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The state of research on obesity and its perspectives in terms of prevention and treatment

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Historically, the awareness of the increase in obesity cases is a relatively recent phenomenon. With a generation lag, it is in phase with progressing consumer society, one of the components of which has been the rising availability of abundant, varied and cheap food products.

From being previously a rare social occurrence, obesity has become a disease .

I. A complex disease

A. With multiple causes

1. Genetic determining factors

The influence of genetics in the development of obesity has been proven by the high correlation observed in the BMI (body mass index) values in "identical twins" who have the same genetic, as opposed to the genetic observed in fraternal twins.

Moreover, there have been 8 monogenic genes identified as direct obesity factors, and 22 genes as predisposing to obesity which, though they are but risk factors, together with environmental strains, are conducive to eating habit disorders.

2. Biological determining factors

Physiologically, our organism must maintain a balance between food intake and energy expenditure. This is so-called "energetic homeostasis".
Such daily balance seeking activity is controlled by a signal network that informs the body on its energy reserves. Any malfunction of this data processing system may suffice to trigger excessive food intake or, on the contrary, anorexia.
The predominant axis of this food intake regulatory system is constituted by a permanent exchange of information between the stomach and the brain hypothalamus.

In the long run, hormone transfers (leptin, insulin) from certain organs (fat tissue, pancreas) toward the brain also become involved, and condition decreased food intake and increased energy expenditure. However, subjects presenting obesity have been observed to develop resistance to the action of this type of hormones.

Another neurological interference occurs additionally, which grants a hedonic value to unnecessary food intake and results in dopamine release in the brain, which the organism associates with reward.

3. Determinant factors related to birth and perinatal events

Converging studies have evidenced that there is:
– a connection between the mother's obesity and the child's predisposition to such;
– a positive correlation between weight at birth and the risk of becoming overweight;
– weight gain « windows » which enhance the risk factors (the first three months of life and around the age of three).

4. Determinant factors related to individual behaviour

Sedentary lifestyle, time spent in front of the television, soft drink consumption, snacking, reduced sleep time in teenagers, are prevailing individual behaviours in the case of obesity.

5. Social-cultural and economic determinant factors

Specifically-national food culture (for instance, the French model of shared meals, as opposed to the Anglo-Saxon individualistic one) may either reduce or enhance the risk for obesity.

There are also some economic factors at play. The budgetary constraints of low income families refer them to cheap, fatter and sweeter products. The food supply of fat and (fast) sugars has diversified. Lastly, in some cases, declining commodity prices has led to an increase in individual servings.

Likewise, the disappearance of the most physical trades and the development of mass or individual transportation means *de facto* reduce the daily energy expenditure.

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The usually combined implication of these various causes, make obesity a multiple-factor chronic disease that is difficult to reverse (hypertrophy of adipose tissue, hyperplasia, that is to say, a cumulative process of creation of fat cells).

B. A booming disease

According to WHO estimates, approximately 400 million adults suffer from obesity, and 1.6 billion are overweight. Obesity has been on the rise since the seventies (in the United States, 13.4 % of the adult population and 5 % of children were involved in 1978, as opposed to 34.3 % and 17 % in 2008, respectively.).

Progression of obesity in North America has been associated with the development of a more morbid type of obesity, which has grown threefold in Canada within 30 years.

This phenomenon, which is a negative consequence of the level of development, has reached Europe, with differences across countries. The United Kingdom has an obesity rate of adults close to the U.S. (in 2010, 37 % and 28 % of men and women were concerned, respectively). France, which was long spared, is no exception to the increase in obesity, although it remains down compared to most European countries (in 2006, 16.1 % and 17.6 % of men and women, respectively).
Depending on their level of development or their genetic susceptibility (Cf. Pacific Islands), the developing countries or emerging economies are affected. In China, the obesity rate now stands at 12.3% in urban areas.

C. A disease with serious consequences

1. Because of the complications it entails

• cancer
A 2007 American Research Institute study on cancer has evidenced:
– a correlation between obesity and the occurrence of certain types of cancer (esophagus, colon, endometrial, breast);
– this correlation to be even stronger in patients with an early history of obesity.

• diabetes
Three quarters of the patients presenting type-2 diabetes are obese, and high-obesity patients are ten times more likely to develop the disease than merely overweight people.

• cardiovascular diseases
Obesity predisposes to cardiovascular risk factors (hypertension, coronary diseases, insulin-resistance, strokes).

• hepatic steatosis
This form of chronic, non alcohol-related hepatitis is, on average, five times more common among the obese population.

2. Because of the social costs it generates

• In the United States
Aside even from the losses incurred by the withdrawal from the labour market of the obese, the financial weight of obesity in the United States increases dramatically (78.5 billion dollars in 1998 vs 147 billions in 2009), i.e., 1.5 times more than the financial burdens due to cancer.

• In France
In France, the financial load of obesity had been assessed, in 2008, to 4 billion euros. This figure is expected to increase, particularly as the development of obesity is correlated with that of long-term illnesses (which represent 60 % of health insurance expenditure), including diabetes, cancer and certain cardiovascular diseases.

