Metabolismo glucídico en trastornos psicóticos y afectivos

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4 Junio 2015

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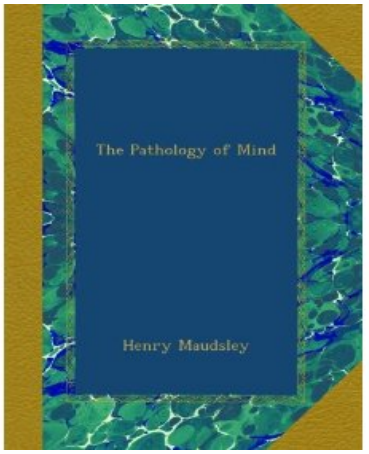
HISTORICAL BACKGROUND

In 1674, Thomas Willis, the famous British physician who identified glycosuria as a sign of diabetes, was the first to address the natural history of comorbid depression and diabetes when he wrote that diabetes was caused by “sadness or long sorrow and other depressions.”

HISTORICAL BACKGROUND



"Diabetes is a disease which often shows itself in families in which insanity prevails: whether one disease predisposes in any way to the other or not, or whether they are independent outcomes of a common neurosis, they are certainly found to run side by side, or alternately with one another more often than can be accounted for by accidental coincidence or sequence".

"Diabetes is a disease which often shows itself in families where insanity prevails"
Henry Maudsley "Pathology of the mind" 1899

HYPERGLYCÆMIA IN MENTAL DISORDERS.

BY DR. F. H. KOOY.

(*Psychiatrische-Neurologische Kliniek, Groningen, Holland.*)

CONTENTS.

Blood-sugar in Dementia Præcox.

I examined ten sufferers from dementia præcox. It is a well-known fact that the opinions of the various authors diffe to this chapter of psychiatry. Even in the su Kraepelin's text-books different conceptions of d found, while Bleuler's (1911) definition of deme more comprehensive.

Blood-sugar in Mania.

We have but little information about the amount of blood-sugar in mania, as the illness is doubtless rare. Schultze and Knauer examined six cases, Raimann four, and Heidema three cases. My material, as regards true mania, is also rather poor, but the Spanish influenza has furnished the hospital with so many psychoses, of which several showed typical maniacal symptoms, that a discussion may be justified. Schultze and Knauer found no glycosuria in their cases except occasionally, when the patients were recalcitrant or excited. In accordance Raimann found a high assimilation-power in mania. Heidema, however, found a rather high amount in his three cases: 1·13, 1·28, and 1·60 per mille before breakfast.

HISTORICAL BACKGROUND

Vol. 59 JUNE, 1924 No. 6

The Journal
OF
Nervous and Mental Disease
An American Journal of Neuropsychiatry, Founded in 1874

ORIGINAL ARTICLES

BLOOD ANALYSIS AND SUGAR TOLERANCE TESTS IN MENTAL DISEASE

By Thomas M. Barrett, M.D.

The average of all the findings for both disease classes gives the following:

	Mg. per cent				
	Nonprotein nitrogen	Urea	Uric acid	Creatinine	Sugar
Manic depressive psychosis.....	33.4	13.5	2.2	1.3	109
Dementia precox	33.8	16.2	2.3	1.4	114
Total average	33.6	14.9	2.3	1.4	112

The average of intolerance toward an abnormally large glucose meal shown by our manic depressive cases may be compared with the average intolerance shown by our dementia precox cases in the following figures:

	Fasting	1st hour	2nd hour	3rd hour
Manic depressive psychosis.....	111	145	125	102
Dementia precox	109	147	131	102

HISTORICAL BACKGROUND

THE CARBOHYDRATE TOLERANCE OF MENTALLY DISTURBED SOLDIERS *

H. FREEMAN, M.D., E. H. RODNICK, PH.D., D. SHAKOW, PH.D., AND THELMA LEBEAUX, M.A.**

As part of a broad investigation of the physiological processes of military neuropsychiatric subjects a study dure the patients were usually composed, no test being made on an unwilling or unduly excited subject.

TABLE 1

EXTON-ROSE GLUCOSE TOLERANCE TEST

MEAN VALUES OF DIAGNOSTIC GROUPS

Diagnosis	No.	Blood sugar		
		Fasting	30 min.	60 min.
		mg.	*mg.*	*mg.*
All Psychoses	66	83.8	117.4	129.7
Schizophrenia	38	82.4	118.8	126.7
Paranoid Schizophrenia	7	84.4	132.0	118.0
Non-Schizophrenia	28	84.5	115.6	134.2


Mood and Psychotic Disorders and Type 2 Diabetes: A Metabolic Triad

HISTORICAL BACKGROUND

Table 1. Are patients with mood and psychotic disorders at higher risk for type 2 diabetes? Pre-DSM-III investigations (adapted from reference 45)

Study (reference)	*N*	*Diagnostic method*	*Results*
Kooy, 1919 (39)	40 mood disorder 10 DP 20 controls	FPG	Hyperglycemia in melancholia, catatonia
Raphael et al, 1921 (92)	7 controls 29 DP MDI 7 D	OGTT	Hyperglycemia in DP, MDI (subjects excluded for obesity)
Lorenz, 1922 (93)	107 inpatients	OGTT	Hyperglycemia in catatonia, depressed MDI
Kasanin, 1926 (94)	40 inpatients	OGTT	Hyperglycemia in 22/40 (55%)
Bowman et al, 1929 (90)	295 inpatients 41 controls	FPG >7.5 mmol/L	Diabetes: 14% inpatients, 0% controls
McCowan et al, 1931 (95)	85 psychotic 12 controls	OGTT	Hyperglycemia in mania, melancholia
Tod, 1934 (96)	36 inpatients	OGTT	Hyperglycemia in mania, melancholia and stupor
Whitehorn, 1934 (91)	951 "excited" inpatients	FPG >8.75 mmol/L	13% diabetes (age; chronicity)
Diethelm, 1936 (97)	26 patients	OGTT	Hyperglycemia during acute illness, especially anxiety
Tod, 1937 (98)	28 inpatients	OGTT	Hyperglycemia in patients reduced by hypnotics
Braceland et al, 1946 (99)	29 schizophrenia 25 controls	2h insulin (0.1 U/kg)	Greater insulin resistance in schizophrenia
Freeman, 1946 (100)	95 soldiers, psychosis, 20 controls	2h insulin (0.1 U/kg)	Greater insulin resistance in schizophrenia, MDI

