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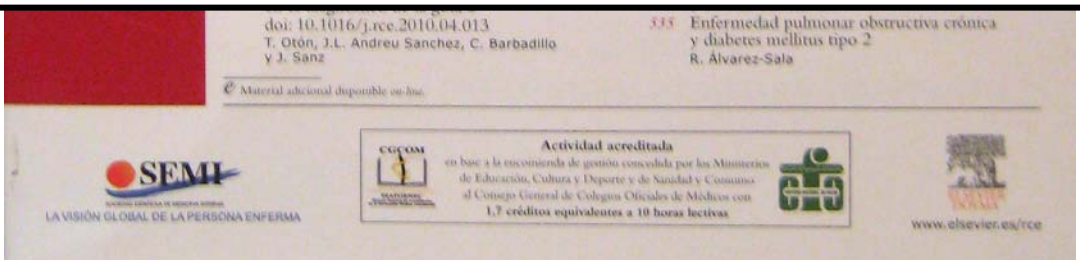


SEMI
LA VISIÓN GLOBAL DE LA PERSONA ENFERMA
FEMI
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OVIEDO
17-20 Noviembre 2010
Auditorio-Palacio de Congresos "Príncipe Felipe"
II Congreso Ibérico de Medicina Interna
VII Congreso de la Sociedad Asturiana de Medicina Interna
Nuevas EVIDENCIAS en el manejo de la GOTA:

Hiperuricemia como FRCV

Dr. Juan García Puig,
Unidad Metabólico - Vascular
Servicio de Medicina Interna (Prof. Arnalich),
Hospital Universitario La Paz, Madrid.

Hospital Universitario La Paz

Madrid

IdiPAZ
Instituto de Investigación
Hospital Universitario La Paz

El Dr. Juan García Puig ha sido consultado por AstraZeneca, BMS, GSK, Novartis, y Pfizer, y ha colaborado en investigaciones de las siguientes empresas farmacéuticas: AstraZeneca, BMS, Boeghringer, Chiesi, GSK, Menarini, MSD, Novartis, Recordati, Sanofi-Aventis, Sankyo, y Servier.

Indice

Prof. Gerald Reaven.

25 Abril, 2003.

The metabolic syndrome: a glance at its history

Panteleimon A. Sarafidis[a] and Peter M. Nilsson[b]

Although the modern era of what we now call the 'metabolic syndrome' or the 'insulin resistance syndrome' seems to have started less than two decades ago with the description of syndrome X by G.M. Reaven in the late 1980s, the history of this syndrome is much longer. In particular, a considerable number of scientists, starting as early as almost 90 years ago, have described the very common coexistence of the various components of the syndrome, including hypertension, and some of them gave several names to this clustering. On the other hand, during the past few years several international organizations have tried to form a reference context of what is included under the terms 'metabolic syndrome' and 'insulin resistance syndrome', proposing various 'definitions' for them. This review summarizes the history of the syndrome, from the early descriptions and other valuable contributions to the recent attempts to define it, as a small piece in honour of the pioneer workers in this field during the twentieth century.
J Hypertens 24:621–626

Journal of Hypertension 2006, 24:621–626

Keywords: metabolic syndrome, insulin resistance syndrome, syndrome X, history, definitions

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Accepted 15 November 2005

The history of a research field

The first descriptions of the clustering of various components of the metabolic syndrome are more than 80 years old and go back to the period when Banting and Best discovered insulin [12]. In Vienna, Austria, during the First World War, two physicians, Karl Hitzenberger and Martin Richter-Quittner, made clinical observations in patients with metabolic abnormalities. They discussed the interdependence of metabolic and vascular hypertension [13], as well as the relationship between blood pressure and diabetes mellitus [14]. These Austrian researchers were only able to publish their results after the war had ended [13,14].

At about the same time, two physicians – a Swede, Eskil Kylin, and a Spaniard, Gregorio Marañon – published independently and almost simultaneously in the same journal (*Zentralblatt für Innere Medizin*) two papers under almost the same title: 'Hypertension and diabetes mellitus' (Hypertonie and Zuckerkrankheit) [15,16]. In these papers the two physicians described the usual coexistence of hypertension and diabetes mellitus of adults and proposed common mechanisms for the development of these disorders. A year later, Kylin expanded his observations, adding high uric acid levels to the two former disturbances and describing a 'hypertension–hyperglycaemia–hyperuricaemia syndrome' (Hypertoni–Hyperglycemi–Hyperurikemi syndrom) [17]. In parallel with these descriptions, in 1936 Himsworth was the first to divide subjects with diabetes mellitus into insulin-sensitive and insulin-resistant [18], providing great help in the later understanding of the pathophysiology forming the background of the metabolic syndrome.

Zentralblatt für innere Medizin

in Verbindung mit

Brauer, Hamburg; v. Jaksch, Prag; v. Leube, Stuttgart; Naunyn, Baden-B.; Schultze, Bonn; Seifert, Würzburg; Umber, Berlin;

herausgegeben von

FRANZ VOLHARD in Halle.

42. Jahrgang.

VERLAG von JOHANN AMBROSIUS BARTH in LEIPZIG.

Nr. 45. Sonnabend, den 12. November 1921.

Inhalt.

Hypertonie und Zuckerkrankheit.

Vorläufige Mitteilung.

Von

Dr. Eskil Kylin in Göteborg (Schweden).

Auf dem Nordischen Intern. Kongreß in Kopenhagen 1919 berichtete ich zum erstenmal[1] über die klinischen Kapillardrucksstudien, welche es mir ermöglicht hatten, die Hypertonie in zwei Formen einzuteilen; nämlich eine Form von arterieller Blutdrucksteigerung ohne Kapillardrucksteigerung und eine Gruppe mit sowohl arterieller Blutdrucksteigerung wie auch

[1] Selbstbericht im Ztrbl. f. innere Med. 1920.

Zentralblatt für innere Medizin

in Verbindung mit

Brauer, Hamburg; v. Jaksch, Prag; v. Leube, Stuttgart; Naunyn, Baden-B.; Schultze, Bonn; Seifert, Würzburg; Umber, Berlin;

herausgegeben von

FRANZ VOLHARD in Halle

43. Jahrgang

VERLAG von JOHANN AMBROSIUS BARTH in LEIPZIG

Nr. 10. Sonnabend, den 11. März 1922.

Inhalt.

Über Hypertonie und Zuckerkrankheit.

Von

Dr. G. Marañon,

Médico del Hospital General de Madrid.

Das Problem der Beziehung zwischen Hypertonie und Diabetes, welches kürzlich Eskil Kylin (1) wieder aufwarf, ist einer der am wenigsten bekannten vielen dunklen Punkte, welche die Pathogenie der diabetischen Zustände umgeben. Nachstehend können wir einige Daten anführen, welche in dieser Hinsicht vielleicht von Interesse sind.

Die klassischen Verff. von Abhandlungen über den Diabetes lenkten schon die Aufmerksamkeit darauf, daß häufig Diabetes und Arteriosklerose, im allgemeinen begleitet von Hypertonie, zusammen auftreten. Die einfache Darstellung der Statistiken kann jedoch nur ein bloßes Zusammentreffen zum Ausdruck bringen, angesichts der größeren Häufigkeit, mit der der Diabetes mellitus sich nach dem 40. Lebensjahre einstellt, zu einer Zeit, in der auch die hypertensiven Störungen des Gefäßsystems ein-

The history of a research field

The first descriptions of the clustering of various components of the metabolic syndrome are more than 80 years old and go back to the period when Banting and Best discovered insulin [12]. In Vienna, Austria, during the First World War, two physicians, Karl Hitzenberger and Martin Richter-Quittner, made clinical observations in patients with metabolic abnormalities. They discussed the interdependence of metabolic and vascular hypertension [13], as well as the relationship between blood pressure and diabetes mellitus [14]. These Austrian researchers were only able to publish their results after the war had ended [13,14].

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¿Prevalencia del Síndrome Metabólico en Madrid?

(FIS, 2006/34; 00-11).

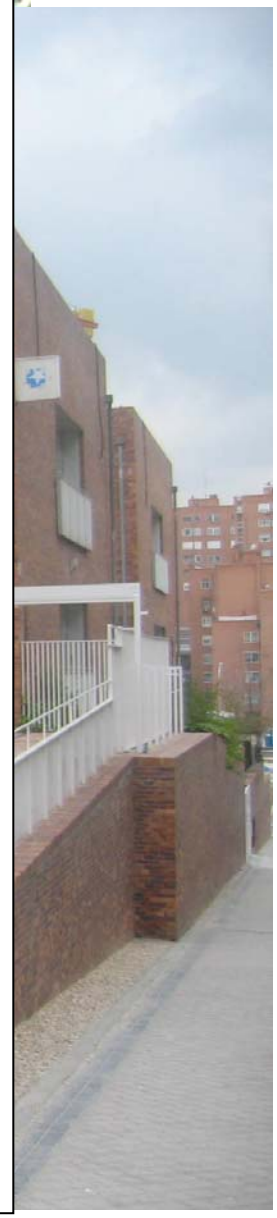
Colaboración Hospital – Atención Primaria.

GRUPO

M A P A

Monitorización Ambulatoria de la Presión Arterial

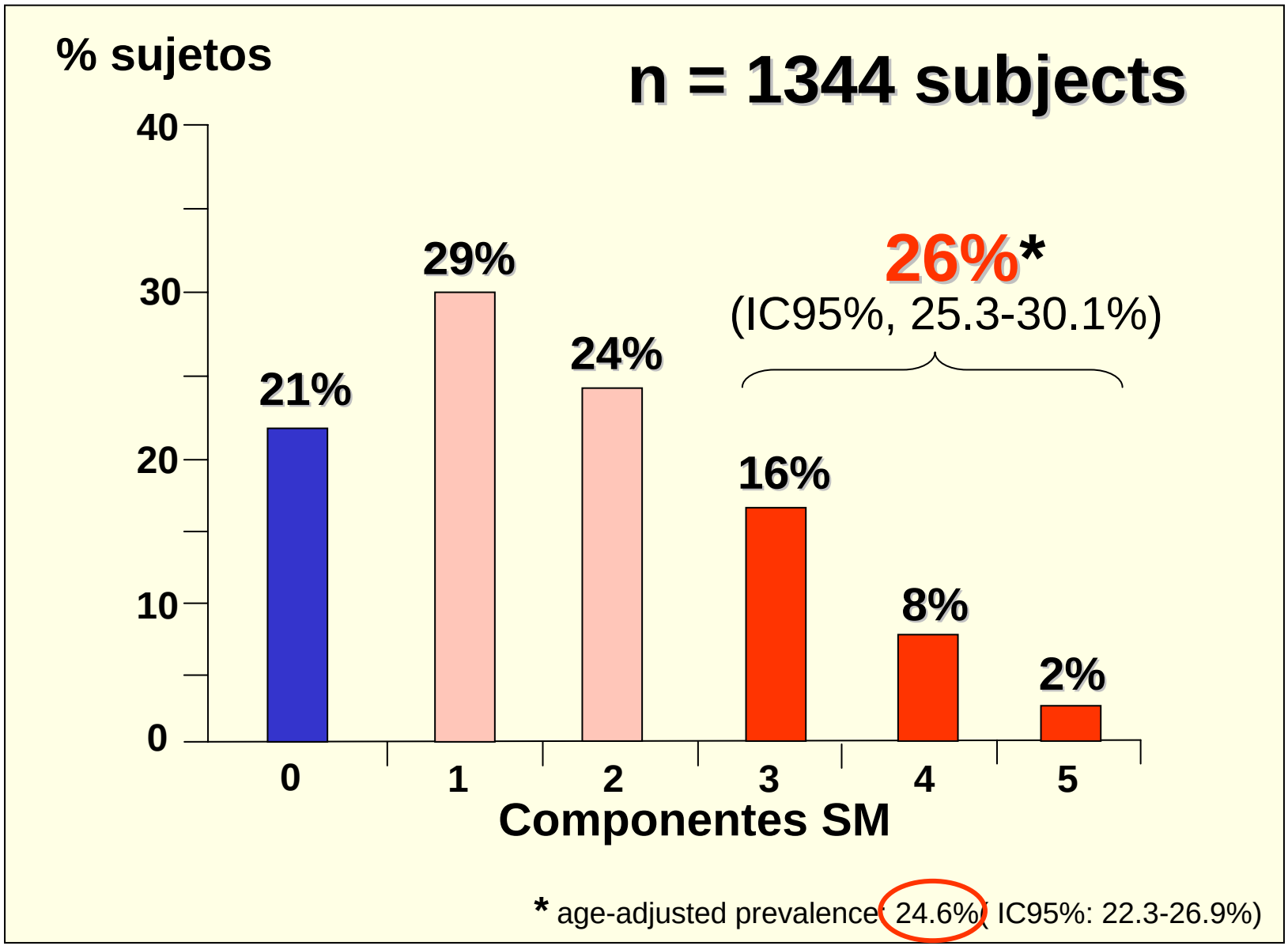
(1993-2010)



