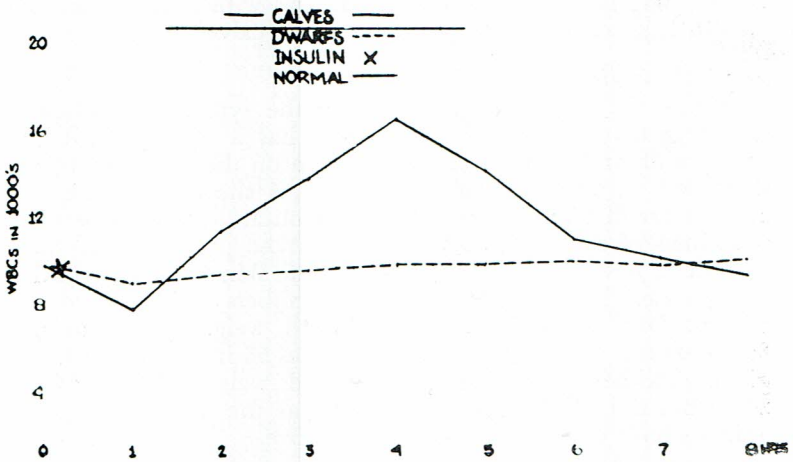

Fig. 1 Chart showing comparative effects of insulin on total leucocyte count of dwarf and normal calves. Chart drawn from average hourly counts of 10 dwarfs and 12 normals. A considerable number of later counts show no appreciable change.

The Condition in Cattle

Blood-chemistry studies have been particularly unrewarding in our investigations and those of others on even large numbers of animals. Blood-glucose, blood-cholesterol, NPN and total amino-acids seem to be consistently within normal limits (Fransen, 1955, and Massey et al., 1957). Preliminary analyses of calcium and phosphorus and of blood-phosphatase have shown nothing suggestive, but are being continued.

However, blood-cell studies have been more rewarding. Response of dwarf calves to "stress", as represented by relatively large doses of insulin (one unit per kg.), is quite different from that of their normal counter-parts. The reports of Massey et al (1957) revealed that normal animals responded to such treat-

ment by a quick, marked rise in total white cells, nearly doubling in number within three hours, and returning approximately to normal in about seven hours, while dwarfs responded only slightly and very slowly, never increasing in number more than about 15 per cent and returning to normal at an even slower rate. This tendency is verified by our studies (Fig. 1). In our series, as in theirs, as the total count increased in the normals, the relative lymphocyte count decreased sharply, and the total granulocyte count increased to such an extent that in some counts their relative proportions were nearly reversed. Dwarf animals, on the other hand, showed a slow, long-lasting decrease in granulocyte count and an increase in the lymphocyte count. Nearly absolute eosinopenia was present in many "normals", but was not so marked in dwarfs. Blood was withdrawn from, and insulin injected into, the jugular vein of calves.

Physical Findings

While varying in degree, grossly, the typical dwarf-calf is short-legged, short-bodied, pot-bellied, has a characteristic unsteady walk and stance. The tail is high on the back due to the shortened vertebral column; the head is short and wide, the animals are dish-faced with a bulging frontal area and a peculiar roundness of the skull, and there is marked prognathism. Such an animal never attains normal size. The skin is loose, wrinkled and coarse. Measurements of two members of our herd are typical. One, a female, is 18 months old, weighs 480 pounds, is 36 inches tall at the withers and measures 56 inches at the heart-girth. Another, a male, is 9 months old, weighs 190 pounds, is 24 inches tall and measures 40 inches at the heart-girth. Both animals have the stigmata described above.

Dwarf calves drink amazingly large amounts of water, eat incessantly, and excrete large amounts of urine and copious, foul-smelling feces. They are particularly susceptible to respiratory diseases and to "bloat" and "scours". They are short of breath, breathe noisily when disturbed and frequently have a catarrhal discharge.

They are generally short-lived, though we have two heifers who are now more than two years old. While "snorters" have been known to breed, it is not common, in our experience, and we have not seen a product of such breeding.