Origins

RO1 DK069265 from the National Institute of Diabetes and Digestive and Kidney Diseases

Diabetes in neuropsychiatric disorders

- FEP (20% Affective)
- AD
- MDD
- Controls

Oral Glucose Tolerance Test

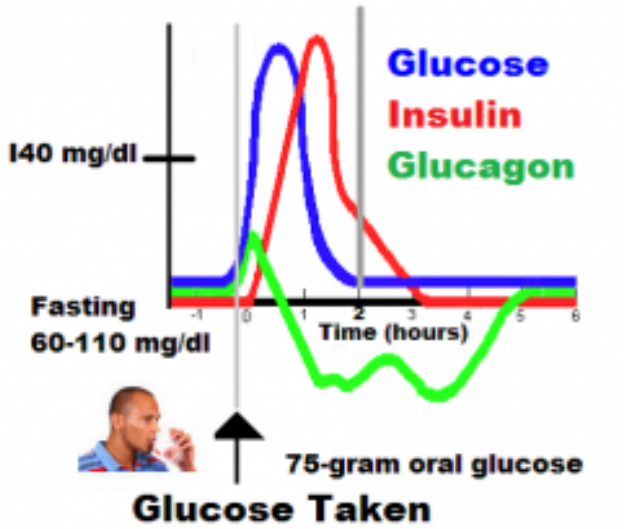
No food or drink 8 to 12 hours prior to test

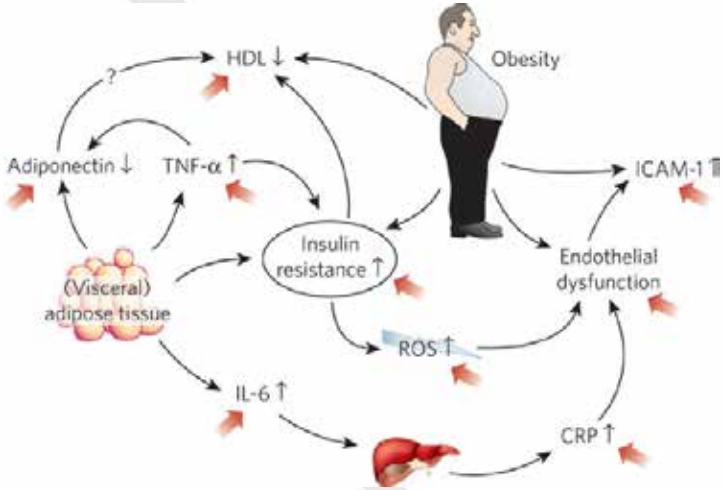
Drink glucose

Blood is tested two hours later

High glucose level = potential diabetes

ADAM.





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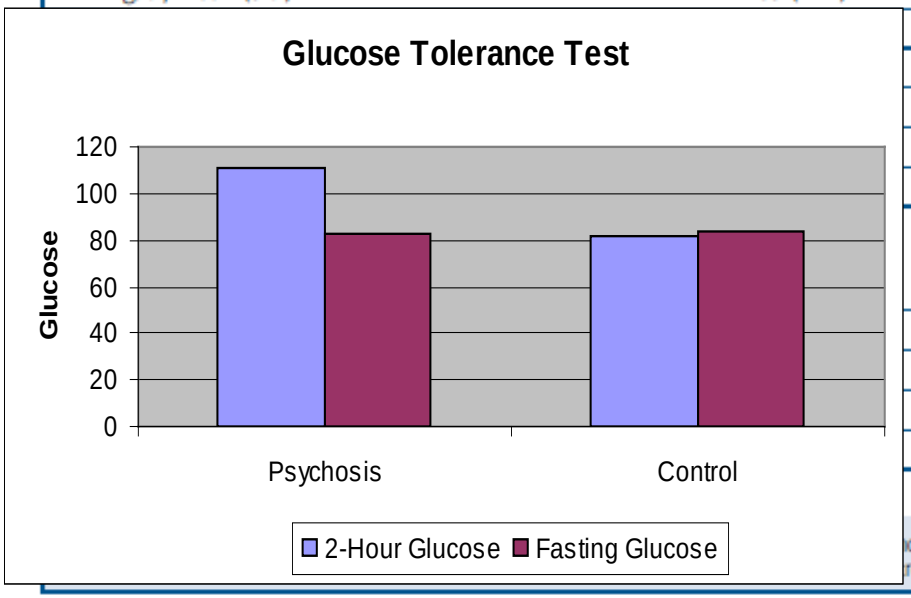
BJPsych The British Journal of Psychiatry (2009) 194, 434–438. doi: 10.1192/bjp.bp.108.053645

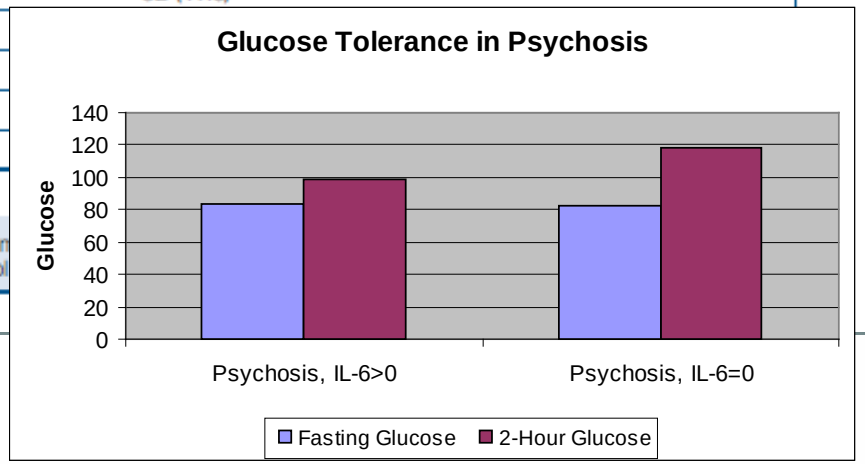
Metabolic profile of antipsychotic-naive individuals with non-affective psychosis

