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THE MAJOR FORMS OF HEREDITARY ECTODERMAL DYSPLASIA*

(WITH AN AUTOPSY AND BIOPSIES ON THE ANHYDROTIC TYPE)

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MY nearest neighbour country general practitioner to the southwest has recently written a book in which he reminds us that there are no illegitimate children; only illegitimate parents. Similarly, it seems that the rare things in medicine are not rare; only observers are rare.

There are two forms of dysplasia confined to ectodermal tissues, and which descend according to Mendelian laws. Both are said to be most uncommon. One type I have recognized and observed for over forty years, and I have had correspondence about cases from Boston to Seattle and from Winnipeg to St. Louis. It is so well marked that my children recognize it on the street, and it is so common that I have seen over 50 cases and know where there are a couple of hundred more. The other type is said to be so rare that it appears that less than three dozen cases have been reported in the whole world; but as soon as it was suggested cases began to show up in Montreal. When fully developed one type perspires freely and the other does not; so they have been called the hydrotic and the anhydrotic types, respectively.

The earliest growth of the fertilized egg results in three layers. From the outer layer or ectoderm we get the outer skin, the hair, nails, sweat and sebaceous glands, tooth enamel, the lining of the nose and mouth and certain other openings, the nervous system, the adrenal medulla and the pituitary body.

The hydrotic type acts as a Mendelian dominant, not sex-linked. Males and females are affected equally, males and females transmit it equally, and one-half of the children of the defectives show the defect. It never skips a generation. If a child has the defect either his father or his mother had it before him. All the subjects are hybrids. Two of them have never married and therefore it has never been seen in the human subject except in the heterozygous state. Experiments with this type in mice would indicate that the condition is lethal or sublethal in the homozygous state. There are probably several thousand of these people in America, but it seems clear that all have descended from one individual who lived in France more than 200 years ago, and that the whole group is the result of a single mutation.

The affection always shows in the nails, which are short, thick, and slowly growing. In extreme cases there are no nails at all on either hand or foot. It is important to note that all grades of the dysplasia can be found. With this nail defect there is almost always some hair defect. Some subjects have no hair of any kind anywhere, and those who have it complain that it does not wear well. It has not the normal resistance to rubbing by hat bands, etc. It breaks off close to the skin where there is much friction. This is probably due to imperfect keratinization. The skin of the palms of the hands frequently appears rough and thickened, is of poor quality and cracks readily. We have been calling this condition a hyperkeratosis but in reality it is a dyskeratosis. In general, cancer of the working surface of the hand is quite uncommon, but two of these people developed it there. One was a washerwoman and the other a carpenter. Another subject had a cancer of the tongue.

Skin pigmentation is marked and is peculiar enough that those who live among the cases

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can often recognize it on the street by the colour alone. It affects certain parts more particularly, the knuckles, elbows, axillæ, nipple areola, pubes, and the ischial tuberosities, etc. One boy had a deep pigmentation of the umbilicus and the linea alba such as is seen in pregnancy. Naturally it was a false alarm! Blood pressures are usually low and such people may live to good old ages. These low blood pressures and pigmentations suggest Addison's disease. The adrenals are under the control of the ectodermal anterior pituitary body, and the medulla itself is ectodermal.

At one time it was thought that the whole condition was due to hypothyroidism, but it is easily shown that this is not so. Low basal metabolic rates however are so constant that they require explanation.

The pituitary body is derived from the ectoderm, the anterior portion very directly, and certain of the functions deviate to the right or left of normal. These will be discussed in conjunction with the findings in the anhydrotic type. David[1] did reciprocal transplants of skin between the normal and defective mice. The normal skin remained normal on the defective mouse and the defective skin remained defective on the normal mouse. Again, normal mice and defective mice were placed into a parabiotic union (*i.e.*, artificial Siamese twins). Neither skin was affected by the serum of the other mouse. These two experiments seem to show conclusively that the cause is not endocrine.