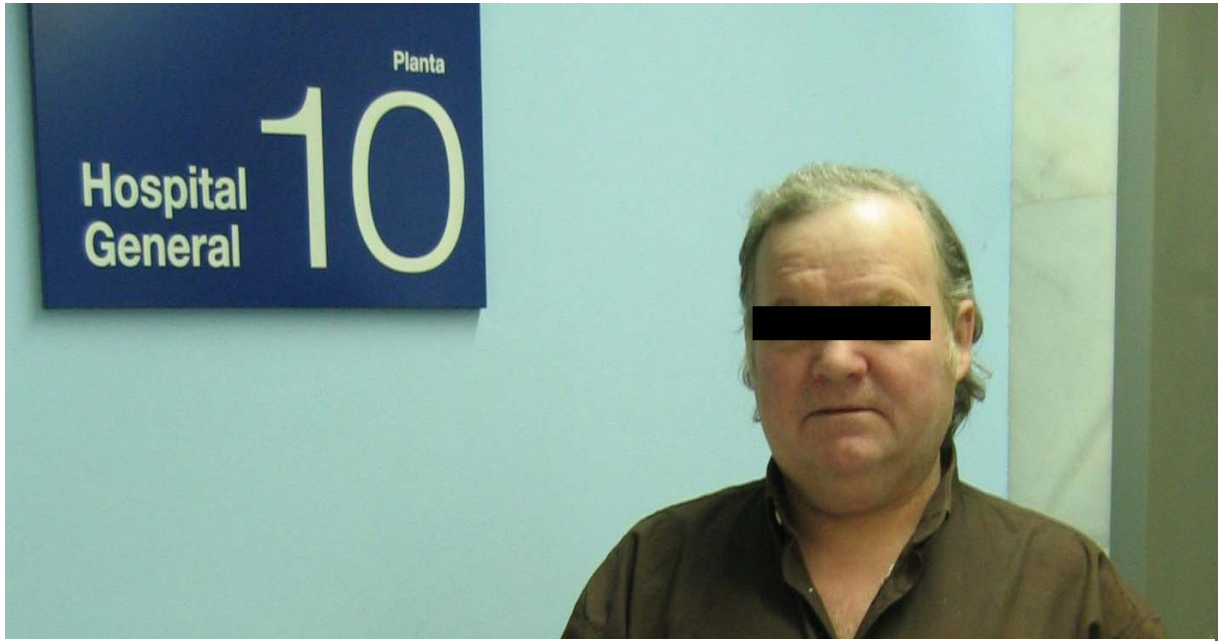
Grupo MAPA-MADRID (1993-2010).

Reunión. 03 Marzo 2010.

Resultados: componentes del SM.



Martínez Mª A, et al. Metabolism 2008;57:1232-40.



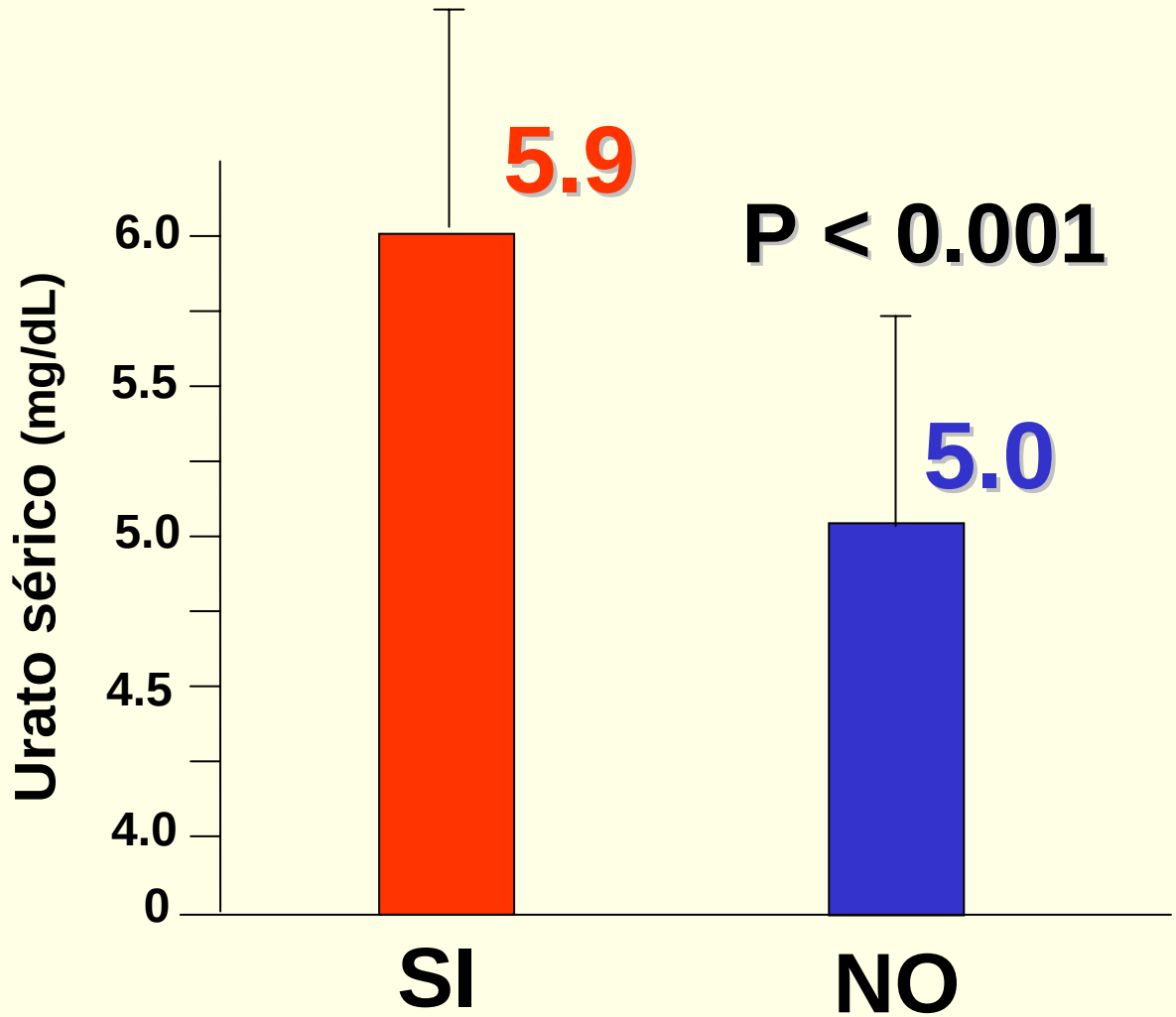
Síndrome Metabólico

- Gluc, 116 mg/dL.
- TG, 325 mg/dL.
- Urico, 8.2 mg/dL

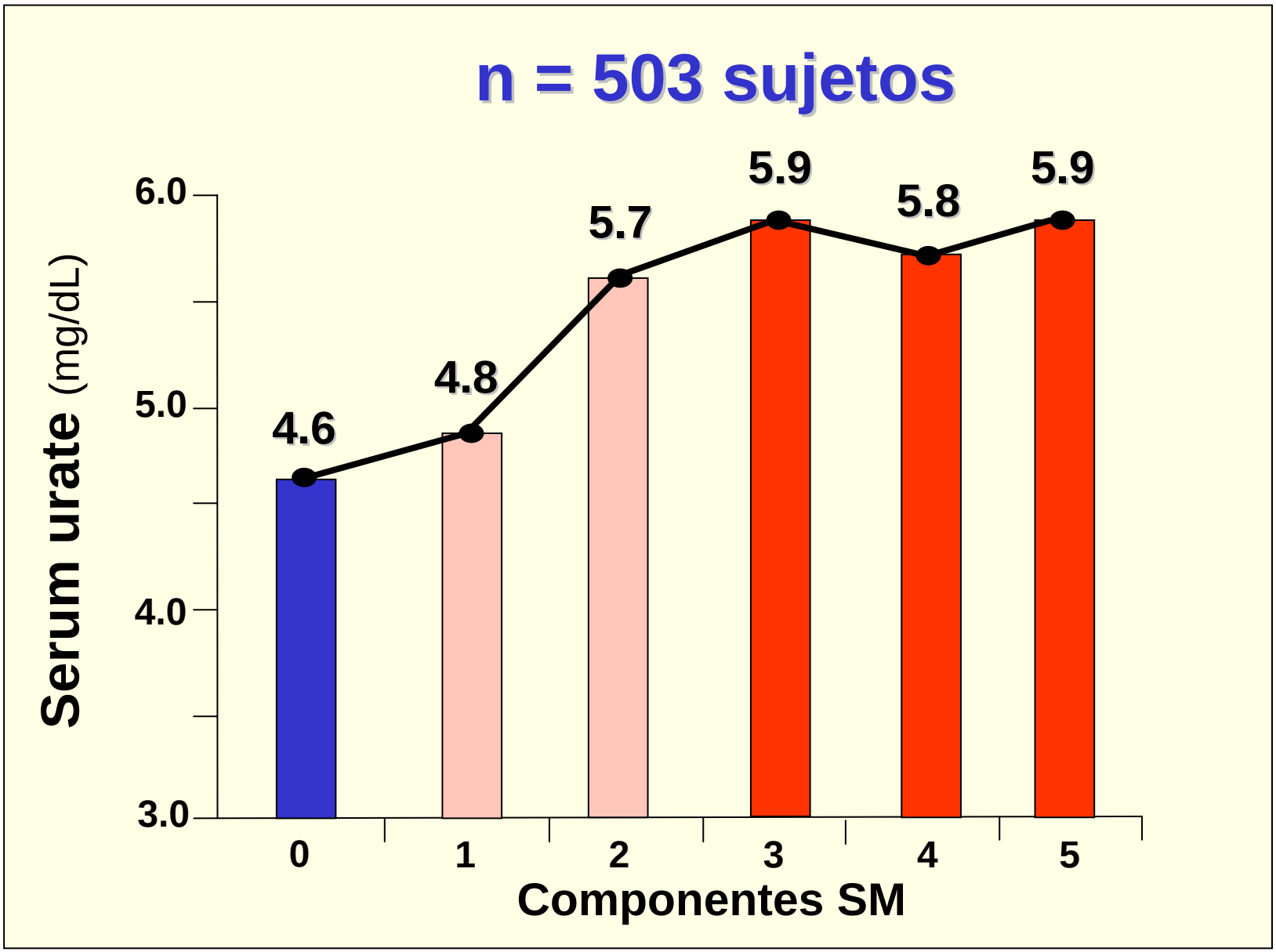
¿Uricemia en el Síndrome Metabólico?