Emilio Fernandez-Egea, Miguel Bernardo, Thomas Donner, Ignacio Conget, Eduard Parellada, Azucena Justicia, Enric Esmatjes, Clemente Garcia-Rizo and Brian Kirkpatrick

Table 2 Metabolic measures in newly diagnosed, antipsychotic-naïve individuals with non-affective psychosis and the control group

	Psychosis group (n=50)	Control group (n=50)	Statistics	P
Fasting glucose				
mmol/l, mean (s.d.)	4.55 (0.66)	4.65 (0.38)	t=−1.015	0.313
mg/dl, mean (s.d.)	83 (12.1)	84 (6.9)		
		9.6 (3.8)	t=0.644	0.576
		4.5 (0.29)	t=−1.298	0.197
		136.5 (32.1)	t=1.014	0.262
		81.3 (28.7)	t=1.014	0.313
		1.40 (0.56)	t=0.509	0.612
		4.49 (1.06)	t=5.148	<0.001
		82 (19.3)		





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Brain, Behavior, and Immunity 28 (2013) 49–53

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Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Short Communication

Abnormal glucose tolerance, white blood cell count, and telomere length in newly diagnosed, antidepressant-naïve patients with depression

Clemente Garcia-Rizo[a,*], Emilio Fernandez-Egea[b,c], Brian J. Miller[d], Cristina Oliveira[a], Azucena Justicia[b], Jeffrey K. Griffith[e], Christopher M. Heaphy[e], Miguel Bernardo[a,f,g], Brian Kirkpatrick[h]

[a] Schizophrenia Program, Department of Psychiatry, Neuroscience Institute, Hospital Clinic, University of Barcelona, Barcelona, Spain
[b] Department of Psychiatry, University of Cambridge, Addenbrooke's Hospital, CB2 0QQ Cambridge, UK
[c] Cambridgeshire and Peterborough NHS Foundation Trust, Huntingdon PE29 3RJ, UK
[d] Department of Psychiatry and Health Behavior, Georgia Health Sciences University, Augusta, GA, USA
[e] Department of Biochemistry and Molecular Biology, University of New Mexico School of Medicine, Albuquerque, NM, United States
[f] Institute of Biomedical Research Agusti Pi i Sunyer (IDIBAPS), Barcelona, Spain
[g] Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Spain
[h] Department of Psychiatry, Texas A&M University College of Medicine and Scott & White Healthcare, Temple, TX, USA

	Depression ($N = 15$)	Control ($N = 70$)	
Mean age (years)	30.7 ± 10.0	27.8 ± 6.8	$p = .549$
Gender: % Male	60.0	62.2	$p = .836$
% living in catchment area	80.0	68.6	$p = .378$
Mean BMI	23.4 ± 4.1	23.7 ± 2.9	$p = .766$
Mean number of cigarettes/day	9.9 ± 12.7	6.2 ± 8.3	$p = .219$
Cortisol (μg/dL)	19.2 ± 8.6	22.1 ± 6.3	$p = .130$
Mean fasting glucose (mg/dL)	84.9.4 ± 11.2	83.4 ± 6.8	$p = .632$
Impaired fasting glucose%	13	0	$p = .002$
Mean 2 h glucose (mg/dL)	125.0 ± 67.9	84.6 ± 25.6	$p < .001$
Impaired glucose tolerance/ diabetes%	20	4	$p = .035$
Mean telomere content[a]	87.9 ± 7.6	101.2 ± 14.3	$p = .009$
Mean White Blood Cell count (10^9/L)	6.4 ± 1.3	7.1 ± 1.8	$p = .182$
Mean lymphocyte count (10^9/L)	2.1 ± 0.6	2.5 ± 0.7	$p = .028$

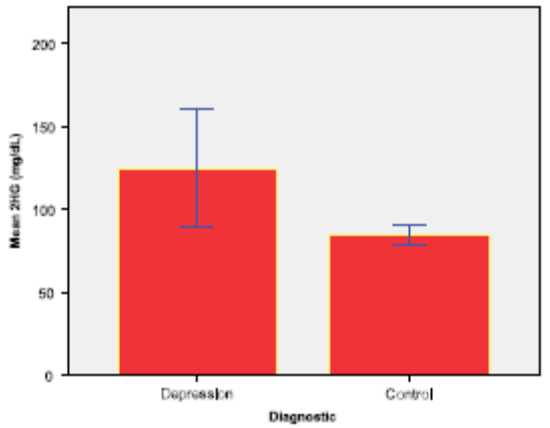

Fig. 1. Mean 2 h glucose load (2HG) (mg/dL) (Error Bar: ±2 Standard Error).

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DOI: 10.1111/acps.12194

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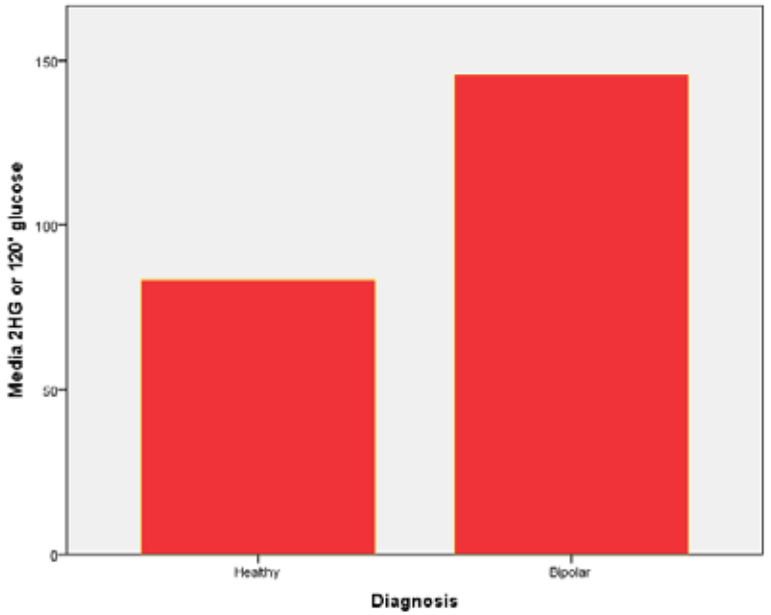
Discussion paper