There are many neurological defects in the group, *e.g.*, stammering. The number of mental defectives is abnormally large.

Eye troubles are common. Part of these, such as conjunctivitis and pterygium, are probably due to mechanical causes such as absence of the lashes. Another part is inherent. Strabismus is common, and I have seen one case of double congenital cataract. The lashes, the lens, and the conjunctiva are all ectodermal.

From a study of 40 cases in four generations I have compiled a chart which confirms the belief of the families that the average condition has decreased in intensity from generation to generation. I feel sure that I have seen improvement in the individual case through improved living conditions, and am equally certain that the same thing occurs in families. The statisticians point out, however, that the figures are not sufficient to establish with certainty that there is a definite trend which will continue (see Chart 1).

The condition is quite definitely not luetic, but syphilis does occur. (For a more extended description with illustrations and charts see my previous article in this *Journal*[2]).

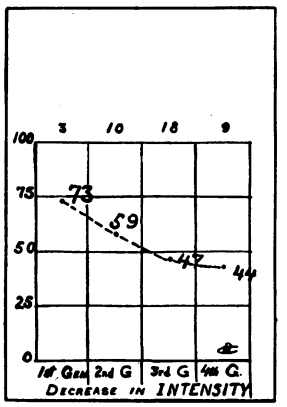

Chart 1

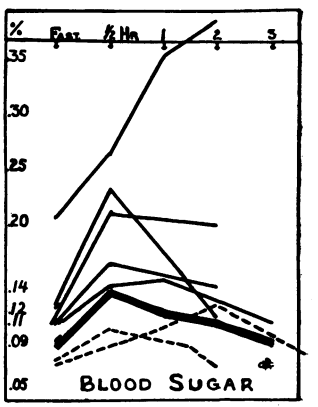

Chart 2

Chart 2.—Heavy line is Joslin's average normal. Narrow lines are curves of the hydrotic type. Broken lines are curves of the anhydrotic cases.

THE ANHYDROTIC TYPE

Only about 30 cases have been described. The defect is a recessive, and there is rarely a history of it in the family. Two of our patients were brothers. (In two or three instances it has appeared, possibly, as a dominant, but the evidence has not been completely satisfactory). Practically all the cases are in males, and it is generally stated that the condition is sex-linked, but certain cases have been reported in the female, and in mice both sexes are affected. Our four cases are in males. The distinctive marks of the condition are: (1) Diminished sweating; sweat glands are absent even up to 100 per cent. (2) Dental aplasia—missing teeth and deformed teeth and the teeth may be entirely absent. (3) A rhinitis which has usually been called "atrophic" but which is really a "hypoplastic rhinitis". Our autopsy showed almost a complete absence of the mucous glands of the nose and throat. (4) Some abnormality of the hair.

Cases have been reported from India, Russia, Germany, Sweden, France, England, among the Jews, United States of America, and from Australia. Our cases are from French and English Canada.

This world-wide distribution means one of two things, *viz.*, either the original mutation occurred a very long time ago, or, more likely, it is a mutation which occurs very readily and has

done so a number of times. In either event it is obvious that three dozen cases do not begin to represent the true number of them. There must be hundreds. Unlike the hydrotic type there is no apparent impediment to marriage in the heterozygous state. On the other hand it is absurd to suppose that the clinicians of the world would miss a condition which is so distinctive when it is fully developed. In the hydrotic type I can show every grade of the defect, and all the evidence points to the fact that there is every degree of severity in the anhydrotic cases also. The evident discrepancy between the theoretical and the observed incidence is probably explained by unrecognized cases which fall into three groups.

First, there is a large group of severe cases with almost complete lack of sweat glands, which therefore have no emergency temperature control. Hyperpyrexia occurs on the slightest excuse. Two of our infants suddenly showed temperatures of 108° F., apparently due to being too heavily covered in hot weather. Also, as we are able to show by autopsy for the first time, there may be lack of the mucous glands of the nose and throat. The accepted teaching is that the nasal mucosa warms the air, moistens it and washes it relatively free from germs before entering the lungs. It is the first line of defence of the body. The ultra-modern air-conditioning systems of our day really had their prototype in the nose and throat of our ultimate great grandfather Adam (see Figs. 4a and 5a).