Entre 1344 sujetos, 503 AU

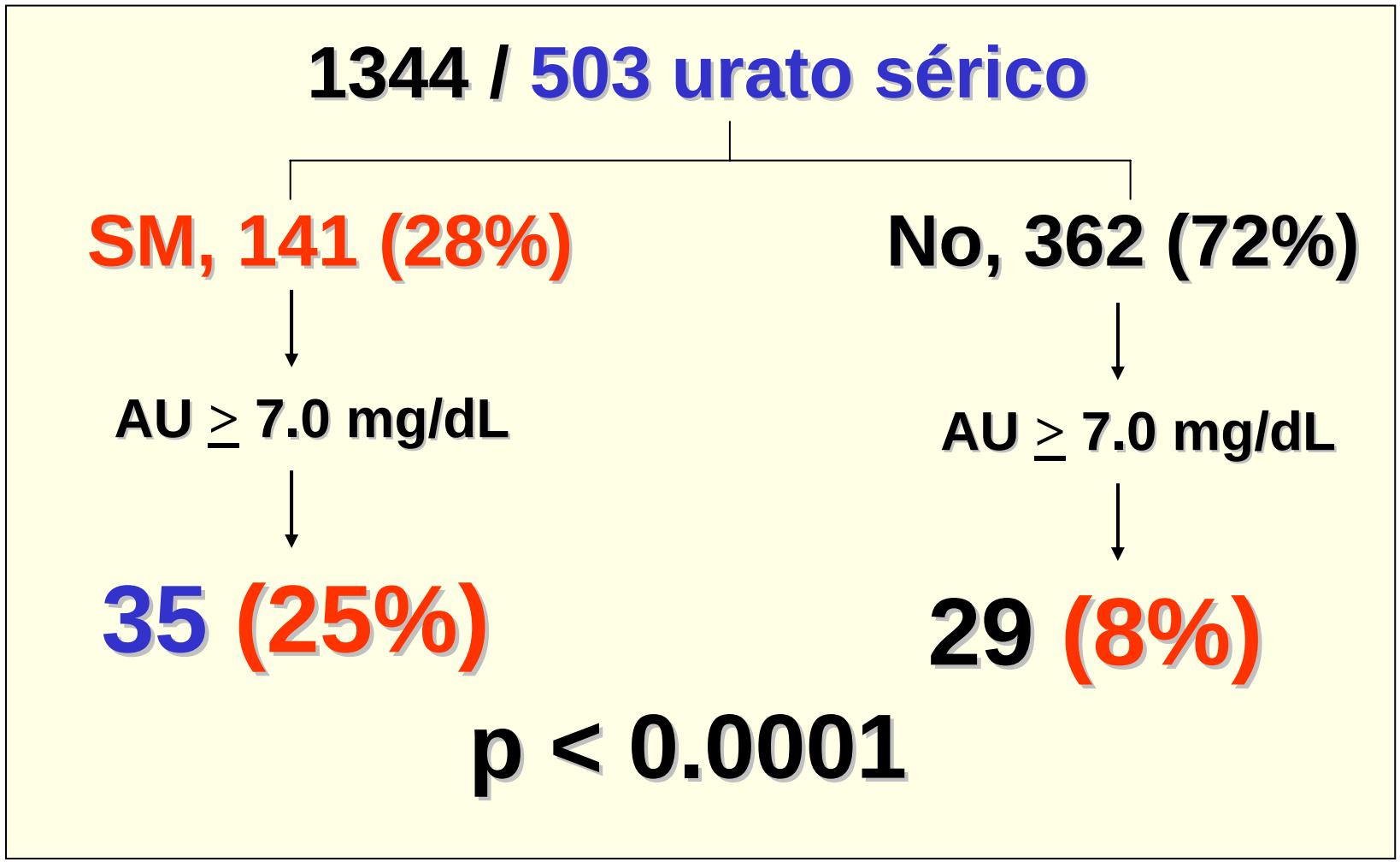
362 (72%) sin SM
141 (28%) con SM



¿Uricemia en el Síndrome Metabólico?



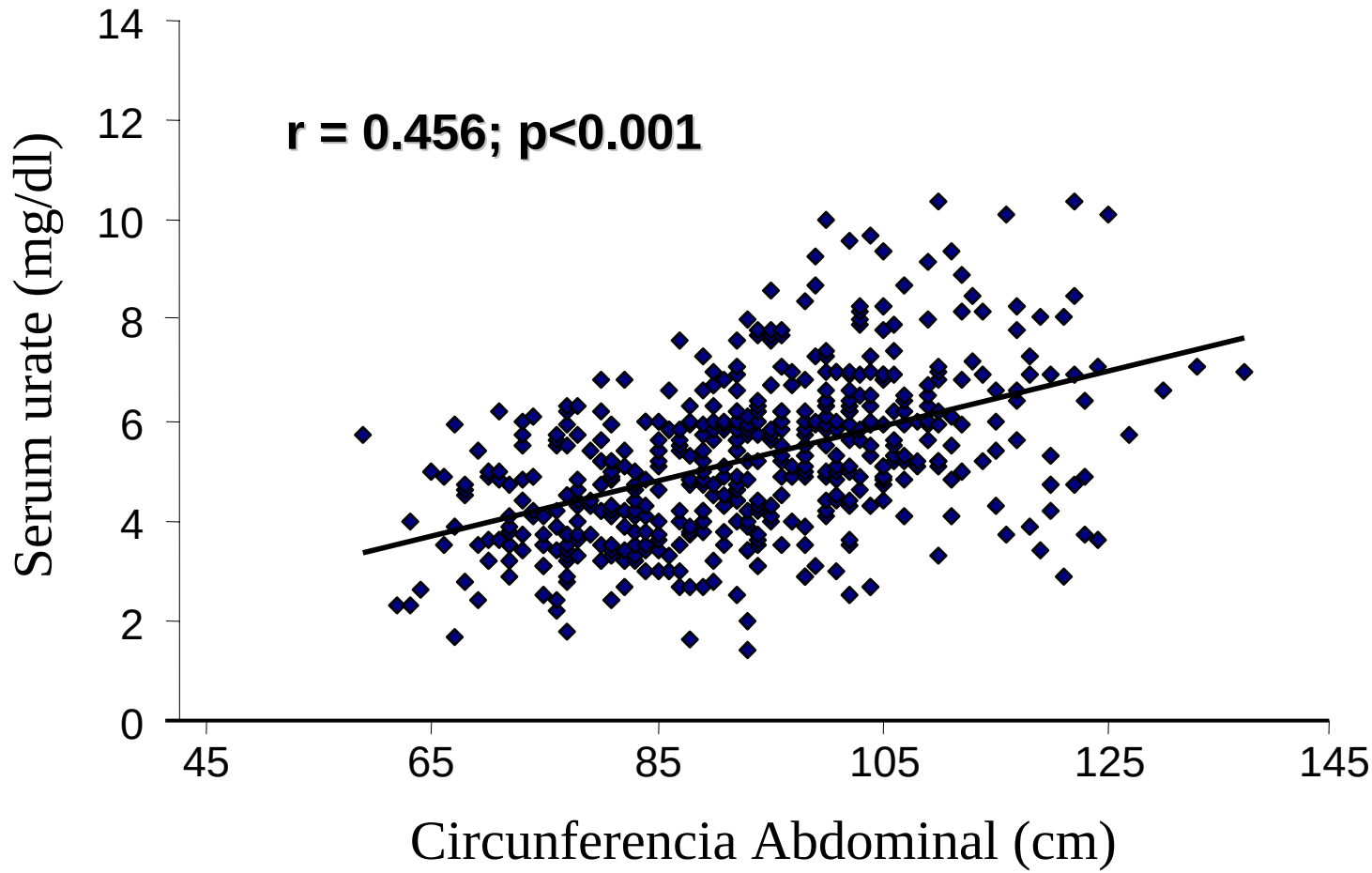
¿Prevalencia de Hiperuricemia en SM?



Correlación entre AU y componentes del SM

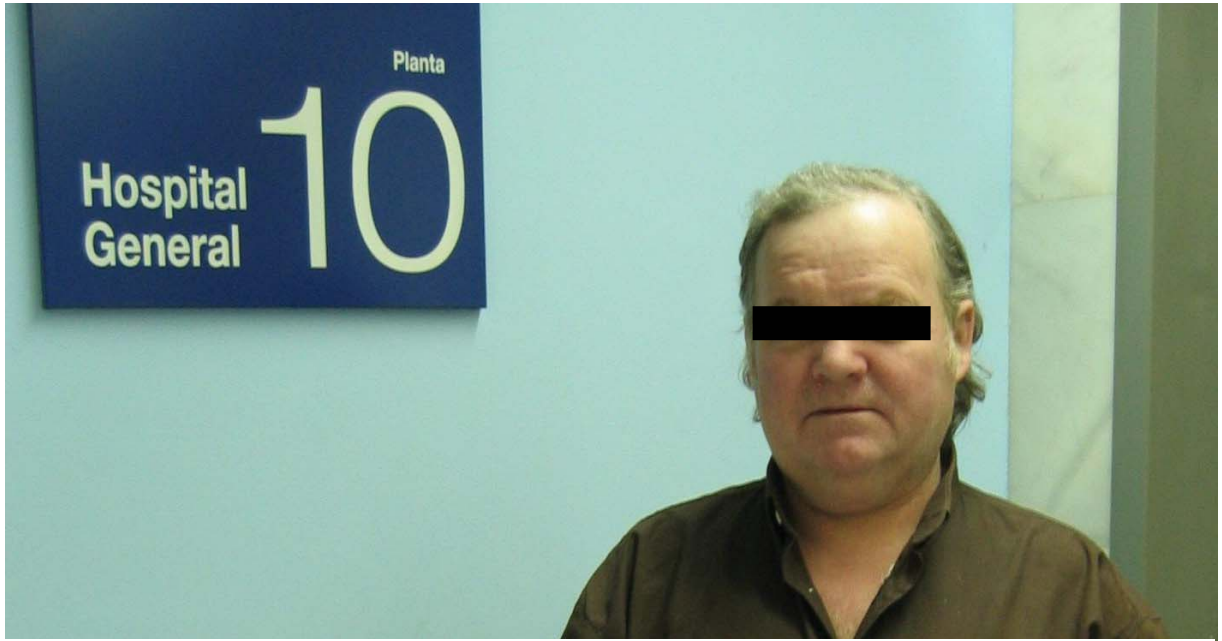
	Urato Sérico (r)	P
Circunferencia abdominal	0.456	<0.001
Triglicéridos	0.288	<0.001
HDL-CT	-0.269	<0.001
PA Sistólica	0.256	<0.001
PA Diastólic	0.226	<0.001
Glucosa	0.149	=0.01

Correlation entre Urato Sérico y Circumferencia Abdominal



Indice

1. Acido úrico y Síndrome Metabólico.
   - Hiperuricemia en SM (25%),
   - Marcador de obesidad abdominal.
2. ¿Hiperuricemia asintomática deletérea?
3. Alopurinol: Un gran fármaco!! …..

