METABOLIC COMPLICATIONS OF HUMAN OBESITIES

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Foreword

The physicians of the University Hospitals of Marseilles are glad to open the 6th of these International Meetings of Endocrinology, which have followed an almost quinquennial rhythm since the creation of the chair of Endocrinology.

With alacrity I wish to express my gratitude to the authorities present in this room, to the President of the University Aix-Marseilles II, the Deans of the Faculties of Medicine, Pharmacy and Dental Surgery, the Director General of Public Assistance, the President of the Hospital Medical Committee, the speakers and the audience who will take part in the discussions, the Institut de Recherches Servier who have so generously absorbed the financial responsibility. I also thank the group which I have had the honour of leading for many years and whose work will be evoked.

As a supporter of francophones, I owe apologies to those who support it more than I do. However, to us the international majority of the Symposium seemed to justify the use of the english language, with of course simultaneous translation.

The physicians and biologists who have observed the metabolic complications of obesities in relation to their clinical peculiarities and have studied their mechanism, have gathered today in this city, the most ancient one in France, where Greek sailors 25 centuries ago brought, along with Noah's vine and Athena's olive tree, the strictness of scientific mind and the worship of beauty. To each of our colleagues I address the heartiest welcome and my wishes for success in our endeavours.

Everybody knows that the prognosis of obesities differs strongly from one patient to another. Therefore, factors besides fat excess intervene to start, accelerate, and aggravate the complications of overweight or inversely to prevent, slacken, and reduce them. Among those factors, genetic predispositions are in the foreground before the effects of environment.

Human adipose tissue differs from others by its topography, probably linked to the upright posture. This characteristic is a major factor of overweight complications to which our group drew attention long ago. Several teams in the world, all present here, have devoted important studies to this topic. Those studies will be presented, discussed for three days and published before the end of the year.

Among these groups, a seat of honour falls to the Swedish school headed by our secretary general, Per Björntorp. We owe him a great part of our knowledge on the analysis of the differential behavior of adipocytes and on the mechanism of overweight metabolic complications. With respect to the Marseilles Group, it was a delight to see the birth and steady progress of Göteborg's work.

Dear Per, in the past, Marseilles gave to your country a queen, who today lies in a chapel of Riddarholmskyrkan. A very pretty girl, she had preferred your future king to our future emperor. Today our city is glad to greet you again, welcome you and honour your scientific work. As for me, I want to tell you, with my thanks and congratulations, the great joy I feel meeting you once more in our Faculty.

JEAN VAGUE

Introduction

It is increasingly clear that human obesity is not a homogenous entity. The importance of clearing up this problem is apparent by a comparison with for example hematology, which in a way shows similarities with the obesity field. In obesity research focus is currently placed on the cell showing the symptoms of the underlying cause to disease, the adipocyte, like hematologists did not long time ago with the erythrocyte. This does not necessarily mean that something is basically wrong with the cells in question, but the underlying cause to disease might be found by such studies. To continue the comparison, it was of course not possible to understand and treat iron deficiency anemia and pernicious anemia before their basic nature was revealed. Similarly, the adequate clinical handling of human obesity will not be possible before we understand for example the correct indications for treatment.

Several attempts have been tried through the years to characterize subgroups of human obesity. One of the earliest was that described by Jean Vague already almost 40 years ago. Vague and his group have then reported through the years a number of clinical, morphological and biochemical observations separating *android* and *gynoid* obesities. Other authors have also made similar observations. It is, however, only recently that the significance of this way of subdividing obesity has been apparent. The most recent work in this area has amplified the concept in more details and added possibilities to understand what is occurring functionally.

With this background it was thought to be pertinent to arrange a symposium on the most recent developments in this area, at the location where Jean Vague has been and still is active in his pioneer research.

The program for the symposium consists of three main sections. The first is an epidemiological overview with double focus, both from prospective studies, and also starting out from obesity-related conditions, hypertension, diabetes mellitus type II and hyperlipidemia to examine the adipose tissue distribution in these conditions. Then comes a section where different mechanisms for explanation of adipose tissue distribution and function are presented as well as possibilities to see how the associations to complicating diseases might be explained. Finally, a section was included where energy balance differences between men and women are examined. As a start, however, a new development to actually measure with precision the disease (or diseases) we are discussing, and, of course, an introduction of the whole typic of this symposium by notre maitre Jean Vague.