Lacking this defensive apparatus and lacking temperature control, these infants probably die off with rhinitis, otitis media, pneumonia, and hyperpyrexia with or without convulsions. They die before the distinctive dentition has occurred and before they are old enough to complain of the heat, and the true condition is not suspected. Two of our cases would have fallen into this group. We have here a previously unrecognized cause of death in infancy.

The second group probably consists of those passed over as congenital syphilis. Our profession has been prone to consider any abnormal skin and tooth condition as luetic. One of our patients, aged 3, would have been so classified.

It seems probable, according to my theory, that the third group is made up of those cases which are relatively mild. No one asks whether a drop of sweat is produced by one gland working actively or two at half speed. The grown-ups have dentures and in the case of children the clinician supposes that the teeth have fallen out, or that there is delayed eruption. The chief complaint of our fourth patient was ozæna. The other factors were present but were made endurable.

In the average cases reported the absence of sweating makes life miserable. Hot weather, hot rooms, hot drinks, or heavy clothes cause elevations in temperature and suffering. One of these patients, who was working in the hay field, hired a boy to fetch water from a brook and throw it over him. Another capitalized his misfortune by becoming a life-guard at a beach. All grown subjects have learned to carry a wet cloth with which to moisten themselves, in order to control the temperature by evaporation.

Through the courtesy of the Children's Memorial Hospital and the Royal Victoria Hospital, of Montreal, I am able to report three of their cases. The fourth case was seen privately.

THE TEETH

Patient 1.—Age 4 months. No buds were visible by x-ray. Microscopic examination at autopsy showed no tooth foci.

Patient 2.—Age 6 months (brother of patient 1). None erupted; x-ray shows only three buds in the lower jaw and many missing in the upper jaw.

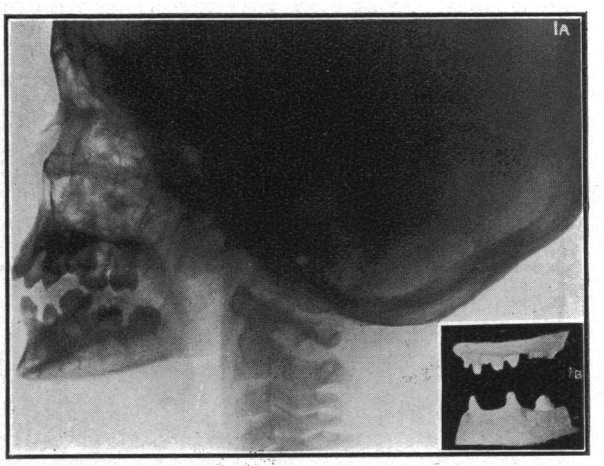

Fig. 1a (Patient 4).—Note sparseness of teeth and buds. **Fig. 1b.**—Plaster cast of teeth.

Patient 3.—Only two teeth were erupted at 3 years. X-ray shows four teeth in the upper jaw and only one bud in the lower jaw. This is possibly a canine.

Patient 4.—At seven years has 12 teeth erupted. The four upper molars and two lower molars are fairly normal. Anteriorly there are four uppers and two lowers. These cannot be identified by shape as they taper from a round base to a point. This is the primitive form of teeth. The lowers occupy the position of cuspids and are very literally canine in shape. The points were so long and so sharp that they had to be ground off by the dentist, because of injury to the opposing jaw. (In mice this may become a cause of death). X-ray shows only 6 unerupted buds, and he has lost no teeth. This makes a total of 18 against a normal of 52 (Figs. 1a and 1b).

THE SKIN

Patient 1.—At birth the nurse notified the mother that the child had some skin disease and prognosticated trouble in this respect.