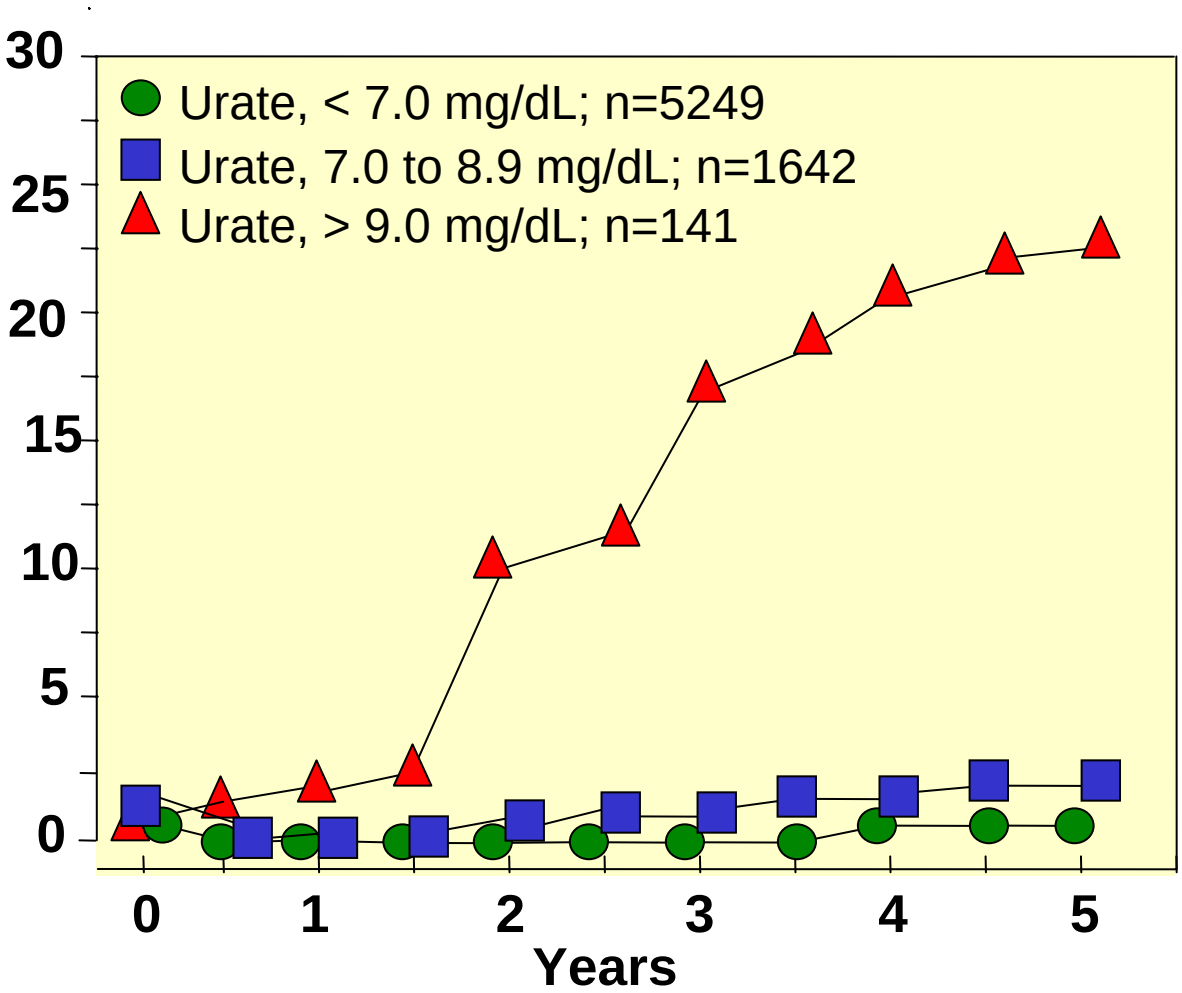


Síndrome Metabólico

- Gluc, 116 mg/dL.
- TG, 325 mg/dL.
- Urico, 8.2 mg/dL

Incidence of gouty arthritis

Cummulative incidence of gout by prior urate (%)



Campion EW, et al. Am J Med 1987;82:421-6.

Hiperuricemia Asintomática:

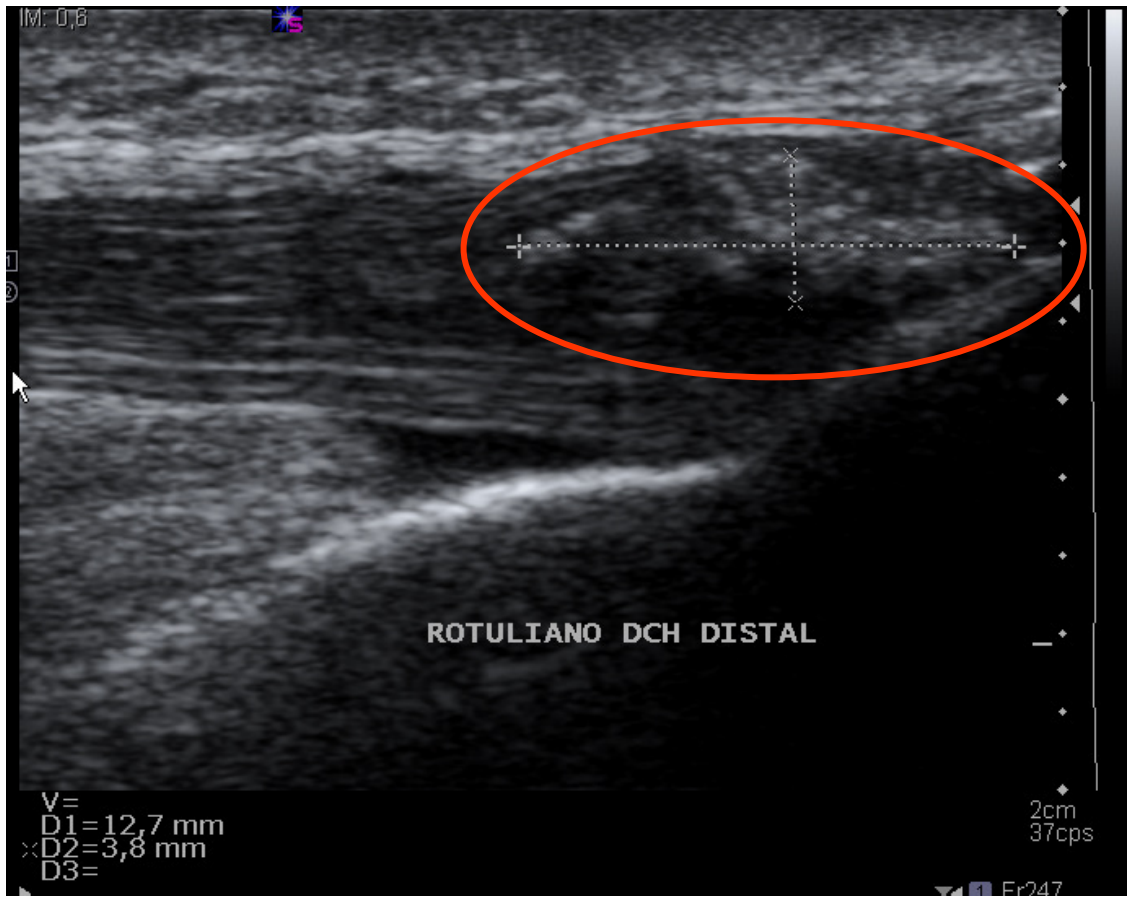
Impacto de la ULTRASONOGRAFIA.