Post-Mortem

While post-mortem findings vary considerably, the following findings are true in a majority of our twelve cases. At autopsy the skin is loose, baggy, and wrinkled, but thick and leathery. The lungs and heart are grossly normal, the thymus consistently enlarged, occasionally (two of our cases) to the point that it extends from the mediastinum up to where it is mixed with submaxillary and sublingual glands and seems to replace the

thyroid. This condition was noted by Nickerson (1917). The thyroid is small and irregular in form and location, when found. Parathyroids are frequently not found. The liver is slightly enlarged and bloody, the gall-bladder large and distended. The pancreas is irregular in shape and location, and markedly reduced in size. The stomach, rumen and intestinal tract all are consistently distended, over-loaded, and the contents are foul-smelling and only partially digested. Ascites-like abdominal fluid is often present, even in freshly-sacrificed animals. The kidneys are frequently malformed, occasionally unilateral or with one ureter missing. The adrenals are usually difficult to find, small, and occurring in small, widely-separated masses, occasionally unilateral. The gonads are generally malformed, occasionally unilateral, and in both sexes the other genital organs are usually poorly developed. The pituitary is frequently smaller and oddly-shaped, short in anterior-posterior diameter, wide in lateral diameter. In one of our "snorter" cases, the pituitary was not found at all, and no sella turcica was to be found. This condition corresponds to that found in the first report of a lethal "Dexter-Monster" type (Downs, 1928). The shape of the brain is altered especially at the base to conform to the changed shape of the dwarf skull. The brain is smaller, more spherical than normal, with the inner table of the skull molding the sulci of the brain. The hypothalamic area is smaller, shorter than normal, with the ventricle dipping to the basicranium. One of the most constant and outstanding of our findings is the early and complete fusing of the spheno-occipital synchondrosis which accounts for the small size of this area. This also has been pointed out by Julian and his associates (1957) and by others, and suggested by Stockard (1941) in achondroplastic dogs.

Histology

There are indications that the pars distalis of the pituitary shows a relative decrease in total volume, although, as has been noted previously, in the case first cited, Downs (1928), and in one of our present series (Downs et al. 1958, 1959, Pennebaker and Downs, 1959) the entire hypophysis was missing or so small and misplaced in the malformed basicranium as not to be found. A very common finding is a "mixing" of the three major portion of the gland. Although our pituitaries were sectioned sagitally, they often show invasion of anterior lobe by posterior and intermedia or vice versa, and with the cells of the pars intermedia appearing quite "secretory" in character. In the anterior lobe there is an apparent increase in the comparative number of chromophobe cells, with many of these cells larger and having agranular, neutral staining cytoplasm, fewer basophils, and an almost complete absence of acidophils (Fig. 4, 5). The posterior lobe shows many more nuclei than normal. Consistently the entire organ including the stalk shows a great in-

crease in blood-filled sinusoids. This is apparently a reflection of the phenomenon which Popa and Fielding (1930) have noted. Histological studies on the dwarf hypothalamus are now in progress, in both calves and mice.

In those animals where thyroid tissue is located, the gland is smaller than normal, the follicles show a vacuolated appearance at the periphery, acinus cells are "lower", and many undifferentiated acinus cells are present. Parathyroids when present are apparently normal. The thymus, though enlarged, is microscopically normal.

The adrenals are usually "lobulated" or found in scattered, small masses so that valid study of their architecture is difficult, but one gets the strong impression of a lessened "cortex-to-medulla" ratio, with the cortical cells not grouped in the usual fairly definite cord-like fashion and individual cells are larger than normal with pale, washed-out cytoplasm as though "empty" of secretion.

The pancreas is often found only in small masses scattered through the peritoneal fat, and has a lessened comparative amount of islet tissue than is normal in cattle (Gomori, 1943).

The sex-glands are usually retarded and frequently malformed. Even in older animals, fewer mitoses in spermatogonia are seen than is normal for the age of the animals. Tubules are small and frequently filled with a syncytial fluid. Interstitial tissue is compartively increased and has the appearance of "primitive" connective tissue with more nuclei than would be true normally of such tissue. Ovaries are small, with few advanced follicles, mature ones being extremely rare.

The kidneys seem to have more and larger, "looser" looking glomeruli than normal, with disturbed architecture general.

The liver cells are larger, paler-staining than normal, with larger sinusoids, and irregular cell-columns.

The Condition in Mice

In December, 1957, we obtained a foundation stock of dwarf-carrier mice from the Roscoe B. Jackson Laboratory of Bar Harbor, Maine, and are now conducting studies on these similar to those outlined above on dwarf Hereford calves.