Patient 2.—He was breast-fed for 6 weeks, but this was stopped because the baby would develop a rash on the side of the face that was against the mother during nursing. The skin was always dry, and the child resented being heavily clothed and cried when dressed to be taken out of doors. The skin was very dry and there was a tendency to desquamation.

Patient 3.—The skin was dry, shiny, with almost complete lack of hair.

Patient 4.—At birth was covered by a sort of scum which was two weeks or more in disappearing. "Eczema" all over the body gave a great deal of trouble for two years or more. The ears cracked and so did the elbows.

THE SWEAT GLANDS

Patient 1.—Skin sections for microscopic examination were taken from the axilla, anterior and lateral chest wall, from the back, abdomen, pubic region and the scalp. No definite sweat gland cells were found in any section.

Patient 2.—Sections were taken from the breast, (Fig. 3a), axilla, left lumbar, sole of foot and posterior aspect of the scrotum. No sweat glands were found in any area.

Patient 3.—The section was from the mid-line in the back, the thoracic region. No sweat glands were found.

Patient 4.—Sweats visibly, but less than others in the family.

Attempts had been made to cause sweating in patients 2 and 3 by the use of pilocarpine. For obvious reasons these were futile. First discovered by accident and later confirmed by design, patients 1, 2 and 3 showed rapid elevation of temperature if unduly covered or surrounded by heat.

THE SEBACEOUS GLANDS

Patient 1.—A few sebaceous glands were found in the skin taken from the back, but were absent or rudimentary in all the other areas examined (Fig. 2a shows a section from the pubic region).

Patient 2.—No trace of sebaceous glands was found, even on the posterior aspect of the scrotum.

Patient 3.—One normal sebaceous gland was found. However, there are fairly numerous masses budding off from the hair follicles which appear to be immature sebaceous glands.

Patient 4.—No biopsy.

