It is interesting to consider what part the autonomic hypertrophy played in the overgrowth of the limb. Were they parts of the same process, or were the hypertrophied sympathetic nerves responsible, even partially, for the generalized overgrowth of the limb, through disordered vaso-constrictor and secretory impulses?

FIG. 4. Patient's mother.

leg, which was stated to be similar to the initial lesion affecting her son.

The patient's mother (Fig. 4), who was about 40 years of age, was 5 feet in height, and her physique suggested achondroplasia. The patient was her only child. Despite a certain degree of deformity of her infant's limb at birth, there was no special trouble at the confinement. She said that her parents were normal, but that her grandmother showed similar lesions to hers, which consisted of over 2,000 minute cutaneous tumours and scattered subcutaneous swellings; freckles and patchy pigmentation of the skin; and a diffuse swelling on the dorsum of the right

few cases, where repeated blood counts were carried out, considerable fluctuations in the degree of eosinophilia were observed. One case showed 17 per cent. at one time and only 0.8 per cent. on another occasion four months later. It is possible, therefore, that eosinophilia may have been temporarily present in others of our series, but was not discovered by a single blood count. It was noticeable that an increase in the eosinophilia occurred in several cases during the very hot weather in July and August, 1928, being lower before and after these months. This observation we intend to confirm next summer if climate permits. It would be interesting to know the degree of eosinophilia in insulin cases in hot countries.

The Cause of the Eosinophilia.

So far we have only established the presence of eosinophilia in a large proportion of insulin-treated diabetics and its absence in non-insulin cases. No factor other than the insulin has been discovered to account for this eosinophilia. The following ways in which insulin may be responsible suggest themselves.

1. Insulin, by virtue of its physiological action, might produce an eosinophilia. This is hardly likely, and the fact that we have found an eosinophilia in a case of diabetes insipidus treated by injections of pituitary extract is against this possibility.

2. The eosinophilia may be an allergic phenomenon produced in susceptible patients by the protein nature of insulin or by protein impurities in the solution. The latter, however, are almost absent in the brands of insulin (B.D.H. and B.W.) used by most of our patients. Moreover, there has been no sign of local allergic phenomena, such as wheals and urticaria, in these cases.

3. Insulin, being an acid solution, has an irritative effect on the skin and subcutaneous tissues, manifested locally by stinging and oedema at the site of injection. Eosinophilia is possibly produced by this constant skin irritation in the same way that it is so frequently associated with skin disease.

No definite explanation of insulin eosinophilia can be offered at present. The possibilities are being further investigated.

SUMMARY.

An eosinophilia has been found in 10 out of 20 diabetics treated with insulin. It is absent in cases treated without insulin.

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EOSINOPHILIA IN INSULIN THERAPY.

A PRELIMINARY REPORT TO THE MEDICAL
RESEARCH COUNCIL.

BY

R. D. LAWRENCE, M.D., AND O. B. BUCKLEY, M.B.,
M.R.C.P. M.R.C.P.

THE occurrence of a high degree of eosinophilia in a diabetic patient treated with large doses of insulin was first observed in 1927.¹ Various blood counts gave percentages of 12, 20, 11, 15, and 17.5, and a thorough investigation showed none of the usual causes of eosinophilia to be present. It therefore seemed possible that insulin therapy *per se* might be responsible for the abnormal blood count, and this point has been investigated in other diabetics. It has been found that, of the 20 insulin cases examined, 10 show an eosinophilia varying between 4 and 20 per cent.

Non-Insulin Diabetics.

As far as we are aware, no abnormal eosinophilia has been reported in diabetics. To control this point blood counts have been carried out on 12 diabetics who were not having insulin. In only one (and he suffers intermittently from eczema) has an eosinophilia of over 4 per cent. been found. The others are mostly between 0.5 and 2 per cent., the same as in the non-diabetic population attending our out-patient departments. An eosinophilia of 4 per cent. or over has therefore been taken as a definite degree in classifying our results.

Insulin Cases.