II. The contribution of research to prevention and treatment of obesity

Conventional drug therapies fail to treat the disease: whether we are dealing with treatments restricting food intake or decreasing the intestinal absorption of nutrients, these drugs are either ineffective or accompanied by deleterious side effects that have warranted the withdrawal from the market of some of them.
But other avenues of research are emerging.

A. Research on the improvement of prevention policies

Some societal programs that are designed to curtail the increase of the phenomenon are of undeniable effectiveness. This is the case with the EPODE program which stemmed from experiments carried out in the school, at Fleurbaix-Lavantie.
Current research in the field focuses on the need for early prevention and on the ways of promoting physical activity.

1. The need for early prevention

• The impact of foetal exposure on the development of obesity
The development of obesity among the young can be fostered by prenatal exposure regardless of the lifestyle adopted later in life (overweight mother, gestational diabetes, cigarette smoking). Such influences encourage finer targeting of risk exposure.

• The focus on the acquisition of dietary and behavioural habits during childhood

2. The major role of physical activity

Studies – more particularly the INSERM collective expertise on physical activity – have shown its importance:

– in the prevention of weight gain and weight regain, and,
– in reducing obesity-related diabetic coillness.

B. Some promising avenues of research in the medium term

1. Halting the development of obesity

• Activating brown adipose tissue
The presence of this adipose tissue that acts as a regulator of weight gain is lower when people are obese.

Research studies conducted in this field focus on:
– the modes of activation of this tissue,
– the transformation, which was already carried out on rodents, of white adipose tissue into brown adipose tissue.

• Studying intestinal microbiota
Intestinal bacteria are involved in the management of energy metabolism. It was evidenced that some groups of bacteria could enhance the extraction of energy from foods and, therefore, promote weight gain. Research therefore aims at changing the microbiota populations depending on the type of food.

• **Ensuring that early nutrition does not promote obesity** by making progress in understanding the impact of perinatal and early-childhood nutrition on the regulation of food intake habits later in life.

2. Delay or alleviate the consequences of obesity

• Increasing satiety for like nutrition, and identifying more precisely the interrelationships between the digestive system and brain in food intake;
• Screening for subjects at risk of developing abdominal obesity;
• Delaying the occurrence of type-2 diabetes in obese subjects.

3. Progress in the understanding of epigenetic phenomena

Environmental stress, and in this particular case, eating-related stress, can promote the expression of inactivated genetic markers.
Many studies have shown the implication of environmental, pre- and postnatal exposures, in food metabolism formation.

There are many research opportunities opening up with epigenetics:
– the establishment of a relationship between changes in the epigenetic profile and a particular physiological phenotype;
– the analysis and characterization of epigenetic changes induced by the nutritional environment;
– the determination of the reversibility of epigenetic modifications through nutritional interventions.

III. Need for a continued effort toward ensuring coherence of obesity research

A. Some already acquired initiatives

1. Reconciling the fields of basic and clinical research

As of 1992, the INRA / INSERM association has led to the creation of four human nutrition research centers, each backed by a University Hospital Centre (CHU).

The creation of clinical research centres that can carry out trials as well as clinical research programs jointly developed by INSERM and CNRS, have helped professionalize clinical research.

2. Structuring research around sets with a real critical mass

The pooling of infrastructures around the INRA proteomic platforms (8 platforms created in 5 years), as well as the "Research infrastructures" created in the setting of the 7th European Framework Programme for Research and Development, aimed at providing coherence to European research tools, point toward that goal.

This is also the case of the Federative Research Institute of Toulouse, which regroups human pathology research with the studies of the National Alliance for Life Sciences and Health, which has, as one of its goals, to pilot the joint programming of projects set up between 7 research institutions, universities and University Hospital Centres (CHUs).

B. Removing obstacles toward better coordination of research efforts on obesity

Besides the multiplicity of funding windows that the NRA action has not been able to overcome, there are specific barriers to research in obesity.

The impact criterion (that is, the number of articles published in journals with a high impact factor), which has become one of the evaluation factors for assessing the quality of the work of researchers, is not entirely relevant in areas related to public health. It prefers indirect scientific interests at the expense of therapeutic research.

C. The development of some fields in obesity research

Additionally, besides the need for research focusing on fundamental aspects (molecular, genetic and metabolic), it would be desirable to encourage research in neuroscience and social behaviour, and clinical research on the intra-species variety as concerns weight gain.

IV. PROPOSALS

I. Implement the recommendations made in the many reports already published on the issue of obesity.

II. Reduce social-cultural inequalities and promote social insertion of lower social-professional categories.

III. Focus on measures to change the Environment:

- **limit children's exposure to advertising and marketing,**
- **improve the quality of the food supply,**
- **change the environment to reduce sedentary lifestyle and increase physical activity.**

IV. Set up a comprehensive prevention plan:

- **introducing an international interdepartmental governance,**
- **setting up a committee to identify the scientific advances to take into account in the operational struggle against obesity,**
- **focusing on prevention among the population at risk locally,**
- **assessing systematically the impact of the measures taken.**

V. Promote body diversity.

VI. Regulate dieting.

VII. Systematically check for visceral adiposity.

VIII. Develop early prevention.

IX. Expand the fields of obesity research.