"Is bipolar disorder an endocrine condition?" Glucose abnormalities in bipolar disorder

	Bipolar Disorder (N=7)	Controls (n=50)	P value
Age (years)	29.4[8.9]	28.9[5.4]	.804
Gender (%Male)	86%	66%	.413
Socioeconomic Status* (N=6/49)	5.5[3.2]	6.7[2.1]	.236
Cortisol (µg/dL)** (N=7/49)	18.8[7.2]	19.1[5.2]	.906
Cigaretes per day*** (N=6/50)	11.2[12.5]	6.1[1.6]	.648
Body Mass Index	23.4[8.0]	23.7[3.1]	.396
Fasting Insulin (mU/L)**** (N=6/48)	10.8[5.9]	8.9[4.0]	.295
Fasting Glucose(mg/dL)	92.6[17.4]	85.5[6.5]	.275
Impaired Fasting Glucose %	29	2	.037
2 Hour Insulin (mU/L)	48.5[24.8]	26.5[39.4]	.157
2 Hour Glucose (mg/dL)	145.9[16.9]	84.8[27.8]	<.001
Impaired Glucose Tolerance %	86	4	<.001



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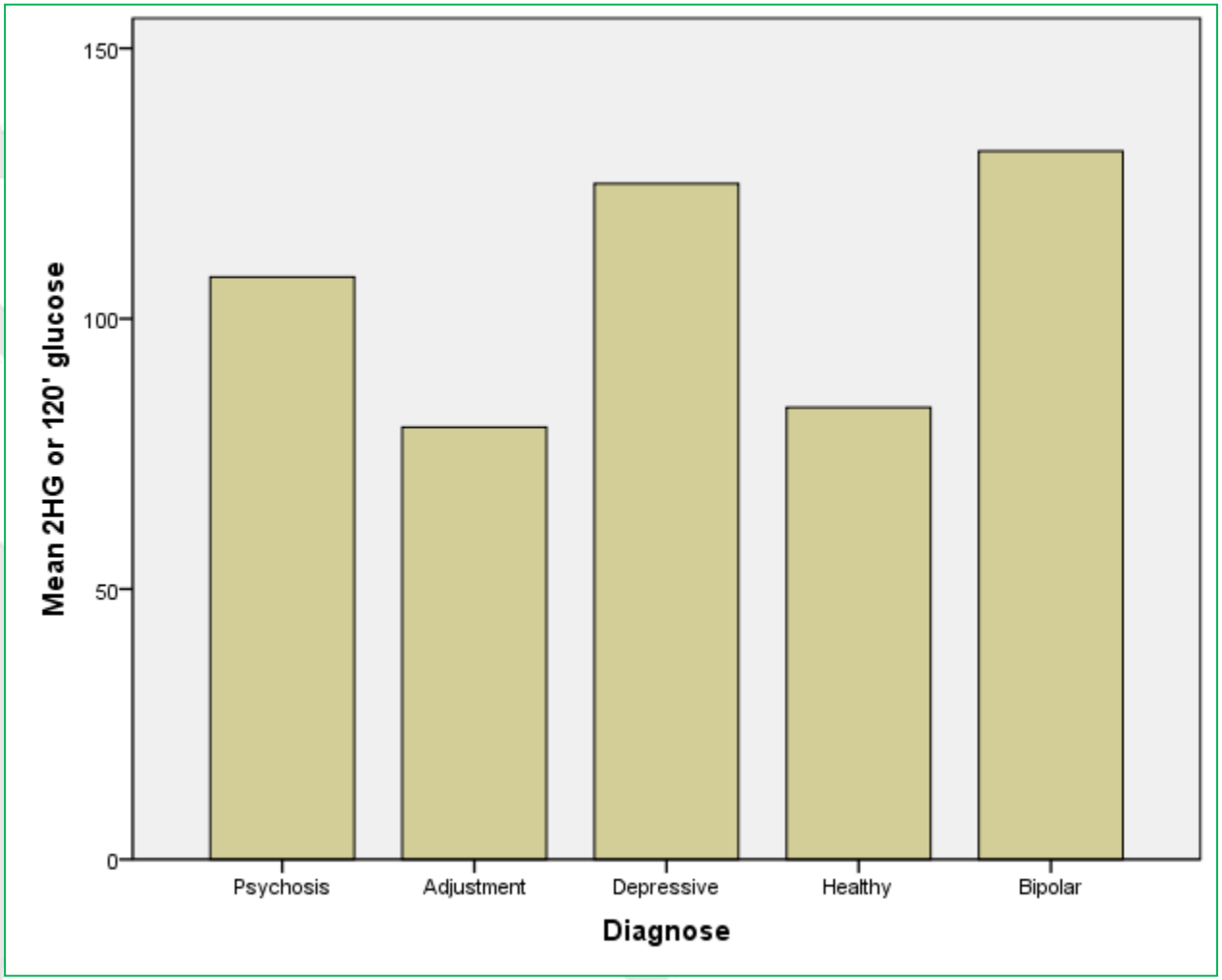

Serious mental disorders present an increased 2HG independently of confounders


Is Abnormal Glucose Tolerance in Antipsychotic-Naive Patients With Nonaffective Psychosis Confounded by Poor Health Habits?