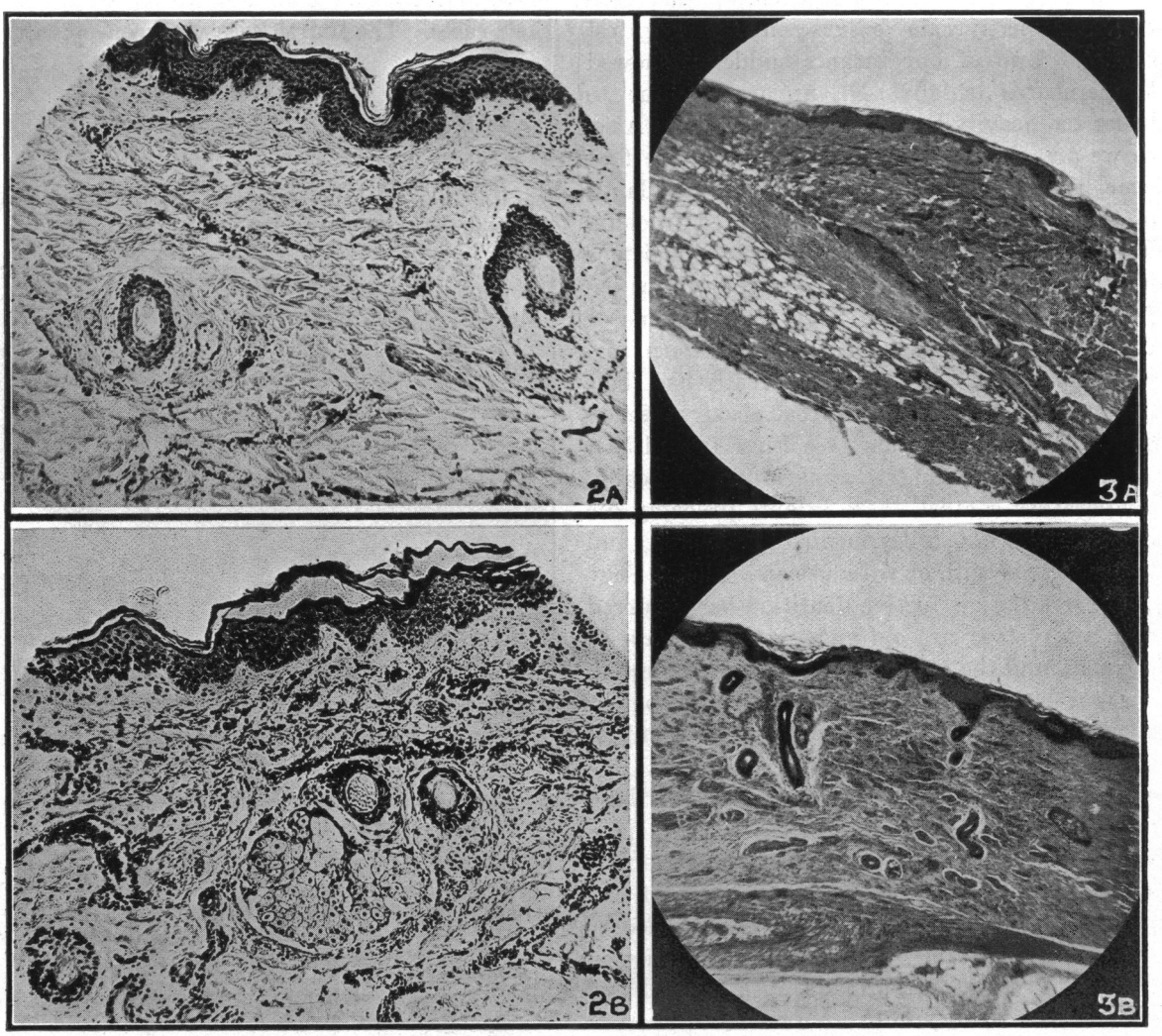

Fig. 2a (Patient 1).—Skin of the pubic region, showing rudimentary sebaceous gland on a hair follicle on one, and a very small one on the other. **Fig. 2b.**—Normal skin control. Baby at full term; sebaceous glands present. **Fig. 3a** (Patient 2).—Breast at nipple in male aged 6 months. **Fig. 3b.**—Normal skin of breast in 2 months' old female infant.

THE BREAST

Patient 1.—The autopsy report states that there was no obvious breast tissue and that the nipples were poorly defined.

Patient 2.—Dr. Wigglesworth took a section through the breast, including the nipple. The block was completely sectioned and no trace of breast tissue was found (Figs. 3a and 3b). Cases have been reported in which the nipples were missing and no breast tissue was palpable, but this seems to be the first time that the absence has been demonstrated microscopically.

Patients 3 and 4.—Nipples were present but breast tissue was not palpable.

THE HAIR

Patient 1.—The hair was sparse, fine, short and fair. There were no eyebrows.

Patient 2.—The hair was white and scanty. The eyebrows were absent and the lashes poorly developed.

Patient 3.—A sparse growth of white hair standing on end. There were no eyebrows and the eyelashes were few in number.

Patient 4.—The hair was light-coloured and rather thin and had abnormal whorls, with irregular direction of the hair slope, *e.g.*, the hair on the left side of the head was directed forward. The eyelashes were pale and fewer in number than normal; the eyebrows were thin, fine and almost invisible until recently. His father, who is a competent observer, was quite positive that a very definite change had occurred in size and in pigmentation of the eyebrows since the use of œstrogenic substances in the nose.

Microscopic sections in these cases seem to confirm the observations made in mice, that in this type the defect is in the hair bulb and is not due to faulty keratinization.

THE NAILS

In all our cases the nails appeared normal.