PER BJÖRNTORP

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ANDROID AND GYNOID OBESITIES, PAST AND PRESENT

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I must speak about android and gynoid obesities, past and present, that is to say, their history and first the history of adipose tissue.
Fuel storage appeared in animals along with mobility. Since then it has had with the latter complex relations in opposite ways, the algebric sum of which determines the strength, rapidity and duration of movement.

I - PHYLOGENY OF WHITE ADIPOSE TISSUE

In Invertebrates, the development of adipose tissue is opposed to that of the liver. Insects and myriapods, lacking a liver, have a huge adipose tissue, the fat body. Arachnids, Crustaceous and Molluscs possessing a liver, with fat storage, are virtually devoid of adipose tissue.

The same opposition persists in Vertebrates. Poikilotherms have only traces of adipose tissue and usually a fat rich large liver. In Homoiotherms, adipose tissue, even in lean individuals, is relatively important and liver triglycerides do not exceed 2%, except when adipose tissue is replete or in various pathological conditions.

Later on, the growing brain in Mammals will require growing glucose supply. In man more than 100 g are needed daily, a quarter of the basal metabolic rate for 1 50th of the body weight. A relatively important fat mass will be necessary for muscle fuel throughout fasting to avoid gluconeogenesis and spare proteins. The clinician will meet this necessary fat reserve increased in depressed patients.

The sexual differences of adipose tissue are present in many animals but usually discrete, even in Apes the nearest to man. About 2 million years ago our ancestor stood up for the first time and used only his lower limbs to walk, run, jump, dance. Probably at the same time, the uniform layer of subcutaneous fat in Primates of both sexes got differentiated in man and woman, realizing a specific human character.

Obviously in relation with upright posture, the mechanical conditions of pregnancy and the necessity of important reserves for the fetus and the newborn, fat in women developed in the lower part of the body, in the pelvis area where it produced less discomfort.

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In man, fat, less useful, was reduced by half and predominated on the upper body, where it did not oppose to mobility and struggle capabilities which were favoured by the broadening of the shoulders and the narrowing of the pelvis, both effects of testosterone. Natural selection probably increased this differentiation which brought about the sexual attraction that we find in the symbolism of fecondity and prosperity in the paleolithic times 20 thousand years ago.

Nevertheless, in a minority of men and women otherwise normal, adipose tissue exhibits the sexual differentiation of the opposite sex.

II - HUMAN WHITE ADIPOSE TISSUE

The sexual differentiation of human white adipose tissue appears as early as the age of 5. From then on the adipose mass of females will become twice that of males. The subcutaneous area is differentiated by its local development. After puberty, fat still predominates in females, as it does in girls and boys, in the lower half of the body. In men, it predominates in the upper half.

Subcutaneous adipose tissue is more accessible to our measurements by various technics than deep seated adipose tissue,with the exception of echotomography and scannography. Its differentiation is particularly accessible in some areas.

a/ The nape of the neck is the only area where adipose tissue is normally thicker in man than in woman. At normal weight the ratio of nape adipose tissue thickness to retro-sacral adipose tissue thickness draws a line peculiar to each sex, almost steady nearing 0.40 in the female, in the male exceeding the value of 1 at 13, of 2 at 20.

In spite of the possibility of mathematic correcting, the use of this ratio is unpractical in obesity and leanness. Other things being equal in both sexes, it increases in leanness and decreases in overweight, because retro-sacral fat is more sensible than nape fat to weight variations.

b/ Abdominal subcutaneous fat is partly related to the development of deep seated abdominal fat. In man it mostly accumulates above the umbilicus and below the umbilicus in the female. The measurement of its thickness in 3 equidistant points above and below the navel draws a distinct profile in male and female. The maximum thickness is at middle distance between xiphoid process and navel in man, at middle distance between navel and pubis in woman.

c/ The ratio of fat thickness in deltoid and trochanter areas is less determined by underlying musculature, pathological conditions excepted. This ratio increases in males at puberty. In females it increases from 50 only and more about

70, when it reaches man's level.