Grossly the dwarf offspring of this breed are much smaller than phenotypically normal ones of the same strain. "Normals" average 28 gms (25-32) at maturity, dwarfs 9 gms (7-12). The dwarf heads are much shorter, proportionately wider, especially so between the eyes. The nose and face are shorter, "blunter" (Figs. 4, 5). They are unsteady in gait, and while usually quite lethargic in disposition, if hurt or excited (as in bleeding) become much more excitable than do the normals. They frequently show polydipsia and polyphagia, and are quite susceptible to

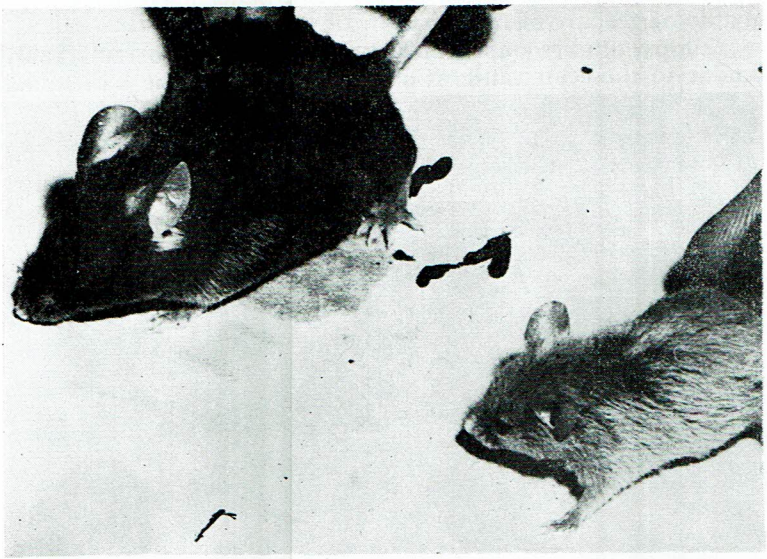

Fig. 4 Normal and dwarf-littermate mice, 3 months of age showing comparative size, stance and profile.

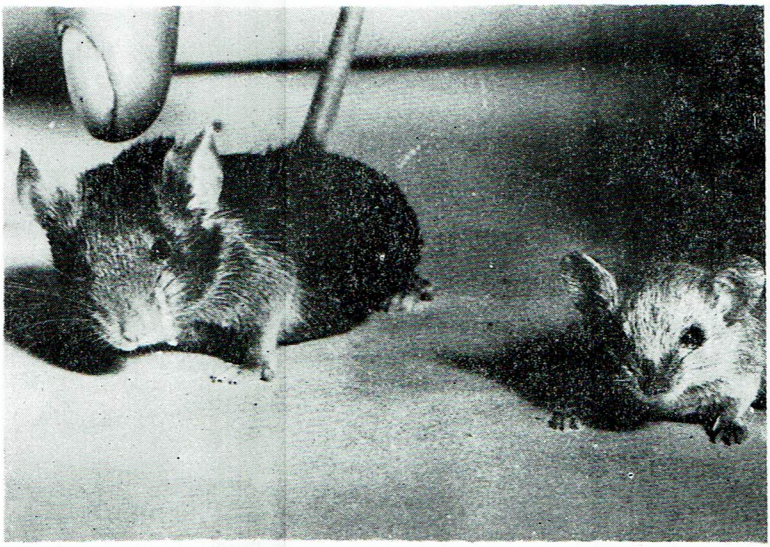

Fig. 5 Same mice showing comparison of shape and relative proportions of face.

both respiratory and digestive-tract disturbances. We have been unable to get any of our dwarfs to breed.