THE UPPER AIR PASSAGES

Patient 1.—This infant had rhinitis, crusting and mucopus in the nasal cavity, otitis media, and died of pneumonia. An autopsy by Dr. Chase showed a most striking decrease, almost amounting to a complete absence, of the mucous glands of the nasopharynx. A very few small glands were found in the turbinates and a few at the lower end of the trachea, but none in the pharynx, larynx, or the upper trachea. Control sections from normal babies show a great contrast which is obvious to all (see Figs. 4a and 5a; normal controls, Figs. 4b and 5b). In the only two previously recorded autopsies no microscopic examination seems to have been made of the tissues of the nose and throat. Weech,[7] however, in his excellent article forecast some lack of development, and Fleischmann[4] did a biopsy underneath the upper lip which showed no mucous glands.

Patient 2 had a rhinitis, a double otitis media, and died of pneumonia.

Patient 3 had had a constant nasal discharge for years and frequent nose-bleeds. The discharge came away in long string-like masses, frequently followed by bleeding.

Patient 4.—This boy had wide upturned nares. He had some sense of smell. He could detect the smell of a skunk but did not notice that of burning peat. He had had nasal trouble for at least three years. (He is now seven). There were small crusts at first, then larger ones. His nose bled easily. For a year the ozæna had been so offensive that the parents thought that they must shape his life toward some solitary occupation. Treatment by Drs. Mortimer, Wright and Collip according to their method[3] with œstrogenic hormones (Progynon B in oil in this case), immediately produced an amazing and delightful transformation in the condition. This improvement has continued and the father now reports that "the nasal condition has improved almost to a cure, so that now we are using Progynon B very little".

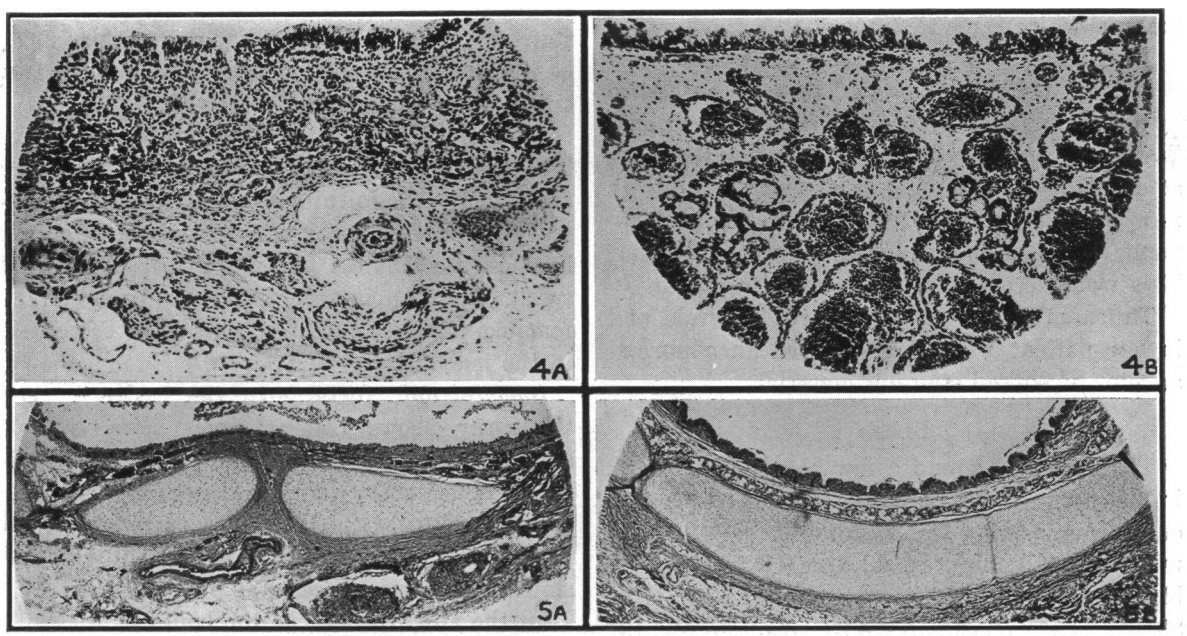

Fig. 4a (Patient 1).—Inferior turbinate. Note the extreme scarcity of mucous glands. **Fig. 4b.**—Normal control of the same age. Note mucous glands between engorged vessels. **Fig. 5a** (Patient 1).—Trachea. Note the complete absence of the collar of mucous glands which lies inside the cartilage. **Fig. 5b.**—Normal control of the same age and at the same level.