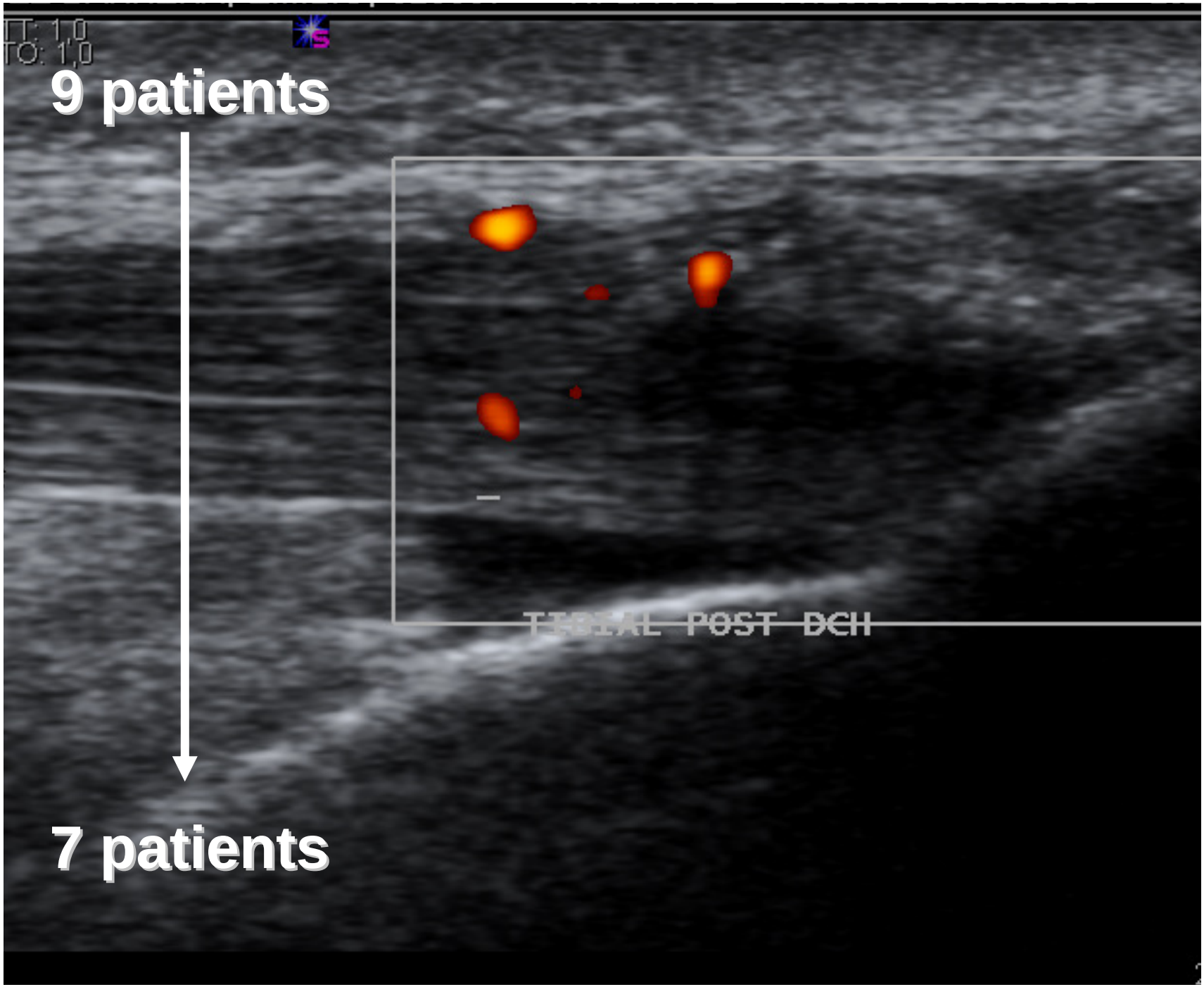
1344 / 503 urato sérico

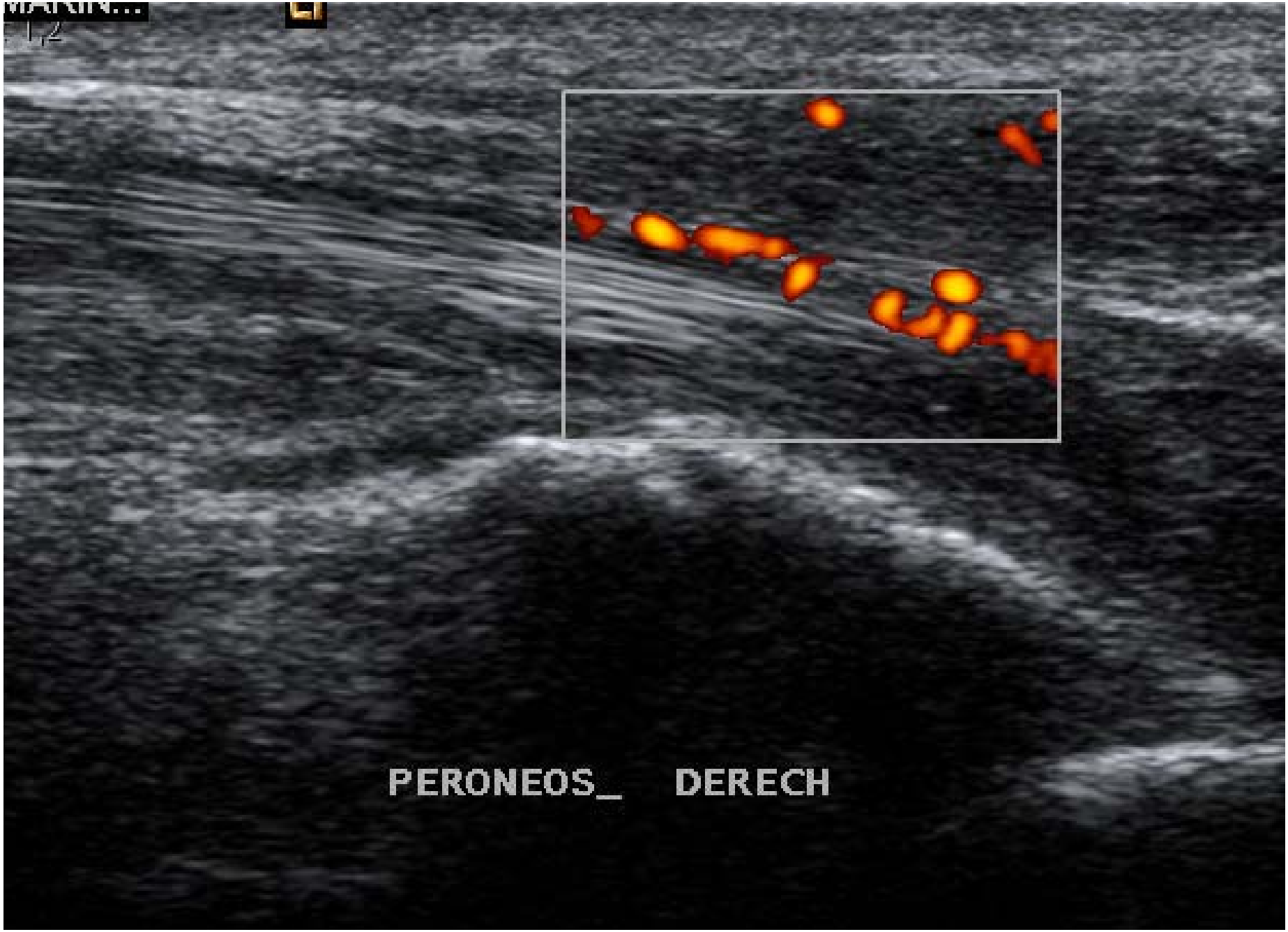
SM, 141 (28%)

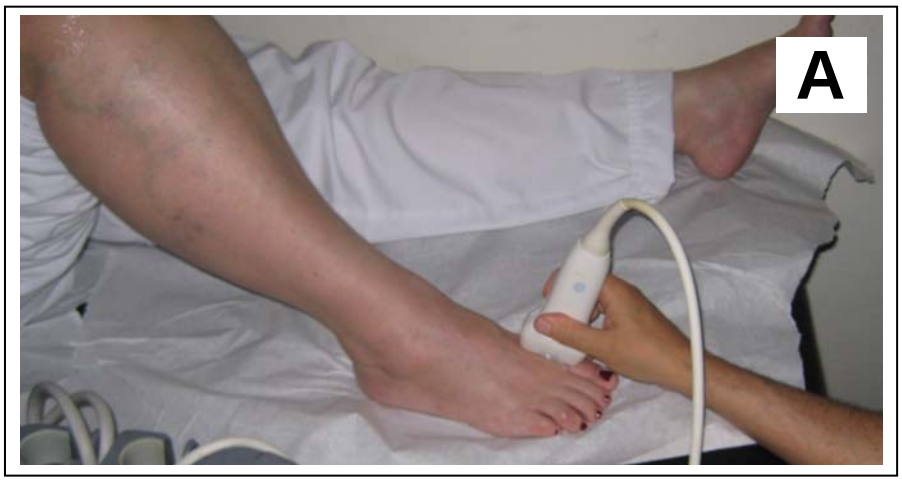
22

9




9 patients
7 patients


PERONEOS_ DERECH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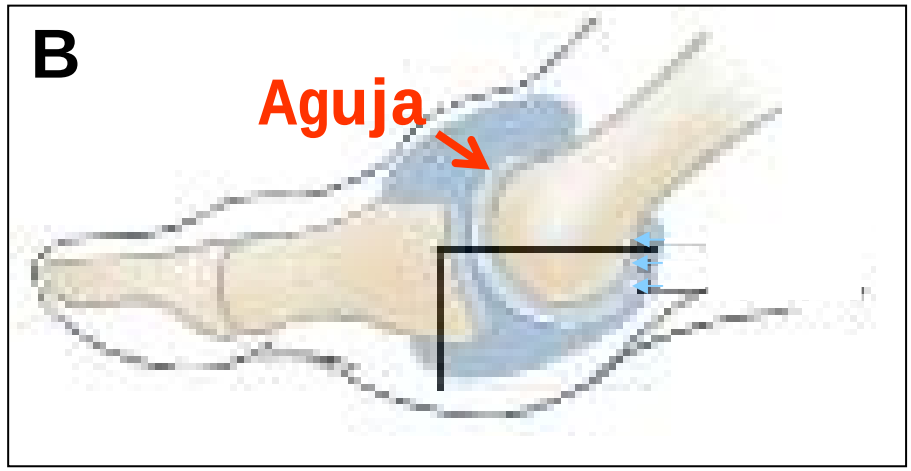
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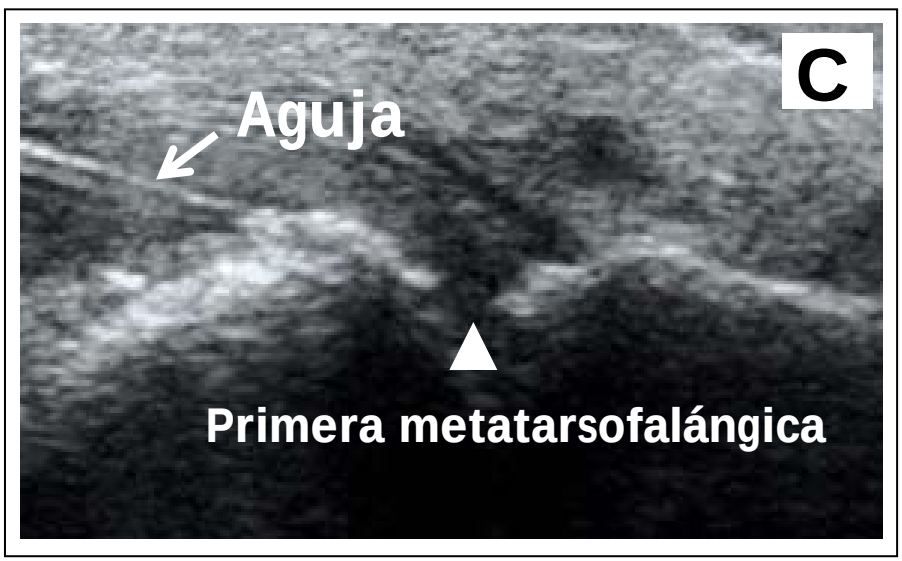
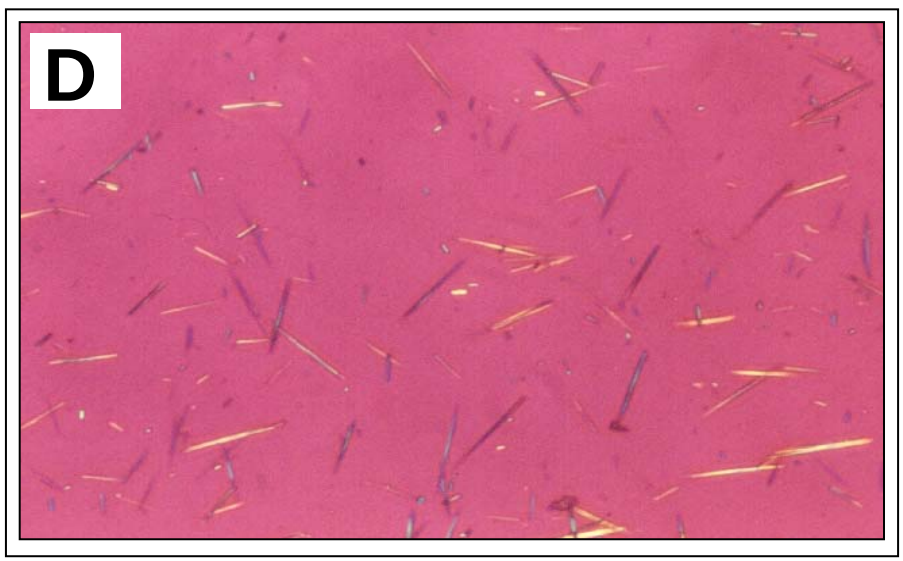
Aguja


C
Aguja
Primera metatarsofalángica


D

Hipertension Arterial

8 estudios PROSPECTIVOS	¿El AU se asocia a enf. CV?
EWPHE, 1991	NO
SHEP, 1996	YES (asociación marginal)
WORKSITE, 1999	YES
PIUMA study, 2000	YES (Curva-J)
SHEP, 2000	YES
Syst, -EUR China, 2000	YES
Syst, -EUR Europe, 2002	NO
LIFE study, 2004	YES (solo en mujeres)

Elevado RCV.