Twenty insulin cases, of all ages and degrees of severity, have been investigated. Of these, 10 have an eosinophilia of 4 per cent. or over, and 5 of 9 per cent. or over. The highest observed is 20 per cent. In none has there been any evidence of parasitic or skin diseases, and the only asthmatic had a low count of 1.6 per cent. No factors have been observed to account for the production of eosinophilia in half these cases and its absence in the other half, such as general allergic tendencies, varying skin reactions at the site of insulin injections, or variations in the diet followed. On the whole the eosinophilia bore no relation to the size of insulin dose, although one insulin-resistant case, on 200 units a day showed the highest figure. In a

INSULIN FAT ATROPHY A TRAUMATIC ATROPHIC PANNICULITIS.

BY

HAROLD AVERY, M.B., B.S.LOND., M.R.C.P.,
MEDICAL REGISTRAR, CHARING CROSS HOSPITAL, LONDON.

A PECULIAR form of local fat atrophy in the subcutaneous tissues following repeated insulin injections has been described, and a case was shown by me before the Clinical Section of the Royal Society of Medicine.¹ In all cases, despite instructions to the contrary, the insulin has been repeatedly injected into the one area instead of varying the site. The situation of the atrophy varies with the site of injection, the arms, thighs, and abdominal wall having been affected. A dimpling of the skin first appears, the depression then spreading in area and extending deeply. As a rule the underlying tissues are not affected, but where the injections have been given deeply the underlying muscle may also atrophy; the skin may adhere to the underlying tissues, but does not itself undergo any change in texture. Neurological changes are generally absent,^{2,3} the integrity of the somatic and sympathetic nerve supply being demonstrated by the presence of all forms of sensation, and the pilomotor (goose-skin) reflex on faradic and direct galvanic stimulation⁴; impairment of pain, tactile and thermal sensation may, however, occur.⁵ In one of the cases reported no sign of the atrophy remained two and a half years after ceasing injections, though the depression had been deep and distinctly felt through the clothing.⁶ The

following brief account of my patient's history is fairly typical.

A married woman, aged 56, a Dutch Jewess, large and rather obese, has suffered from diabetes mellitus for fifteen years. There is a strong family history of the complaint, two sisters and two maternal uncles suffering from diabetes, and her mother having died in diabetic coma. The urine has been intermittently sugar-free, but the patient will not keep to a strict diet. Thirst, polyuria, and pruritus vulvae have not been present for some years. There are now no abnormal symptoms except a feeling of lassitude and ill health when the diet has been too generous; physically she appears quite healthy.

Insulin therapy was begun in March, 1927, 20 units twice daily being injected into the arms, more or less in the same area each time, some of the injections being given deeply. In March, 1928, the patient noticed a dimpling of the arms in the injection area, which began to extend deeply. Synthalin treatment was attempted, but was useless in controlling the glycosuria, and insulin therapy was therefore continued by injections into the thighs.

Physical Examination.—The patient has well-covered arms, but on each side of the point of injection below the insertion of the deltoid there is a deep depressed area where subcutaneous fat seems to have entirely disappeared. The skin here appears perfectly normal and is not adherent to the underlying muscle; there are no sensory nervous disturbances, objective or subjective, and the pilomotor reflex is intact. The muscle at the bottom of the depression feels abnormally thin, and the humerus can easily be felt through it. Power and function in the arm are not impaired; indeed, the condition gave rise to no symptoms until the patient's fear was aroused by the indiscreet remarks of a medical attendant who prophesied paralysis, so that she now complains of a feeling of weakness. The thighs show an early stage of the same lesion. The fasting blood sugar (November 8th, 1928) was 0.142 per cent., and urine sugar 1.84 per cent.