Considering that ozæna appears in the earlier years, that it has a familial tendency, that usually there is a dyspituitary state as shown by x-rays of the skull, one is permitted to wonder if, frequently, the basis of ozæna is not hypo-

plasia rather than atrophy. Certainly the cases of dysplasia and ozæna overlap.

Fleischmann,[4] basing his ideas on many measurements of "ozæna skulls", a family tree, and his mouth biopsy findings, comes out flatly in favour of the hypothesis that all ozæna is a part of this hereditary ectodermal dysplasia. This theory is very enticing, but the facts of ozæna are too abominably stubborn for such an all inclusive conception as yet. It does seem rational, however, that many cases of ozæna are a manifestation of an ectodermal defect, if not this particular one.

Endodermal Mucous Tissue

The endodermal mucous tissue was normal in the case which came to autopsy.

Thurnam[5] in 1847 noted a thick ivory-like skull, and this has been confirmed as a feature by nearly all the writers who have considered it since. Patient 4, at seven years, has the characteristic parietal bulges, etc., and, judging by x-ray readings standardized with the penetrometer, the skull is that of a boy five years older. This would seem to indicate dyspituitarism.

Thurnam also found an enlarged thyroid and in our patient 1 Dr. Chase noted an abnormal amount of colloid staining material.

Blood

Thannhauser[6] found a low blood sugar curve in his case. In our patient 3 the sugar tolerance curve was: fasting 76; 30 minutes, 107; 90 minutes, 90; 120 minutes, 68 (see Chart 2); red blood cells 5,030,000; leucocytes 11,800; Hgb. 83 per cent; phosphates 4.23; cholesterol 213; Ca. 11.4.

Internal Secretions

Argument that the glands of internal secretion derived from the ectoderm are involved in both types is as follows. (It is only fair to state that the endocrinologists are by no means prepared to concede that the facts, as set down, constitute proof.)

The anterior lobe of the pituitary body is derived from the ectoderm of the oral cavity, whose tissue we have been able to show by the microscope to be defective.

Adrenal medulla or the adrenotropic factor of the anterior pituitary.—There are low blood pressures and pigmentations in the hydrotic type and this has also been a feature in some cases of the anhydrotic type (Thannhauser).

Diabetogenic factor of the anterior pituitary.—All the blood sugar curves made so far in the hydrotic type run higher than normal and in the anhydrotic type they are lower than normal (see Chart 2).

Gonadotropic factor.—In the hydrotic type there seems to be delayed maturity in the males. The x-ray films show late epiphyseal union in four cases out of four. Voice change began in one boy when he was nearly eighteen. The anhydrotic type in the human cases has occurred so predominately in the male that it is frequently stated that it is sex-linked. Perhaps more truly there is a sex association. In mice the females of the recessive hairless type are usually sterile and the œstrous cycles are less frequent than normal. David says that the sterility or decreased fertility does not seem to be due to defects in the reproductive system of either the males or the females.

Lactogenic factor.—In the hydrotic type the breasts function particularly well. In the other type, while the pituitary connection is admittedly vague, Nature is so serious about this milk business that unless there is a fair amount of sweat gland primordium she suppresses the female altogether and even takes away the breast in the male.

Somatotropic factor.—In the hydrotic type the x-ray shows bone changes suggestive of acromegaly and which can be produced in animals experimentally by the growth factor of the anterior pituitary. There are tufted terminal phalanges, thick skulls, prominent frontal sinuses, and heavy occipital protuberances.

In the anhydrotic type the bones of the skull at least are regularly abnormal.