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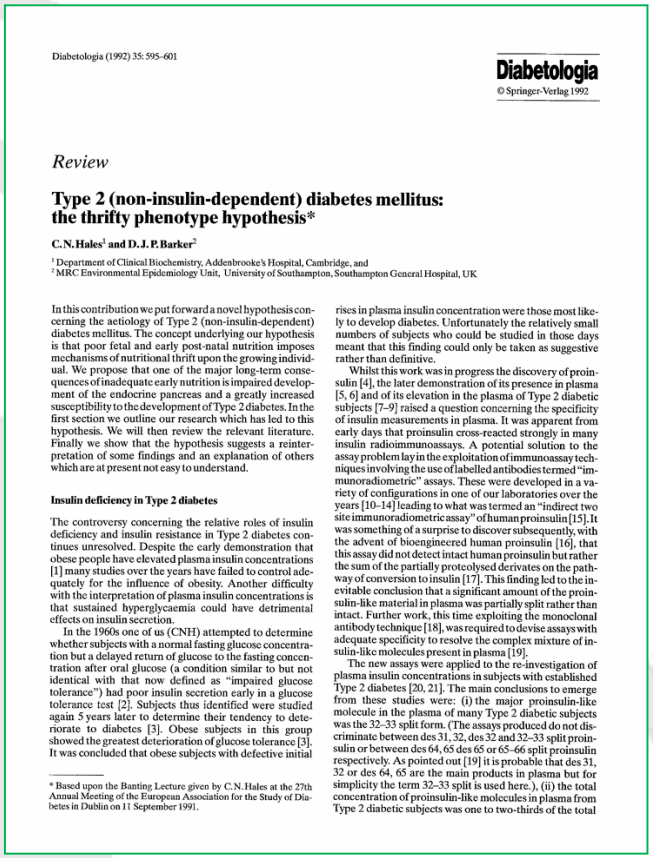


Diabetologia (1992) 35: 595–601

Diabetologia

© Springer-Verlag 1992

Review

Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis*

C. N. Hales[1] and D. J. P. Barker[2]

[1] Department of Clinical Biochemistry, Addenbrooke's Hospital, Cambridge, and
[2] MRC Environmental Epidemiology Unit, University of Southampton, Southampton General Hospital, UK

In this contribution we put forward a novel hypothesis concerning the aetiology of Type 2 (non-insulin-dependent) diabetes mellitus. The concept underlying our hypothesis is that poor fetal and early post-natal nutrition imposes mechanisms of nutritional thrift upon the growing individual. We propose that one of the major long-term consequences of inadequate early nutrition is impaired development of the endocrine pancreas and a greatly increased susceptibility to the development of Type 2 diabetes. In the first section we outline our research which has led to this hypothesis. We will then review the relevant literature. Finally we show that the hypothesis suggests a reinterpretation of some findings and an explanation of others which are at present not easy to understand.

Insulin deficiency in Type 2 diabetes

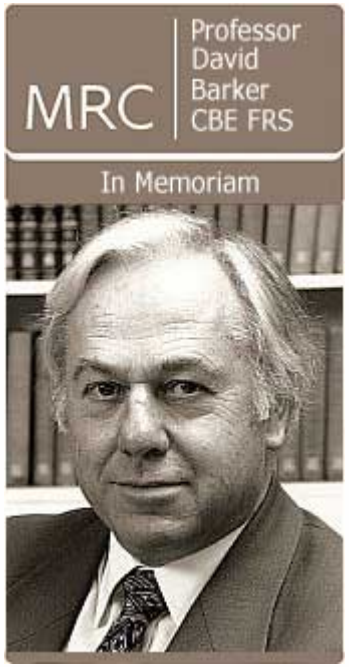
The controversy concerning the relative roles of insulin deficiency and insulin resistance in Type 2 diabetes continues unresolved. Despite the early demonstration that obese people have elevated plasma insulin concentrations [1] many studies over the years have failed to control adequately for the influence of obesity. Another difficulty with the interpretation of plasma insulin concentrations is that sustained hyperglycaemia could have detrimental effects on insulin secretion.

In the 1960s one of us (CNH) attempted to determine whether subjects with a normal fasting glucose concentration but a delayed return of glucose to the fasting concentration after oral glucose (a condition similar to but not identical with that now defined as "impaired glucose tolerance") had poor insulin secretion early in a glucose tolerance test [2]. Subjects thus identified were studied again 5 years later to determine their tendency to deteriorate to diabetes [3]. Obese subjects in this group showed the greatest deterioration of glucose tolerance [3]. It was concluded that obese subjects with defective initial rises in plasma insulin concentration were those most likely to develop diabetes. Unfortunately the relatively small numbers of subjects who could be studied in those days meant that this finding could only be taken as suggestive rather than definitive.

Whilst this work was in progress the discovery of proinsulin [4], the later demonstration of its presence in plasma [5, 6] and of its elevation in the plasma of Type 2 diabetic subjects [7–9] raised a question concerning the specificity of insulin measurements in plasma. It was apparent from early days that proinsulin cross-reacted strongly in many insulin radioimmunoassays. A potential solution to the assay problem lay in the exploitation of immunoassay techniques involving the use of labelled antibodies termed "immunoradiometric" assays. These were developed in a variety of configurations in one of our laboratories over the years [10–14] leading to what was termed an "indirect two site immunoradiometric assay" of human proinsulin [15]. It was something of a surprise to discover subsequently, with the advent of bioengineered human proinsulin [16], that this assay did not detect intact human proinsulin but rather the sum of the partially proteolysed derivates on the pathway of conversion to insulin [17]. This finding led to the inevitable conclusion that a significant amount of the proinsulin-like material in plasma was partially split rather than intact. Further work, this time exploiting the monoclonal antibody technique [18], was required to devise assays with adequate specificity to resolve the complex mixture of insulin-like molecules present in plasma [19].