The accompanying table is an analysis of the recorded cases of this condition. Case 1 is my own; Cases 2 and 3 were described by Barborka⁷; Cases 4, 5, and 6 by Carmichael and Graham³; Case 7 by Chapman⁶; Cases 8 to 12 by Depisch⁵; Case 13 by Mentzer and du Bray,² and Cases 14 to 21 by Rabinowitch.⁸

Case.	Sex.	Age.	Duration of Diabetes in Years.	Duration of Insulin Treatment.	Case.	Sex.	Age.	Duration of Diabetes in Years.	Duration of Insulin Treatment.
1	F.	56	15	1	12	M.	38	7	2
2	F.	34	4	1½	13	F.	54	6	2½
3	F.	60	1½	1½	14	M.	38	5	3½
4	F.	49	5	1½	15	M.	22	2	2½
5	F.	39	18	3	16	F.	14	2½	2½
6	M.	8	—	2	17	M.	8	1½	1½
7	F.	48	—	1½	18	M.	42	1½	1½
8	F.	50	—	1½	19	M.	54	4½	3½
9	F.	45	5	1½	20	F.	33	2½	2½
10	F.	54	4	1	21	F.	28	5½	3½
11	F.	53	—	1½					

Fourteen of the 21 recorded cases have occurred in women, a fact which, taken together with the greater incidence of diabetes in men, suggests that women are definitely more liable than men to suffer from the condition. The age incidence varied between 8 and 60 years, with an average, including two boys aged 8 and a girl aged 14, of 39.5; excluding these children the figure is 44.4 years. The known duration of the diabetes has varied from 6 months to 18 years, with an average of 5.3 years, whilst the duration of insulin therapy before the appearance of the fat atrophy has varied between 3 months and 3 years 6 months, with an average of 1 year 8 months. The dose of insulin has varied from 10 to 120 units daily, being given in one, two, or three injections a day. The duration of treatment before the onset of atrophy appears to bear no relationship to either the dose or the daily number of injections of insulin. The amount of subcutaneous fat is of no significance as some of the patients have been obese and others slender.

In Case 2 there was no further atrophy three months after ceasing injections; in Case 6 improvement began in three weeks, and in Case 7 no sign of the atrophy was present two and a half years afterwards. Cases 6, 14, and

18 were complicated by pulmonary tuberculosis; Cases 3 and 19 had advanced arterio-sclerosis.

In the early days of insulin therapy acute local reactions such as necrosis and sterile abscesses occurred, but with the introduction of better preparations they became rare. An urticarial type of reaction, either local or general, and probably due to protein sensitiveness, is occasionally seen, especially among patients using the American iletin (insulin Lilly), which is prepared from pig pancreas; with the elimination of extraneous substances, and improvement in the technique of preparation, even these reactions are becoming rare. It is unlikely, however, that foreign proteins are the cause of the local fat atrophy described, as in only one of the cases recorded was there any undue immediate reaction³; with this patient there was at first a local reaction with English insulin, but on returning to this preparation after using Lilly insulin no reaction was obtained.

Examination of rabbits shortly after an injection of insulin⁹ elicits no signs of degenerative changes in the connective tissue cells of the panniculus adiposus, but these cells are widely separated by a mucigenous fluid, which produces the localized subcutaneous oedema seen following an injection, and which in the human subject takes eighteen to thirty-six hours to subside. The neighbouring muscles, however, show marked degenerative changes, with leucocytic infiltration, as appears to happen in human muscle if the insulin is deeply injected. Lawrence¹⁰ found that after frequent injections of insulin sections of the skin showed infiltration in the neighbourhood of the vessels by lymphocytes and histiocytes, with some plasma cells and eosinophils, whilst three years after discontinuing the injections there were, in addition, fibrous strands passing down from the corium and dividing the fat into coarse lobules. Mentzer and du Bray, on the other hand, were unable to find lymphocytes in their patient, but recorded the presence of a calcified cyst.

It is perhaps natural to attribute the disappearance of the fat to the presence in the insulin of fat-splitting enzymes derived from the pancreas, but Rabinowitch,⁸ after concentrating down large quantities of insulin (under low pressure and temperature), was unable to detect pancreatic lipase on applying the usual tests—litmus milk, copper soap, olive oil bile, and ethyl butyrate. He therefore concluded that, unless his method of concentration destroys lipase, none is present. The sterilization of the needle is not at fault, as is shown by the diversity of methods employed by the patients (boiling, ethyl alcohol, lysol, and methylated spirit); the brand of insulin used has also varied among the cases (Lilly, Burroughs Wellcome and Co., Chemosan).