Autopsy studies on normal and dwarf mice are remarkably similar to those on cattle. Complete closure of the basicranial

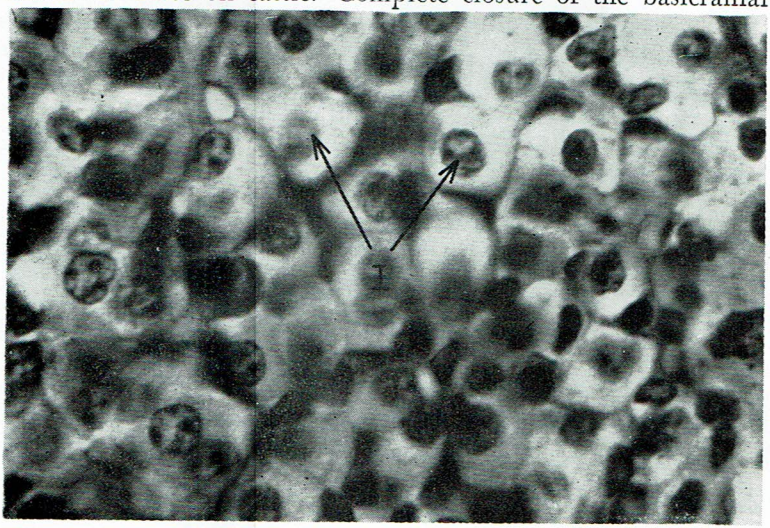

Fig. 2 Sagittal section through anterior lobe of pituitary of 4-months old dwarf heifer calf, showing numerous large chromophobes. (I) H & E x 970.

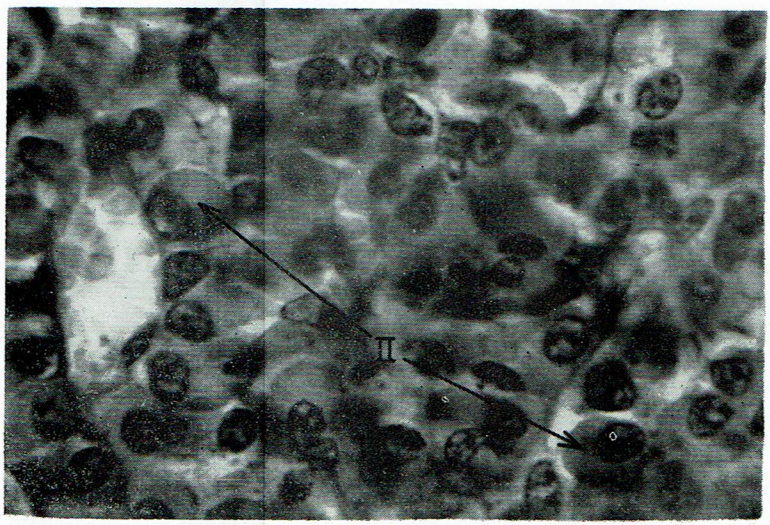

Fig. 3 Section of same gland, different field, showing agranular neutral-staining cells, apparently between cell-types of chromophobes and A or B cells. In many fields these are the only secretory-type cells to be seen. (II) Gomori stain x 970.

suture in dwarf mice is common, as is the spherical form of the smaller calvarium. The gonads are malformed, immature, and frequently unilateral. The anterior hypophysis shows no acidophils, few basophils, but a large number of larger, peculiar staining chromophobes as in the dwarf cattle. (Figs. 2, 3) Both pancreas and suprarenals are scattered, in small masses of cells with irregular architecture. The thyroid is reduced in quantity, and irregular in architecture. The thymus is increased quantitatively but apparently is normal in architecture.

Blood-cells studies on normal and dwarf mice reveal a response to insulin very closely parallelling that obtained in normal and dwarf calves.

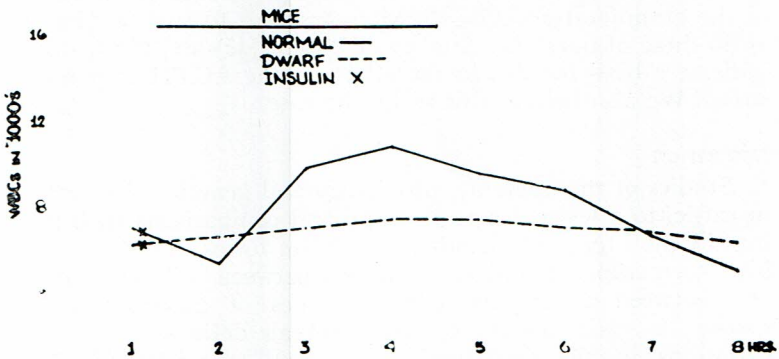

Fig. 6 Chart showing effects of insulin on total leucocyte counts of phenotypic normal and dwarf mice, 20 normals, 12 dwarfs—2-4 months old.