According to David,[1] homozygous dominant hairless mice, although of normal size at birth, seldom mature, and those which do never attain the normal adult size. Up until the time of birth they have been able to develop normally in regard to size. Following birth, however, they grow only slightly, and the suggestion is made that this may possibly indicate the deficiency of some hormone which had been supplied *in utero*.

The thyrotropic factor.—The hydrotic type usually shows low basal metabolic rates. Anhydrotic cases usually show high rates but the simple lack of sweating may explain this.

Mentality

Patients 1 and 2 were considered somewhat below normal.

Patient 3 was backward physically and mentally.

Patient 4 is quite bright. He learns rapidly and excels his brothers. He keeps his mouth shut curiously, to hide his abnormal teeth, even as the hydrotic patients always try to hide their nails.

SUGGESTED MANAGEMENT

1. Appropriate dental treatment for face, saving physically and mentally.
2. A non-sweating occupation in a moist, temperate climate, with a minimum of present or future worry (*e.g.*, a maritime government job).
3. Œstrogenic substances for the nasal condition.

SUMMARY

Some additional observations are made on the hydrotic types of hereditary ectodermal dysplasia including a chart showing that the average severity of cases has been decreasing.

The first four cases of the anhydrotic type to be reported in Canada are presented with biopsies and the third autopsy on record. The condition is much commoner than usually believed. The distinctive marks are diminished sweating, dental aplasia, and a rhinitis which has usually been called "atrophic". This is shown to be hypoplastic, the mucous glands of the nose and throat being diminished in number or wholly absent.

The resultant lack of defense and air-conditioning, combined with loss of emergency temperature control, is probably a hitherto unrecognized cause of death in infancy. Recognition is not made because death occurs before the children are old enough to complain of the heat and before the distinctive dentition has occurred.

The ozæna responded to the use of œstrogenic substances.

Breast tissue was shown to be absent by the microscope.

The question is raised as to what extent ozæna is a hereditary ectodermal defect.

Evidence is given that the endocrine glands of ectodermal origin are involved in the general ectodermal dysplasia.

I have received every encouragement and cooperation from McGill University and the associated hospitals. Among others at the University to whom I am greatly indebted were Drs. Huskins, Reed, Mortimer and Collip; at the Montreal General, Drs. Rhea, Rabinowitch, Bensley and Wright; at the Royal Victoria Hospital, Drs. Meakins, Cameron Stewart and the late Dr. Chase, who did the autopsy; at the Children's Memorial Hospital, Drs. Cushing, Goldbloom, Burgess, Wiglesworth, for his biopsies, and Childe.

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NEW MENSTRUATION TOILET.—Sir,—During the last few months I have often been asked by young women whether I considered this new practice of plugging the vagina with absorbent tampons instead of using sanitary pads advisable and healthy. My reply is that it is not at all a good thing to do, because vaginal plugs become very offensive and infected even when introduced by the surgeon under the best aseptic technique, and when introduced by a woman herself, under ordinary daily conditions during menstruation, the dammed-up blood in the vagina forms a perfect culture medium, and a profuse growth of septic organisms results. This practice is likely to result in vaginitis, cervicitis, and *B. coli* infections, with quite a possibility of sterility following as well as the other well-known complications of the above conditions. Is it realized how popular this practice is becoming? The "outfits" are procurable at many big stores, and are presented to girls by women who extol their harmlessness and many advantages. For health and beauty classes, dancers, factory girls, etc., they have great attractions, as they require no belt and are comfortable and unseen. The literature accompanying them is all that these young women have to guide them. Quite a lot of doctors seem to be recommending them, but I feel sure that they have forgotten what a vaginal plug is like after its removal; indeed, this is a job usually left to nurses. I shall shortly have a series of reports from bacteriologists on the growths obtained from the discharge before and after the use of these popular vaginal plugs, but in the meantime I think it is only fair to the female public to give some advice on the subject, or is it a matter for the Ministry of Health?—E.L.M. Correspondence in *Brit. M. J.*