The new assays were applied to the re-investigation of plasma insulin concentrations in subjects with established Type 2 diabetes [20, 21]. The main conclusions to emerge from these studies were: (i) the major proinsulin-like molecule in the plasma of many Type 2 diabetic subjects was the 32–33 split form. (The assays produced do not discriminate between des 31, 32, des 32 and 32–33 split proinsulin or between des 64, 65 des 65 or 65–66 split proinsulin respectively. As pointed out [19] it is probable that des 31, 32 or des 64, 65 are the main products in plasma but for simplicity the term 32–33 split is used here.), (ii) the total concentration of proinsulin-like molecules in plasma from Type 2 diabetic subjects was one to two-thirds of the total

* Based upon the Banting Lecture given by C.N. Hales at the 27th Annual Meeting of the European Association for the Study of Diabetes in Dublin on 11 September 1991.

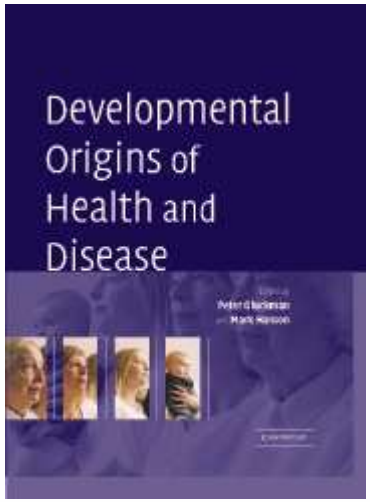


Low birth weight is correlated with **cardiovascular** disease, **diabetes** and **hypertension** in middle age

The thrifty phenotype hypothesis

C Nicholas Hales* and **David J P Barker†**

**Department of Clinical Biochemistry, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK and †MRC Environmental Epidemiology Unit, Southampton General Hospital, Southampton, UK*



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Risk factors of Illnesses

Maturitas 70 (2011) 141–145

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Review

Hungry in the womb: What are the consequences? Lessons from the Dutch famine

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Comprehensive Psychiatry 48 (2007) 470–478

Comprehensive PSYCHIATRY

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Low birth weight and risk of affective disorders and selected medical illness in offspring at high and low risk for depression

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

MECHANISMS OF DISEASE

Effect of In Utero and Early-Life Conditions on Adult Health and Disease

Peter D. Gluckman, M.D., D.Sc., Mark A. Hanson, D.Phil., Cyrus Cooper, M.D., and Kent L. Thornburg, Ph.D.

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The British Journal of Psychiatry

BJPsych

Exposure to obstetric complications and subsequent development of bipolar disorder : Systematic review

Jan Scott, Yvonne McNeill, Jonathan Cavanagh, Mary Cannon and Robin Murray

BJP 2006, 189:3-11.
Access the most recent version at DOI: 10.1192/bjp.bp.105.010579

Reviews and Overviews

Obstetric Complications and Schizophrenia: Historical and Meta-Analytic Review

Mary Cannon, M.D., Ph.D., M.R.C.Psych.

Peter B. Jones, M.D., Ph.D., M.R.C. Psych.

Robin M. Murray, M.D., D.Sc., F.R.C.Psych.

Objective: This pap
ture on obstetric co
factor for schizophrer
the evolution of this
ferent methods and
tive review of the res
population-based stu

Method: Relevant p
by a MEDLINE search
reference lists of pu
through personal co
ers in the field. Stud
chronological order
mon themes or met
techniques were use
findings of prospecti
studies.

Results: The meta-
the prospective popu
revealed that three
tions were significa

ELSEVIER

Journal of Affective Disorders 61 (2000) 101–106

JOURNAL OF AFFECTIVE DISORDERS

www.elsevier.com/locate/jad

Brief report

Obstetric complications in patients with depression — a population-based case–control study

Antonio Preti[a,*], Lucia Cardascia[b], Tiziana Zen[b], Patrizia Pellizzari[b], Maria Marchetti[b], Gerardo Favaretto[c], Paola Miotto[d]

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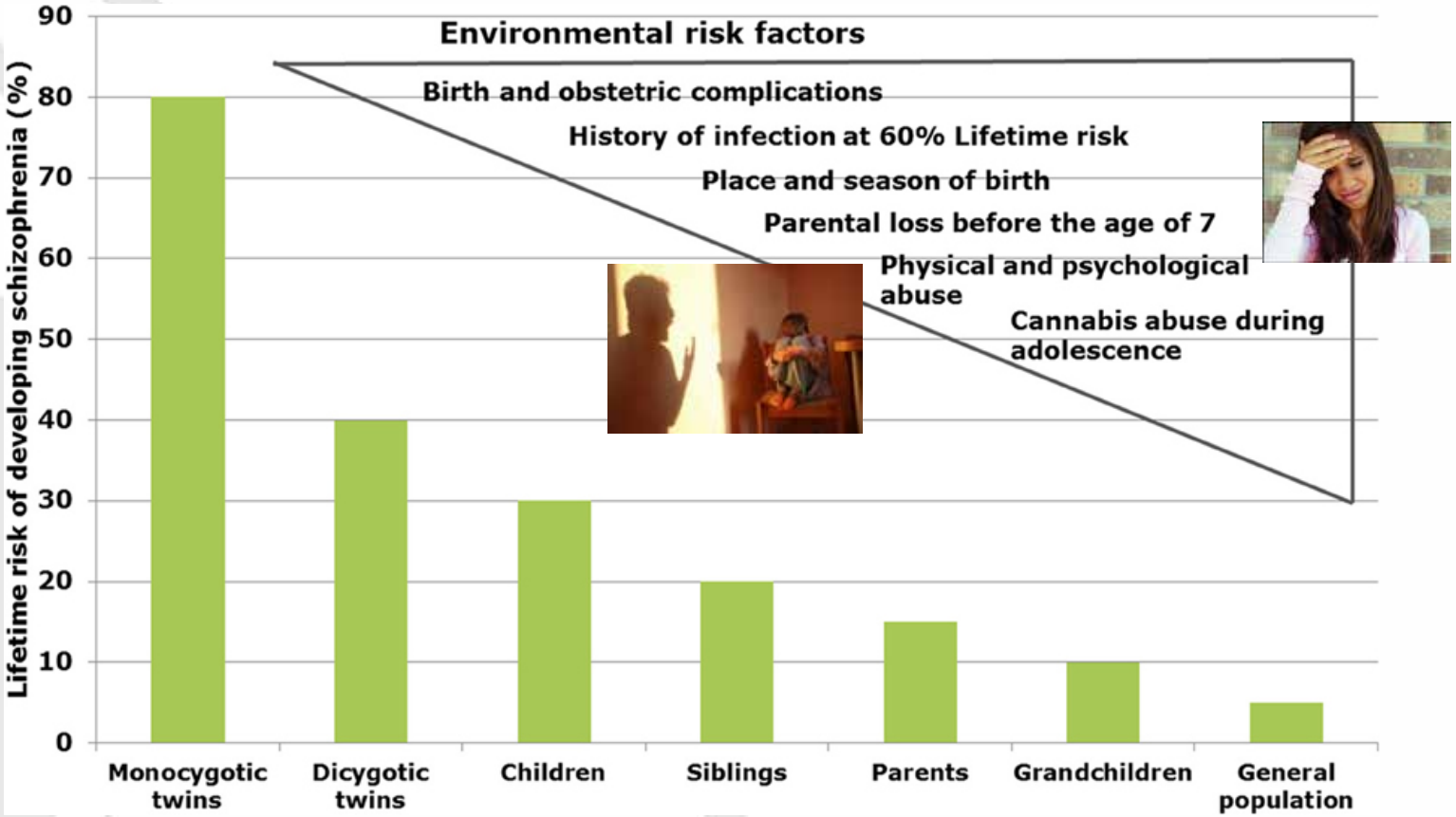
Environmental risk factors
Birth and obstetric complications
History of infection at 60% Lifetime risk
Place and season of birth
Parental loss before the age of 7
Physical and psychological abuse
Cannabis abuse during adolescence
Lifetime risk of developing schizophrenia (%)
90
80
70
60
50
40
30
20
10
0
Monocygotic twins
Dicygotic twins
Children
Siblings
Parents
Grandchildren
General population