The number of adipocytes in the thickness of deltoid and trochanter adipose layer, can also be measured. It analyses this profile, as the ratio deltoid to trochanter adipocyte volume. (DN/TN, DV/TV).

The measurement of the circumference of arm and thigh at their emergence is also practical.

The waist-hip ratio is very different in man and woman. It is useful, though it cannot make out the respective differentiations of fat and bone which are often dissociated. As we have experienced it 5 years only we dont know its value throughout life in both sexes.

Owing to the role of muscle in the regulation of adipose tissue we have used for many years the brachio-femoral adipo-muscular-ratio by the measurement of fat thickness at the four cardinal points of arm and thigh emergence and of the circumference of the limbs at this level. After puberty this ratio is constantly above 1.10 in males, round 0.80 in females until its slightly increase at 50. (BFAMR).

Finally, the development of fat in the mammary area is not a female character. Fat in this region thickens with age. The highest values are found in android obesities of both sexes.

Each of these methods makes it possible to classify the type of obesity. Densitometry, echotomography are more accurate than initial measurements. For the practitioner, arm thigh ratio, waist hip ratio are perhaps the quickest, least expensive and most useful of all.

III - SOME HORMONAL EFFECTS ON ADIPOSE TISSUE

The study of fat thickness, of the number and volume of adipocytes in normal men and women from their early years to old age, before and after treatment by testosterone, estrogens, cortisol, before and after the surgical recovery of Cushing's syndrome demonstrates that :

a/ Testosterone strongly decreases the number and volume of trochanter adipocytes, decreases the number of hypogastric adipocytes.

b/ Estrogens decrease deltoid adipocytes volume, increase strongly trochanter adipocytes volume and slightly trochanter adipocytes number.

c/Cortisol is responsible for a special increase of deltoid adipocytes volume, a significant manifestation of hypercorticism, as the swelling of adipocytes in neck and cheeks.

d/ Regional differences of adrenergic lipolysis have been described by several groups. In ours, the epinenephrin effect in gynoid obese women is identical in

deltoid and trochanter adipose tissue. The α^2 antilipolytic effect is more powerful than the β^1 lipolytic effect on the trochanter adipose tissue of android obese women and men. Similarly an antilipolytic effect has been observed in the hypogastric tissue of men.

The group of BJÖRNTORP has observed that in woman lipoprotein lipase activity is higher in the femoral than in the abdominal region, lateral to the umbilicus, except during lactation when a marked decrease in the lipoprotein lipase activity has been observed in the femoral region.

All those data perhaps help us understand the evolution and mechanism of android and gynoid obesities.

I - CLINICAL COURSE OF ANDROID AND GYNOID OBESITIES

1 Fat reserve is necessary to preserve the glucose amount required by the brain during fasting.

2/ Fat excess is dangerous by its metabolic complications.

3/ A woman has normally twice a man's fat mass, the mass of an obese man. As often obese as man is and fatter, she dies later and less often from obesity metabolic complications.

Why such injustice ? The answer : an obese woman is protected when she keeps her gynoid fat mass, an evidence of her child bearing nature. When her fat is android she dies like a man.

BFAMR in man is over 1, in woman under this value. The multiplication of fat mass by the square of BFAMR suppresses the above differences between both sexes, giving rise to the distinction of a normal and a pathogenic, diabetogenic, atherogenic fat mass.

MORGAGNI in 1719 was probably the first to describe android obesity on the corpse of a woman,in latin "virili aspectu et valde obesa" in whom he also found hyperostosis frontalis interna. Later on, the distinction by MARAÑÓN in Spain, PENDE in Italy, of plethoric and anemic, hypersthenic and hyposthenic obesities showed the way.

Our initial description of android and gynoid obesity was founded on the sexual topography of fat. In android obesity of both sexes fat shows virile characteristics and predominates in the upper half of the body, nape of the neck, shoulders, supra umbilical abdomen. Musculature is usually strong and adipo-muscular ratio relatively little raised. The course towards diabetes, hyperlipemia, hyperuricemia, hypertension, atherosclerosis is very frequent. In contrast, in gynoid obesity of both sexes, the fat shows feminine characteristics and predominates in the lower half, hips, buttocks, thighs, subumbilical abdomen; muscu-

lature is usually less developed and adipo-muscular ratio high. Metabolic complications are rare and weak.