5 estudios PROSPECTIVOS	¿El AU se asocia a enf. CV?
Social ins. Inst. Finland, 1998	YES
Stroke survivors	YES
AtheroGen study, 2002	YES
Acute Stroke study, 2003	YES
CHF study, 2003	YES

Estudios POBLACIONALES: Urato sérico y enf. CV.

18 PROSPECTIVE studies	¿El AU se asocia a enf. CV?
Chicago Heart Association, 1979	YES (CV+CHD death, solo muejres)
Social Ins. Inst. Finland, 1982	YES (muerte CV, H y M sin enf. CV)
Honolulu Heart Program, 1984	NO
Framingham Study, 1985	NO
Gothenburg Study, 1988	NO
Chicago Heart Association, 1989	YES (muerte CV y corom, solo mujeres)
Honolulu Heart Program, 1996	NO (SI para enf. coronaria no bebedores)
British Regional Heart Study, 1997	NO
Augsburg MONICA cohort, 1999	YES (muerte CV)
Framingham Study, 1999	NO
NHANES I, 2000	YES (muerte CV y coronaria)
ARIC Study, 2000	NO
McArthur studies 2001	NO
CV study in the elderly 2001	YES
Belgian population 2001	YES
Gubbio study 2001	YES
NHIC, Korea 2004	NO
Middle-age Finnish men 2004	YES

Indice

1. Acido úrico y Síndrome Metabólico.
   - Hiperuricemia en SM,
   - Marcador de daño vascular en FRCV
2. ¿Hiperuricemia asintomática deletérea?
   - NO en población general.
   - Cuidado!! …. en pacientes con FRCV.
3. Alopurinol: Un gran fármaco!! ……

The Development of Allopurinol

R. Wayne Rundles, MD

Arch Intern Med, 1985;145:339-44.

28.8.85

The Clinical Research Unit (CRU) program of the National Institutes of Health, developed in the late 1950s, proved to be an important innovation in the use of public funds to support medical research. The establishment of these units led to a material improvement in the quality, convenience, and feasibility of many types of investigation involving human subjects. Their contribution in one area is illustrated by studies that led to the development of allopurinol as an agent to control the production of uric acid in gout and hyperuricemia in man. The route by which this drug was developed was serendipitous, and ultimate success depended on the fortuitous collaboration of individuals with biochemical, pharmacologic, and medical research interests working with substantial institutional support.

Historically, the importance of medical research in public health and national defense matters gained recognition slowly for nearly a century before it attracted major support from either private or governmental sources. The first stimulus of major importance was the publication of William Osler's *The Principles and Practices of Medicine* in 1892. Almost immediately this book became not only a bible for students and clinicians, but had an important impact in other realms. In 1895 the second edition came to the attention of Frederick T. Gates, one of John D. Rockefeller's main philanthropic advisors. Mr Gates read the whole volume with the aid of a medical dictionary during a summer vacation and immediately recognized it as one of the few scientific books that had a high literary quality. The author was obviously an enlightened, able, and honest individual who reported that almost all that physicians could do practically for patients in the 1890s was to provide some measure of symptomatic relief, arrange better nursing attention, and give some help regarding prognosis. Since an increasing number of the most common diseases at that time were being shown to be of infectious or contagious origin, it appeared to Mr Gates that the scientific study of medicine, research, and education, which had been haphazardly carried out in most civilized countries previously, offered an unique opportunity to improve the lot of mankind. He arranged for a visit with Dr Osler and then sent a memorandum to Mr Rockefeller that eventually resulted in the founding of the Rockefeller Institute of Medical Research. The initial gift was for $50 million. During Osler's lifetime the total Rockefeller support amounted to $300 million.[1]

A second impetus for increasing our national investment in biomedical research came from lessons learned in World War II. During the war some 3,800 scientists and technologists and 1,700 physicians were mobilized to investigate problems vital to national defense. Between 1941 and 1947 the National Research Council's Committee on Medical Research spent some $25 million, a huge sum in those days, through its six divisions: medicine, surgery, aviation medicine, physiology, chemical warfare, and malaria control.[2] The accomplishments of this wartime effort were indeed impressive, including as they did the development and wide use of penicillin, the sulfonamide compounds, blood banks, the clinical use of blood components, and the development of adrenal steroid compounds, the antimalarials, and other drugs.

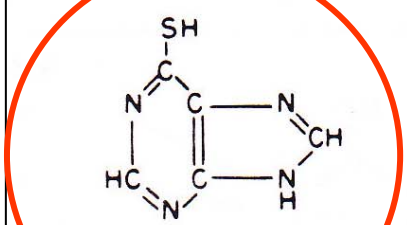
Near the war's end many of the chemical warfare and malaria control experts turned to cancer chemotherapy. Remissions were soon produced in children with acute leukemia by the use of anti–folic acid compounds. With the development of new types of anticancer agents and advances in diagnostic and therapeutic radiology, a substantial number of patients with Hodgkin's disease were cured for the first time.

Public interest was stimulated by these accomplishments. New research programs were launched by the National Cancer Institute, the first of the national institutes of medicine. After several public figures including

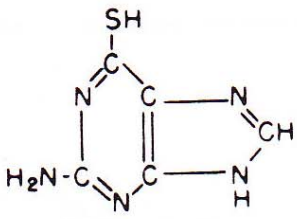
Accepted for publication Oct 25, 1984.

From the Department of Medicine, Duke University School of Medicine, Durham, NC.

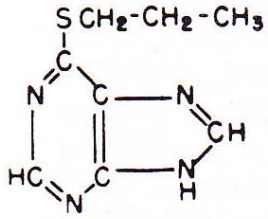
Reprint requests to Department of Medicine, Duke University School of Medicine, Durham, NC 27710 (Dr Rundles).



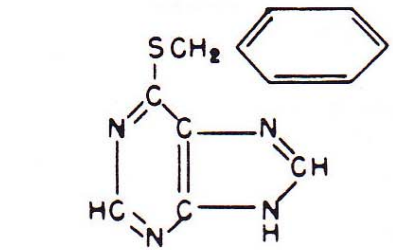
6-Mercaptopurine



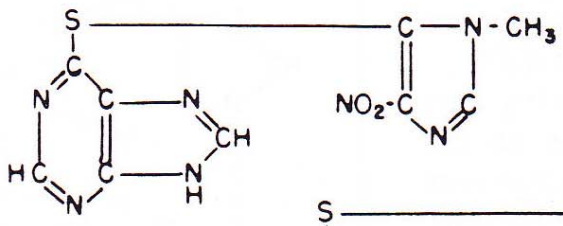
Thioguanine



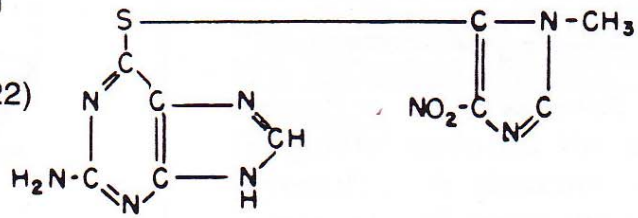
Propyl-Mercaptopurine



Benzyl-Mercaptopurine



Azathioprine
(Imuran, BW57-322)



Thiamiprine
(BW57-323)

Fig 1.—Thiopurine compounds selected for clinical evaluation.