That the reaction in the subcutaneous fat is not specific is borne out by the fact that the early histological appearances following injections of insulin, hypertonic glucose, or saline solutions are identical⁹; whilst the depressed areas of fat atrophy have been observed at the injection sites in narcotic addicts,² and foci of lymphocytes have been found on section. A somewhat similar condition, but far more intense and advanced, is seen in traumatic fat necrosis of the breast, where areas of necrosis and liquefaction in the fat are surrounded by abundant newly formed connective tissue.^{11 12}

It is probable that the injection of insulin or other substances damages the delicate protoplasmic cell envelope of the fat cells so that fat globules are released, and, acting as foreign bodies in the tissue, result in the formation of histiocytes which take on lipophagic activity. When the slight trauma is constantly repeated, atrophy of the fatty layer is likely to result. If the trauma is more severe, as following an injection of ether into the subcutaneous tissues, a similar but more intense reaction may result,¹³ with the formation of a greater amount of fibrous tissue, so that a close resemblance to the appearance in traumatic fat necrosis of the breast is seen.

A patchy atrophy of the fatty layer of the skin resembling the condition under discussion, preceded by the ingestion of the fat by large phagocytic cells, has occurred in association with periods of pyrexia, suggesting an infective origin of the lesion¹⁴; whilst similar histological appearances were described by Parkes Weber in a case of relapsing panniculitis.¹⁵

Conclusions.

The subcutaneous fat atrophy described as following repeated injection of insulin into the subcutaneous tissues is a non-specific reaction, the result of repeated small traumata to the panniculus adiposus, and not due to the presence of any pancreatic lipase in insulin, so that the condition might suitably be called a traumatic atrophic panniculitis.

I wish to express my thanks to Dr. du Bray of San Francisco, Dr. Chapman of Bridlington, Yorks, and Dr. Rabinowitch of Montreal for supplying me with details of their cases.

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Memoranda:

MEDICAL, SURGICAL, OBSTETRICAL.

PAINLESS LABOUR WITH INVERSION OF THE UTERUS.

In view of recent communications on painless labour I believe that the following clinical notes may be of interest.

A multipara, aged 27, had had two previous pregnancies, both of which were normal. She was breast-feeding the last baby when she became pregnant and, therefore, had no idea of the date of commencement of pregnancy.

On November 15th, 1928, she had been performing her daily household duties as usual. At 4.20 p.m. she complained of "slight stomach-ache" with a desire to defaecate; at 4.30 p.m. she had a slight motion, and as a result of straining "felt something come down into her front passage." She arose from the lavatory seat, and without any pain, so she states, delivered herself of a child, which fell to the floor, the umbilical cord being torn. She picked up the infant, went upstairs, and lay on her bed. A friend notified the maternity department of the Radcliffe Infirmary, and a nurse was sent out; she found the patient in good condition with a pulse of 96 per minute, and the child rolled in a blanket. She ligatured the umbilical cord, which was about 9 inches long. The placenta was lying in a pool of blood on the floor. The nurse then examined the mother, and found at the vulva a swelling which she rightly diagnosed as an inverted uterus. She wrapped the organ round with sterile pads and sent for the patient's doctor, who at once ordered the patient to the maternity department of the hospital.

When I saw the patient the pulse was good and she was not in the least degree in a state of shock; I found a partial inversion of the uterus with a portion of the membrane still attached. She was given an anaesthetic, and the surrounding areas and vulvar hair were thoroughly treated with iodine, the inverted portion of the uterus being cleaned up with mercury biniodide (1 in 1,000). I stripped away the membranes and returned the uterus to the pelvis, and the patient was then given a hot intrauterine douche of mercury biniodide (1 in 4,000) followed by saline solution. I injected intramuscularly 1 c.cm. of pituitrin with the same amount of aseptic ergot.

The patient did not have the slightest rise of temperature throughout the puerperium; she and her child left the hospital on the twelfth day, perfectly well. She gave the history that with her first labour she had definite labour pains throughout, but not excessive. With her second confinement "had only about two pains, and these were quite trivial." The present labour was quite painless.

The interesting points of this case are the entire absence of shock, which one usually associates with inverted uterus in the course of delivery; the puerperium absolutely

normal; and the child none the worse for its unusual entrance into the world.