In our first statistics 36 years ago, according as intermediate cases were put on one side or the other, the diabetic and arterial risk of android obesity was multiplied by 6 or 20.

Those data have been widely confirmed with a few differences in the vocabulary. Various names have been used : centripetal or spiderlike and peripheral,abdominal and pelvic obesities were described. Previously,the words truncal,face truncal obesity in hypercorticism had overlooked the fat of nape and shoulders.

Such concepts are right but too restrictive. Of course android obesity is above all a big belly and gynoid obesity big buttocks. But we have seen that it is the upper abdomen which is fat in android obesity and the lower abdomen in gynoid obesity. The deep abdominal fat is more abundant in android obesity. With the coming of age and often intermittent periods of weight loss and gain, the laws of gravity change a prominent belly into an apron. But this apron falls from the epigastrium in android obesity, from the hypogastrium in gynoid obesity.

In men, other virile characteristics are usually observed, proportional to fat virilization. In women, if this coincidence is not rare, more often virile signs in other target tissues are absent or weak. Frequently the shoulders and pelvis bones are entirely feminine. The genital functions of these women are usually normal. Obese or preobese they are normally pregnant. We have observed that the extent, early appearance, the size and degree of coloration of purple striae as the neonatal macrosomia are linked both to excess weight and the degree of android constitution.

The course of obesity towards diabetes may progress through 5 stages : D0 obesity with normal glucose tolerance - D1 obesity with impaired glucose tolerance - D2 obesity with diabetes usually occurring 1 or 2 years after maximum weight spontaneously reached and spontaneous loss of 2 to 4 kgs - D3 former obesity with non insulin-dependent diabetes - D4 insulin-dependent diabetes despite spontaneous weight loss occurring too late. This eventuality is about 15% of the cases of overt diabetes in obesity, death by degenerative lesions usually taking place before.

As long as the last exceeding kgs of stage D3 are not spontaneously lost, the therapeutic, non spontaneous loss of weight improves or even cures diabetes and the associated metabolic disorders.

In 3012 obese patients the highest diabetogenic fat mass is found in overt diabetes D2. It is much lower in D3 and especially in D4, thus suggesting an additional factor involved in the progression towards the insulino-dependent diabetes of obesity. This factor is presently unknown.

A similar relationship of diabetes and atherosclerosis to fat distribution

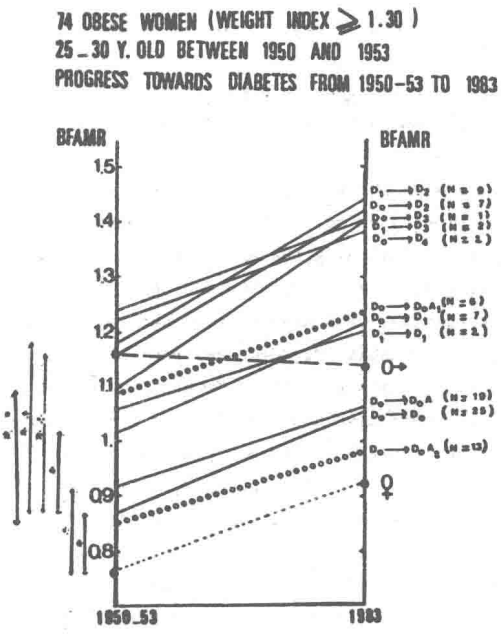

Figure 1 BFAMR: brachiofemoral adipo-muscular ratio. D_0:obesity without glucose intolerance. D_0A:idem, sustained intentional weight loss. D_0A_1:in the group D_0A: 6 patients whose initial BFAMR was>1. D_0A_2:in the group D_0A:13 patients whose initial BFAMR was<1. D1:obesity with glucose intolerance. D2:obesity with diabetes mellitus, weight index consistently>1.30. D3:obesity with diabetes mellitus, lowered weight index<1.30. D4: obesity with diabetes mellitus and secondary insulin dependence. $^{*}p<0.01$, $^{**}p<0.001$. Broken lines:male and female normal weight controls.