The dosage used was based on 0.04 units of insulin for a normal, fully developed mouse, weighing about 28 gms. and graded down proportionately for the small dwarfs. All blood was obtained from the veins at the tip of the tail. Because of the size of the vessels, injections were made intra-peritoneally rather than intra-venously as in cattle, which would account for some differences in response between cattle and mice. In spite of this fact, and unavoidable discrepancies in dosage, the overall similarity in response is striking (Pennebaker & Downs, 1959). In all of our blood-studies, a normal total white cell count and a "differential" were taken, at first using a modified Giemsa-Wright stain, in our later ones the prophylene-glycol and phloxine method, insulin was then injected, and at successive and regular periods the total and "differential" counts were taken. The curves in Fig. 6 represent averages of total number of counts made on normal (20 animals) and dwarf mice (12 ani-

mals) approximately 3 months of age. Data in Fig. 7 are likewise based on averages of differentials on these same animals.

In mice, as the total count rises, (also at about the second hour after insulin) the granulocyte rises sharply in normals, the lymphocyte count showing a coincident fall, the differential count returning fairly rapidly to normal, as the total count does so. An absolute eosinopenia is a consistent finding in the "normals". In dwarfs on the other hand, there is a slight rise in granulocytes, and a slight fall in lymphocytes, neither of which returns completely to normal within an eight-hour period. There is only a slight eosinopenia. An interesting observation is the high incidence of "immature" granulocytes present in the blood of the dwarfs at the peak period and for several hours thereafter. Obviously, the greatest difference to be seen is the failure of the granulocytes of the dwarf to respond to such a stimulus as do those of normals.. Studies of Porter (45) and many others indicate a basis for this in the effect on the ACTH response to stress. We also believe this to be the case.

Discussion

Studies of the anatomy, physiology and genetics of dwarfism in cattle, to a lesser degree in mice, and comparisons with findings in the literature on other vertebrate forms, indicate a very high correlation of similar conditions between different species, and between apparently different types of dwarfism within species. In each case the dwarfism reveals definite and similar variations in the cartilaginous skeleton, especially the basicranium. Consistently there are observable differences, some of them very marked, in the glands of the endocrine system of dwarfs and normals of different species. Although there are significant variations in the findings of different workers, and in their interpretations, there still is a consistent pattern of anterior pituitary and adrenal cortex involvement, with frequent similar changes in other glands noted. This is especially true of the pancreas, and is borne out by the physical findings in these animals. There are indications that dwarf animals respond to stress in similar ways, even in widely different species. Although the pattern of inheritance varies, the condition is undoubtedly an hereditary one in all forms reported.

Studies of Anand and his associates (1955), Bogdanove and others (1955), Cleghorn (1955), Colfer, DeGroot and Harris (1950), and DeGroot and Harris (1950), Flirko and Szentogathai (1957), Harris (1951), Hume (1952), Kirvalo and Talanti (1957), Laquer (1955), Stein and Mirsky (1956) and many others indicate the close relationship between form and function of hypothalamus and pituitary. An equally imposing literature demonstrates the importance of this mechanism to other endocrine