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Acta Psychiatr Scand 2014: 1–3
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DOI: 10.1111/acps.12309

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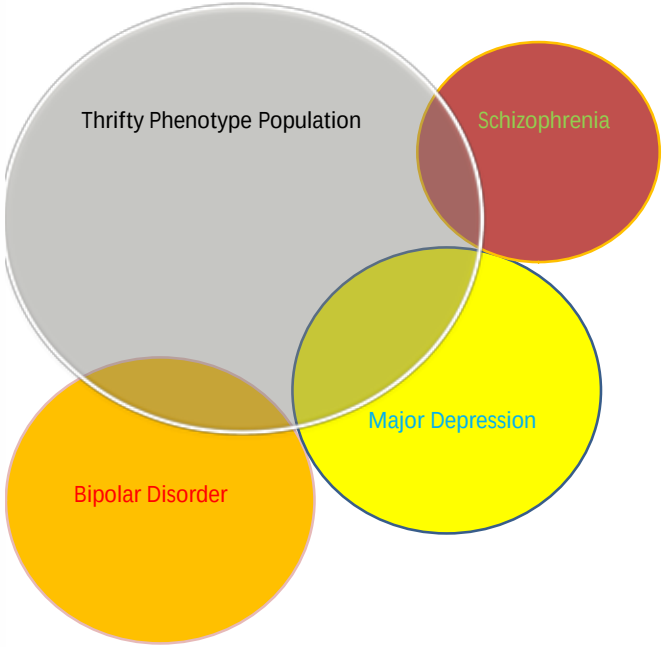
Editorial comment

The thrifty psychiatric phenotype

Van Ockenburg and colleagues (1) assessed the correlation between adverse life events and physiological status in a large population-based cohort, as psychosocial stress might correlate with adverse health outcomes. Although diverse methodological aspects were clinically considered (for instance,

society, those changes will lead to the development of T2DM and CVD. Later, epidemiological studies have shown that not only prenatal, but also postnatal factors can modify the early programming, setting up the present concept of 'developmental origins of health and disease' (DOHaD) (2).



Thrifty psychiatric phenotype schema

Nutrient-plenty enviroment

Metabolic disturbances

Insulin Resistance

Epigenetic Modifications

Abnormal brain development

Severe Mental Illness Diagnose

Abnormal maternal fetal interaction:

- Suboptimal maternal nutrition
- Infections
- Placenta dysfunction
- Stress

Acta Psychiatrica Scandinavica

Editorial comment

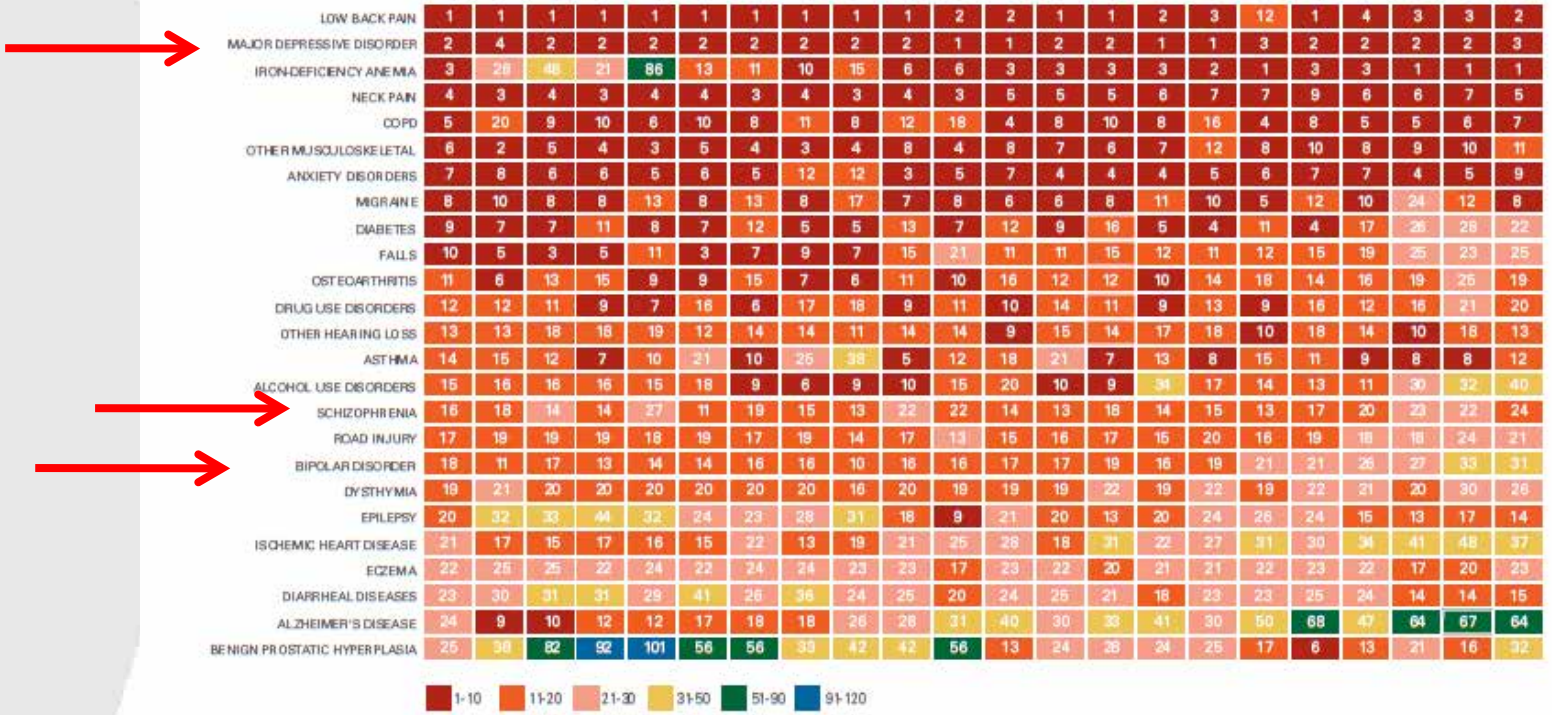
The thrifty psychiatric phenotype

Young patients are metabolically evaluated at early-stage due to the onset of SMI.

THE GLOBAL BURDEN OF DISEASE:
GENERATING EVIDENCE,
GUIDING POLICY

INSTITUTE FOR HEALTH METRICS AND EVALUATION — UNIVERSITY OF WASHINGTON

Figure 15: Rankings of leading causes of disability by region, 2010



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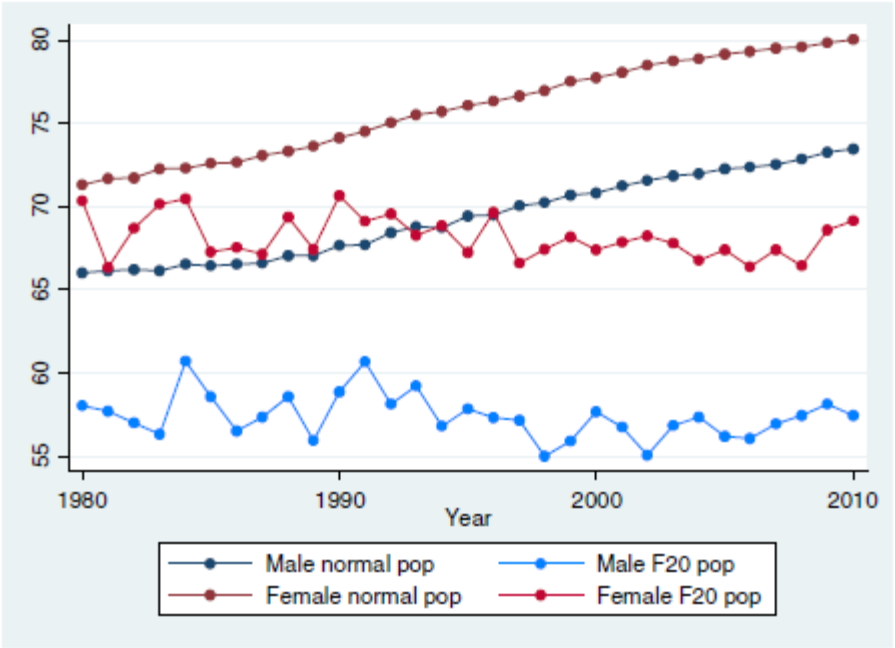
Increasing mortality gap for patients diagnosed with schizophrenia over the last three decades – A Danish nationwide study from 1980 to 2010



Natural Causes of Death in Schizophrenia

	Males		Females	
Cause	SMR	CI 95%	SMR	CI 95%
Infectious	3.4	1.4 - 7.1	1.9	0.6 - 4.3
Respiratory	3.2	2.4 - 4.2	2.7	2.1 - 3.4
Endocrine	2.7	1.6 - 4.2	2.0	1.1 - 3.4
Cardiovascular	2.3	2.0 - 2.6	2.1	1.9 - 2.4
Cancer	1.1	0.8 - 1.3	1.3	1.1 - 1.5

- Overall estimated 20% lower life expectancy
- Cardiovascular disease is one of the main causes of excess mortality

SMR = Standardized Mortality Ratio.

Newman SC, Bland RC. *Can J Psych.* 1991;36:239-245.
Osby U. *Schizophr Res.* 2000;45:21-28.

Resumen

Existen alteraciones glicídicas antes del inicio de tratamiento farmacológico en algunos pacientes.

El uso de psicofármacos agrava esta estado metabólico de riesgo.

Los factores de estrés durante el embarazo y parto condicionan por un lado incremento de la patología cardiovascular y de manera paralela aumentan el riesgo de patología mental.

Es posible que en algunos pacientes, este modelo justifique su envejecimiento precoz y elevada morbi-mortalidad .

Muchas gracias por la atención

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