	BRACHIO-FEMORAL ADIPO-MUSCULAR RATIO		DELTO-TROCHANTER FAT RATIO		ABDO-THORAX-ENDURANCE CIRCUMFERENCE RATIO		EPIGASTRIC-HYPOGASTRIC FAT RATIO		WAIST-HIP RATIO
	1950-53	1983	1950-53	1983	1950-53	1983	1950-53	1983	1983
	25-30 Y.		25-30 Y.		25-30 Y.		25-30 Y.		30-65 Y.
NORMAL MALES	1.26	1.14	0.65	0.68	0.97	0.98	1.39	1.60	0.90
NORMAL FEMALES	0.76	0.98	0.35	0.38	0.92	0.93	0.66	0.70	0.76
25 OBESE WOMEN NORM- GLUC- TOLER-1950-53	0.87	1.05	0.42	0.69	0.92	0.95	0.68	0.83	0.76
10 OBESE WOMEN NORM- GLUC- TOLER-1950-53 DIAB- 1983	1.20	1.41	0.54	0.76	0.97	0.64	0.96	1.18	0.95
11 OBESE WOMEN GLUC- INTOL- 1950-53 DIAB- 1983	1.17	1.44	0.56	0.78	0.97	0.65	0.94	1.14	0.96
13 OBESE DIAB- WOMEN 30-65 Y- 1983		1.48		0.81		0.65		1.16	0.99
13 OBESE DIAB- MEN 30-65 Y- 1983		1.05		0.80		0.99		1.36	0.96

Figure 2 Compared results of the measurements of body fat distribution in the evolution of obese women towards diabetes from 1950-53 to 1983.

was reported in our earlier studies. The same methodology was employed to study 240 obese patients aged 40 to 50, 82 men and 158 women with or without diabetes, in whom unequivocal signs of atherosclerosis were sought in coronary, cerebral, aortic or lower limb arteries. Carbohydrate metabolism was explored concomitantly. No correlation was found between the fat mass and atherosclerosis, whereas atherosclerosis was in close relationship with BFAMR and maximum diabetogenic fat mass. Despite the certainty that other factors, especially genetic ones, are involved, the role played by the upper body fat mass as an atherogenic factor is demonstrated once again.

Those retrospective data had to be compared to a prospective study. For this purpose we have followed up the course of a homogeneous group of obese women (weight index $\geq$ 1.30) aged 25 to 30 between 1950 and 1953, the period of our first investigation, until 1983. In 74 cases the course was followed from stage D0 and D1 ascertained in 1950-53 up to 1983.

The figure 1 shows : a/ The course of BFAMR in men and women of normal weight from 25-30 to 60 years of age. b/ The mean of the obese women who did not lose weight and evolved towards overt diabetes had an initial BFAMR above 1.10. c/ The mean of the obese women who also had an initial high BFAMR and voluntarily got normal weight did not develop diabetes. They would probably have developed diabetes if they had kept their overweight. d/ In contrast, the groups who had low BFAMR did not develop diabetes, whether they had lost weight or not. The former group would probably have never developed diabetes had they kept their overweight.

The figure 2 shows a satisfactory correlation between BFAMR and other quicker methods to appreciate fat topography.

So,high BFAMR at the age of 25-30 is the factor, we won't say causal but correlative of the course of obesity towards diabetes. It has therefore, when glucose tolerance is still normal, often with reactive hypoglycemia, forecasting significance.

V - MECHANISM OF ANDROID OBESITY AND OF ITS COMPLICATIONS

1 - Mechanism of the degree of masculine differentiation of obesities

We have seen that testosterone and cortisol are the hormonal factors of the predominance of fat in the upper body by effects which are somewhat different upon the number and volume of adipocytes.

The adipocytometric analysis carried out in 60 obese females aged 40 to 59 with D0 and D2 demonstrates important relationship between BFAMR and DV/TV and still more DN/TN on the one hand, between diabetes and these 3 parameters on the other hand.