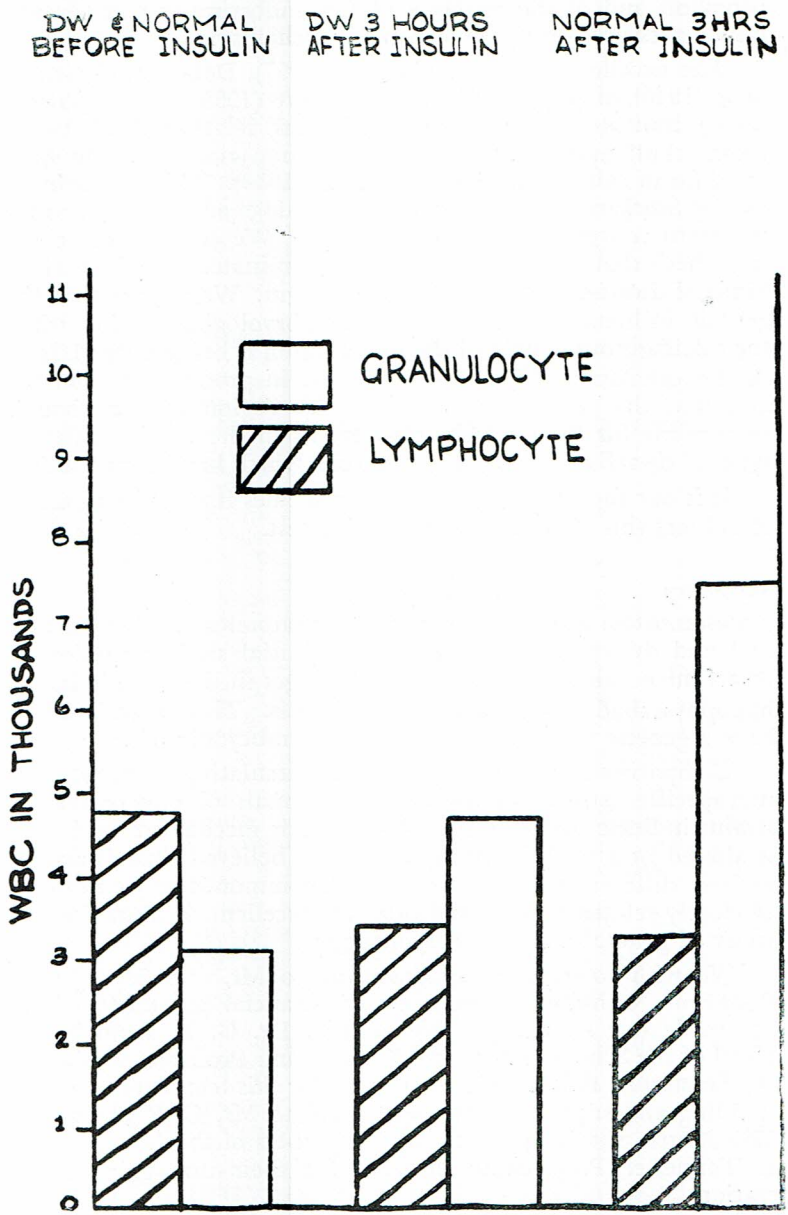

Fig. 7 Chart showing changes (in hourly averages) in differential count as result of insulin injection at peak of effect. (Same series as in Fig. 6). More than twice the number of normals and three times the number of dwarfs completed since these charts were drawn show no significant differences.

behavior, and of the response of the endocrine system to even minor pressures on the homeostatic mechanism.

The excellent reports of DeBeer (1957), DeBeer and Gruenberg (1940), of Kappers (1932), of Gilbert (1935), and of Witschi (1956) indicate the close developmental relationship between brain, skull and more especially the importance of the basicranium in this mechanism (Mortimer, 1938). This was pointed out by Stockard (1941) in his work on dogs and we wish again to accent it from our studies on cattle. We cannot escape the hypothesis that the many "common denominators" in the various kinds of dwarfism point to a similar origin. We suggest that the genetic influence is exerted at the embryological period when the cartilaginous matrix of the basicranium is being formed (and the hypothalamus and pituitary are also in process of formation) and that the genetic influence on this region at this time is responsible for the later chain of events in the several different types of dwarfism in the various species which have been studied.

It is our intention to pursue these studies further in an effort to subject this thesis to an exhaustive test.

Summary

Post-mortem gross and microscopic anatomical studies on normal and dwarf Hereford calves, and initial similar studies on dwarf mice indicate fairly constant changes in the hypothalamic-hypophyseal-adrenocortical axis in dwarfs. This is believed to have a genetic basis, operating early in embryonic life.

Comparisons of the responses of circulating leucocytes to non-specific "stress" in dwarfs and normals of closely related strains indicate that the entire homeostatic mechanism in dwarfs is altered in a fairly constant way. It is believed that dwarfs of entirely different species have more in common than do normals of closely related strains, and offer an excellent medium for the study of general adaptation syndromes.

We wish to express our gratitude to Mr. and Mrs. Justin Potter of Nashville, Tennessee, for financial assistance which has made our studies possible, and to Dr. G. B. Pennebaker, Head of the School of Arts and Sciences and Professor of Biology at Tennessee Polytechnic Institute, for his consistent understanding and support of our work, and to Mr. C. P. Snelgrove, Miss Mattie Sue Cooper and other members of the Library Staff at Tennessee Polytechnic Institute for their unflagging cooperation.

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