Metabolismo de las PURINAS

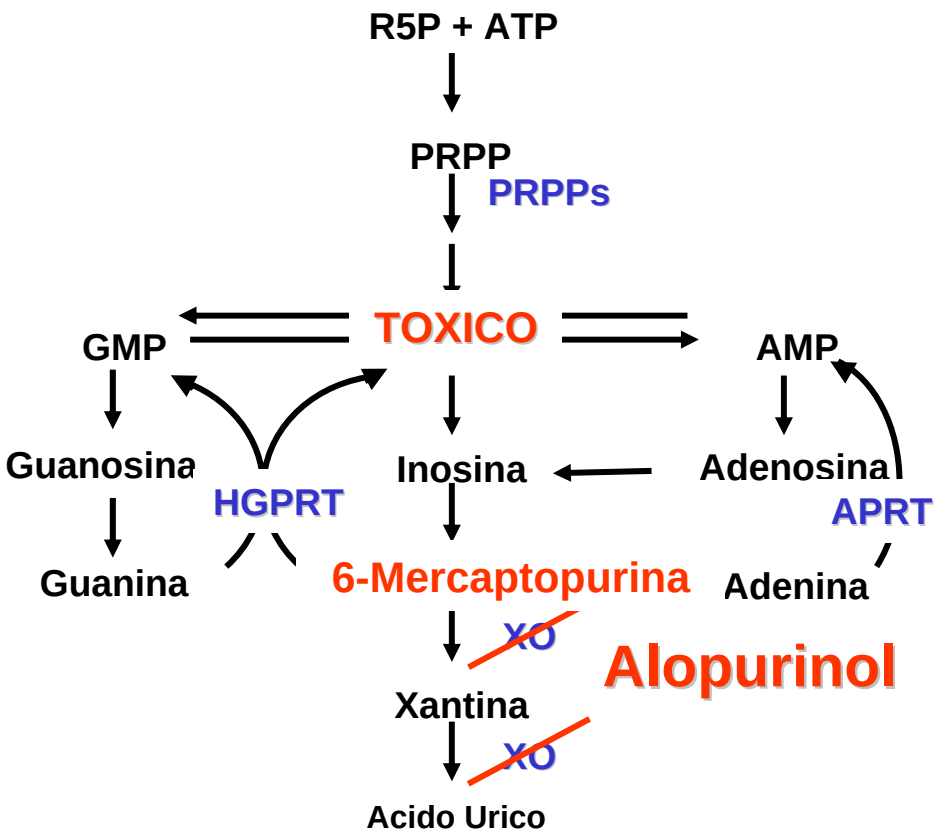
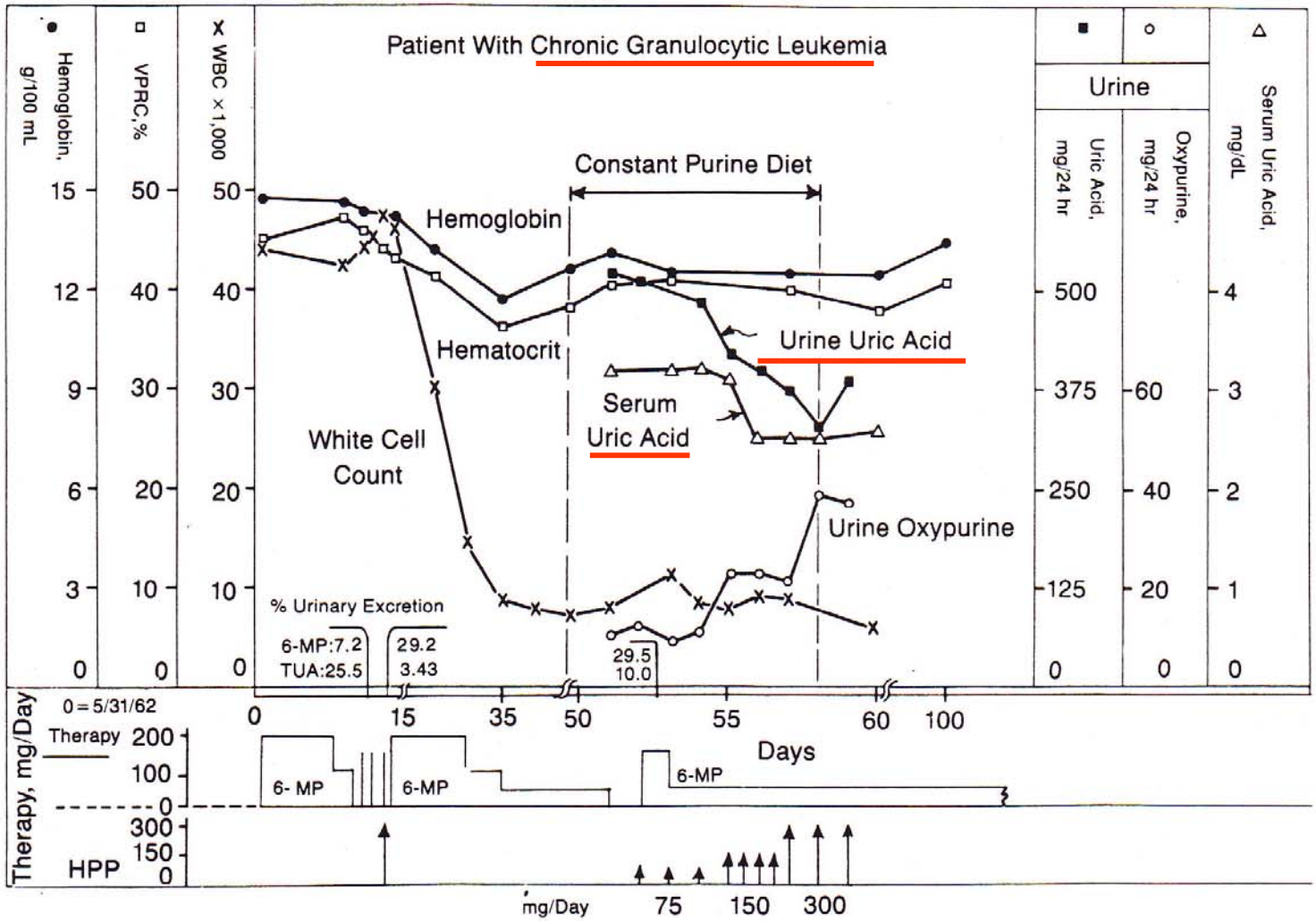


Fig 5.—Effects of allopurinol (HPP) therapy in patient with chronic granulocytic leukemia receiving 6-mercaptopurine (6-MP) (from Scott[30]). Without allopurinol (HPP), urinary excretion of mercaptopurine and thiouric acid (TUA) was 7.2% and 25.5%, respectively. When allopurinol was given with mercaptopurine, excretion was 29.2% and 3.43%, respectively (see text). Hgb indicates hemoglobin; VPRC, hematocrit; WBC, white blood cells.



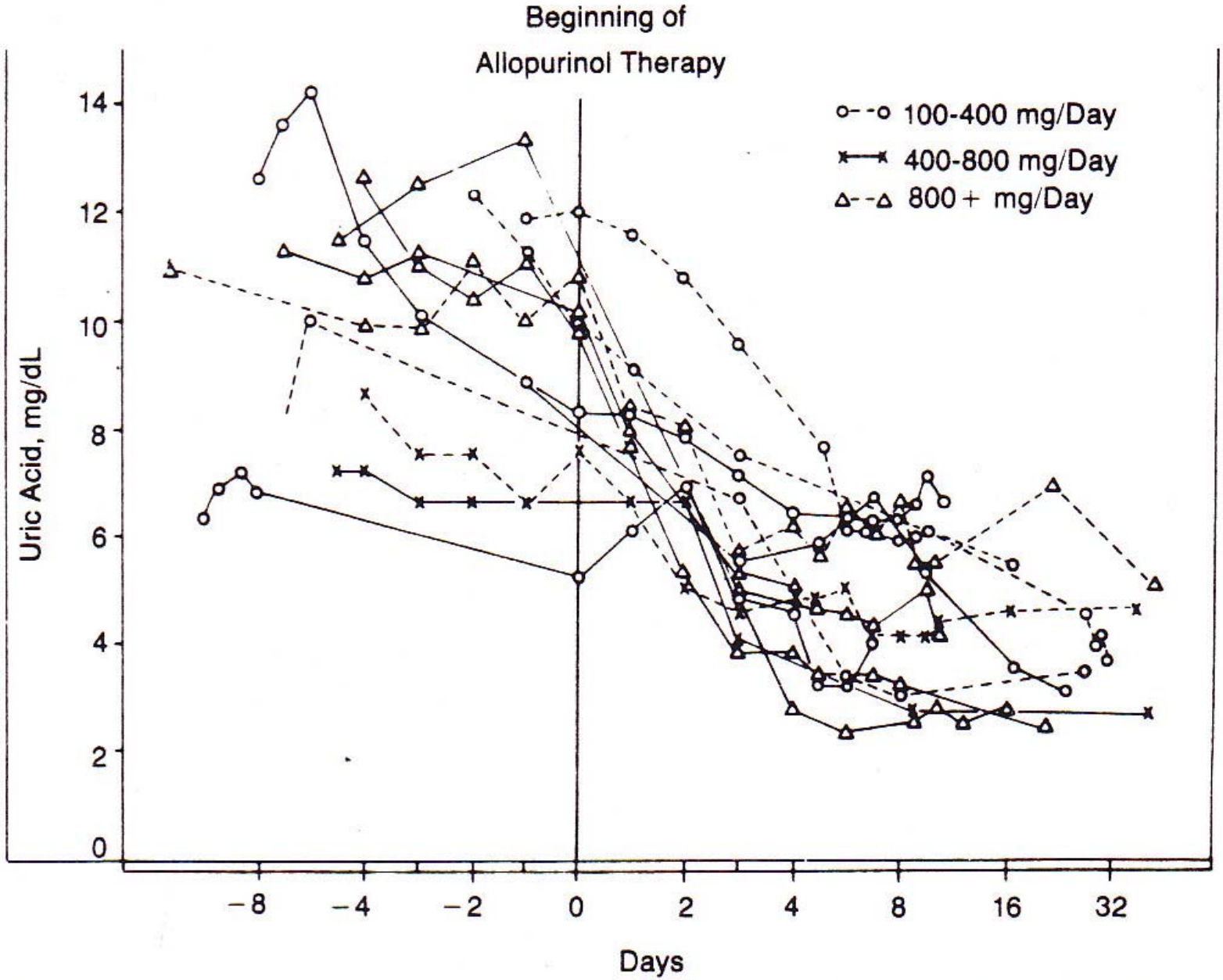


Fig 7.—Effects of allopurinol therapy in 12 patients with gout (from Scott[30]).

Scott JT. Ann Rheum Dis 1966;25(suppl):599-718.

Drugs 48 (3): 339-344, 1994
0012-6667/94/0009-0339/$06.00/0

Drugs, 1994;48:339-44.

New Uses for Allopurinol

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Allopurinol is widely used to manage hyperuricaemia and prevent acute episodes of gout and the damage caused by tophaceous gout. It also has an important role in preventing acute, urate-induced, obstructive uropathy seen during the cytotoxic therapy of neoplastic diseases. Recently, a number of new and exciting indications for allopurinol have emerged. This commentary focuses on the widening uses for this drug.

1. The Discovery of Allopurinol

Allopurinol, one of the first drugs to be developed on a rational biochemical basis, was synthesised by George Hitchings and Gertrude Elion of the Burroughs Wellcome Company, New York (subsequently North Carolina). This work contributed in part to their being awarded the Nobel Prize in Medicine in 1988.[1] Hitchings and Elion were synthesising a series of purine and pyrimidine analogues as potential antineoplastic drugs, and developed 4 important drugs: mercaptopurine, azathioprine, aciclovir and allopurinol (fig. 1).

It soon became clear that allopurinol had no antineoplastic potential, but was a substrate and potent inhibitor of the enzyme xanthine oxidase (xanthine : NAD^+ oxidoreductase). This is the terminal enzyme in the synthetic pathway for purines and catalyses the production of uric acid from hypoxanthine and xanthine (fig. 2). The potential hypouricaemic effect of allopurinol-induced xanthine oxidase inhibition was initially observed in patients with leukaemia who had been given mercaptopurine. Not only did the plasma level and urinary output of uric acid decrease in these patients, but the metabolism of mercaptopurine, and thus its clearance, was inhibited. This was because mercaptopurine is metabolised via xanthine oxidase to nontoxic products. Allopurinol, by blocking xanthine oxidase, results in toxic concentrations of mercaptopurine. In fact, this very important interaction has led to a substantial number of serious adverse effects, including death, as a result of excessive concentrations of mercaptopurine.