I am indebted to Dr. F. G. Proudfoot, K.H.S., the senior honorary obstetric physician, for permission to publish this case.

HENRY R. SPARROW, M.B., B.Ch.,
Obstetric House-Physician, Radcliffe Infirmary,
Oxford.

LOCAL INJURY AS A POSSIBLE CAUSATIVE FACTOR IN SARCOMA.

REPORT OF A CASE.

INJURY has been regarded as an exciting cause of malignant tumours from the earliest times, and especially by the laity. The part played by various forms of chronic irritation in the production of certain types of epithelioma is undeniable. Dealing with bone sarcoma, Coley (*Annals of Surgery*, April and May, 1911), in a review of 970 cases, traced a history of antecedent local injury in 23 per cent. Of these, in 38 per cent. the tumour developed within the first month after the injury, and in 70 per cent. within the first six months. Discount must be made for the numerous slight traumata to which every active individual is constantly subject, and which may be recalled only by close questioning after the development of a tumour. But the following case illustrates so closely the rapid growth of a sarcoma in direct relation to a definite injury that it seems worthy of record, although it is not possible to be certain that the injury did not merely break down and disseminate a small pre-existing focus of malignant disease.

A railway signalman, aged 45, was in perfect health until April 19th, 1928. On that day, while on duty, he was pulling over a heavy signal lever with his left hand and his head was turned fully to the right, as he was speaking to the telephone boy. He felt something snap in the left side of his neck, and at once experienced a sharp pain, severe enough to make him sit down. He consulted his doctor on April 21st. Dr. Harrowell of Great Haywood found on that day a small swelling the size of a hazel nut under the middle of the left sterno-mastoid muscle. The man continued at work until May 4th, when he again saw his doctor, as the swelling was increasing in size. He ceased work on that day. A skiagram taken a few days later showed no evidence of injury to the cervical vertebrae.

On May 13th his condition was as follows: A florid healthy-looking man, cheerful and in no discomfort. The left side of the neck, from the mandible to below the clavicle, was the seat of a brawny swelling, more prominent in the middle, extending forwards to the margin of the larynx, and back to the edge of the trapezius muscle. The swelling was not tender, it did not pulsate, and no thrill was felt or heard over it. The skin at its margins showed a bluish-purple discoloration. The left pupil was contracted and there was definite weakness in the left deltoid muscle. He was afebrile.

He was admitted to hospital on May 19th. The swelling had markedly increased in size in the interval. On May 21st the left arm became oedematous and paretic. Two days later he could only swallow fluids, and his voice was reduced to a whisper. On May 24th an exploratory operation was undertaken in the hope of relieving the laryngeal pressure. The whole left side of the neck was infiltrated with growth; he died some twelve hours later of cardio-respiratory failure.

Post-Mortem Examination.—Body well nourished, left arm oedematous. The swelling of the left side of the neck extended from the mastoid process and occiput above, to the scapula behind, and to below the clavicle in front. It was more prominent in front just anterior to the mid-point of the sterno-mastoid muscle. On dissection the swelling was found to consist of an unencapsuled mass of new growth. The mass extended from the mastoid process down to the first rib, and behind as far back as the scapula. It surrounded the clavicle and was infiltrating the deep fascial planes of the neck and the prevertebral muscles. Posteriorly the skin also was infiltrated by growth. The carotid sheath was completely surrounded, likewise the subclavian vessels and the upper cords of the brachial plexus. The lymph glands of the area were themselves enlarged and infiltrated by growth. In places the growth was of a purplish colour. There was oedema of the mucous membrane of the left arytenoid process. The oesophagus was pressed upon but not occluded by the growth. There was no sign in the mouth, pharynx, or larynx of any primary focus. The clavicle and first rib, though surrounded by growth, were not invaded by it. The mediastinal glands were not enlarged. The viscera showed no secondary deposits and no noteworthy abnormalities.

On microscopic section the growth proved to be an endothelial sarcoma of high malignancy.

The mass of growth removed *post mortem* was roughly conical, with a vertical measurement of 6 in. and a base of 4 in.