2. Clinically Relevant Aspects of Allopurinol Pharmacokinetics

PREMIO NOBEL DE MEDICINA Y FISIOLOGÍA

Dos norteamericanos y un británico comparten el galardón

Tres veteranos investigadores, premiados por sus aportaciones a los nuevos fármacos

RICARDO MORENO, **Estocolmo**

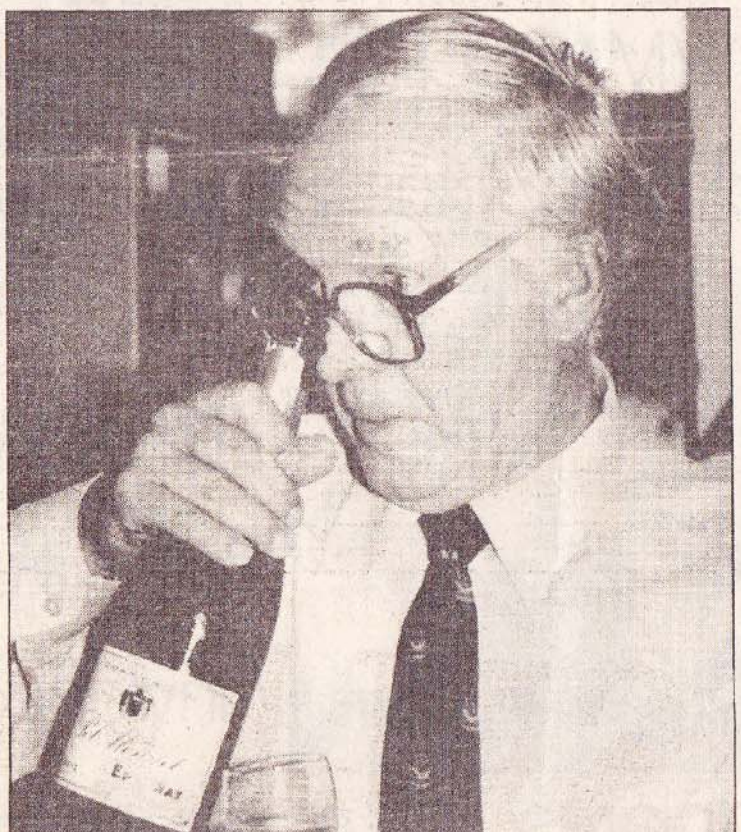
James W. Black, británico, de 64 años, y los norteamericanos Gertrude B. Elion, de 70, y George H. Hitchings, de 83, fueron distinguidos ayer por la asamblea Nobel del Instituto Carolino de Estocolmo con el Premio Nobel de Medicina y Fisiología correspondiente a este año, "por el descubrimiento de importantes principios de terapéutica médica". En realidad, se han premiado dos líneas de investigación: la de Black, que dio lugar a los betabloqueadores, y la del equipo formado por Elion y Hitchings, que vienen trabajando juntos en los laboratorios Wellcome de Carolina del Norte desde 1945.

Del trabajo de Elion y Hitchings han surgido numerosos nuevos medicamentos, desde inmunosupresores utilizados en trasplantes cardiacos hasta antivíricos como la azidotimidina, utilizada en el tratamiento del SIDA.

El premio en metálico, de 2,5 millones de coronas (unos 48 millones de pesetas), será, pues, compartido por los tres investigadores.

Las investigaciones del británico James W. Black han permitido la utilización de las grandes posibilidades farmacoterapéuticas que ofrecen los medicamentos llamados agentes de bloqueo de los betarreceptores o betabloqueantes y desarrollar, en 1964, el primer producto de este tipo, el propanolol. Este medicamento es utilizado en el tratamiento de la angina de pecho, como inhibidor de un nuevo infarto cardiaco en pacientes que ya han sufrido alguno anteriormente, y en el tratamiento de la hipertensión arterial.

El desarrollo del propanolol trascendió a sus aplicaciones clínicas, ya que permitió además



des tan distintas como son la leucemia, la malaria, las infecciones víricas y la gota.

Elion y Hitchings tenían un conocimiento limitado sobre el metabolismo de los ácidos nucleicos cuando presentaron su idea. Comenzaron por estudiar el crecimiento de una bacteria, *Lactobacila casei*, dependiente del ácido fólico y un compuesto de purinas y pirimidinas con el doble propósito de trazar un gráfico de las vías metabólicas que conducen a la biosíntesis de los ácidos nucleicos y por otro lado identificar los antimetabolitos del metabolismo de dichos ácidos.

Tres años después se lograron resultaron resultados prometedores en el tratamiento de la leucemia, pero los experimentos debieron suspenderse en razón de la toxicidad del producto empleado.

En España

Gracias a los descubrimientos de los premios Nobel de Medicina de este año podrán conocerse y

Un científico 'naïf'

EL PAÍS, **Madrid**

"Por el momento me siento totalmente sorprendido. La sorpresa ha sobrepasado casi la alegría que siento", afirmó ayer el británico sir James Black, de 64 años, en sus primeras declaraciones tras conocer el galardón que le había sido concedido. Black se encontraba en su trabajo en el hospital King's College cuando recibió la noticia, y afirmó que muchas otras personas merecían el premio al igual que él. Este especialista en fisiología cardiovascular que ha descubierto medicamentos esenciales para el tratamiento de las enfermedades cardiacas describió su actitud científica como *naïf*. "Cuando comencé, la idea de la interacción molecular no estaba realmente aceptada. Yo adopte una actitud totalmente ingenua y estoy muy contento del uso hecho de mis descubrimientos", declaró ayer a France Presse en Londres.

Sir James Black se dolió de que en la actualidad sea tan difícil para un investigador mantener esta actitud de ingenuidad. "Existe una terrible presión ejercida sobre los investigadores para que sean útiles y prácticos en seguida. Necesitamos mucho más dinero para poder dejar a la gente que haga sus experimentos". Black se quejó también de que sea difícil obtener

George Hitchings.

Gertrude Elion.

Un abuelo cariñoso

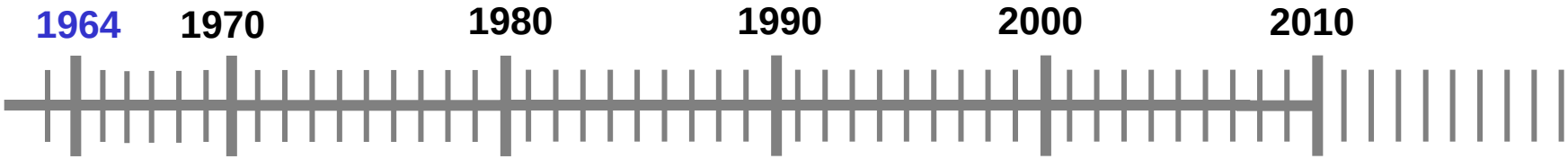
EL PAÍS, **Madrid**

George Hitchings, de 83 años, es padre de dos hijos y abuelo de cinco nietos, y su primera declaración se refirió a ellos: "Es maravilloso para mi familia", dijo ayer. "Estoy más satisfecho por mis descendientes que por mí mismo". Hitchings, junto a Elion, estudió la diferencia en el metabolismo del

Una vida de trabajo

EL PAÍS, **Madrid**

Gertrude Elion declaró ayer que la incredulidad fue su primera reacción ante la noticia de que le había sido concedido el Premio Nobel de Medicina y Fisiología. "Todavía no me lo creo", afirmó Elion, que tiene en la actualidad 70 años y que ha trabajado toda su vida junto a otro de los ganadores, George



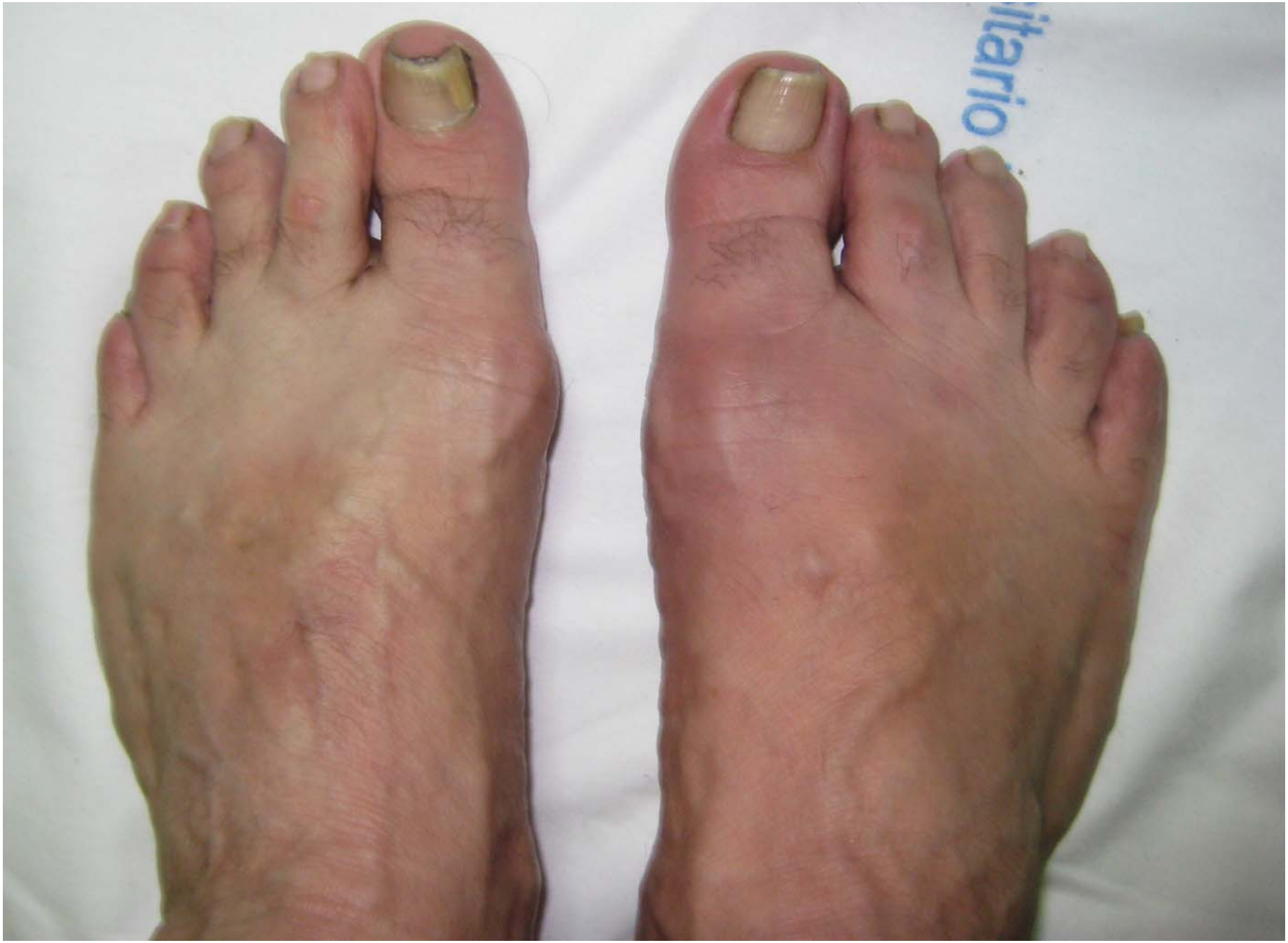
¿Cuántos fármacos siguen … 45 años, sin competidores?

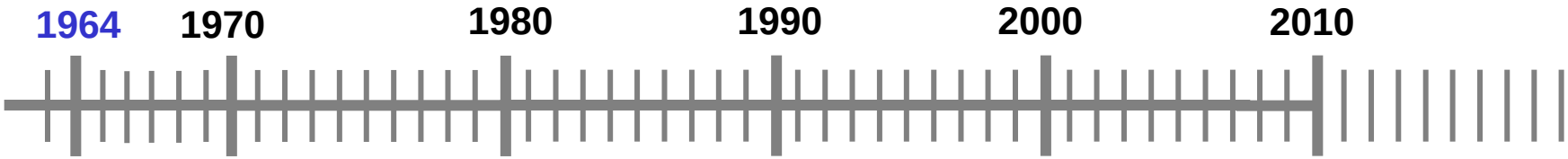
PROPIEDADES

- Muy eficaz
- Bien tolerado
- Cómodo
- Barato

Areas de Mejora

- Crisis de GOTA ⇑⇑





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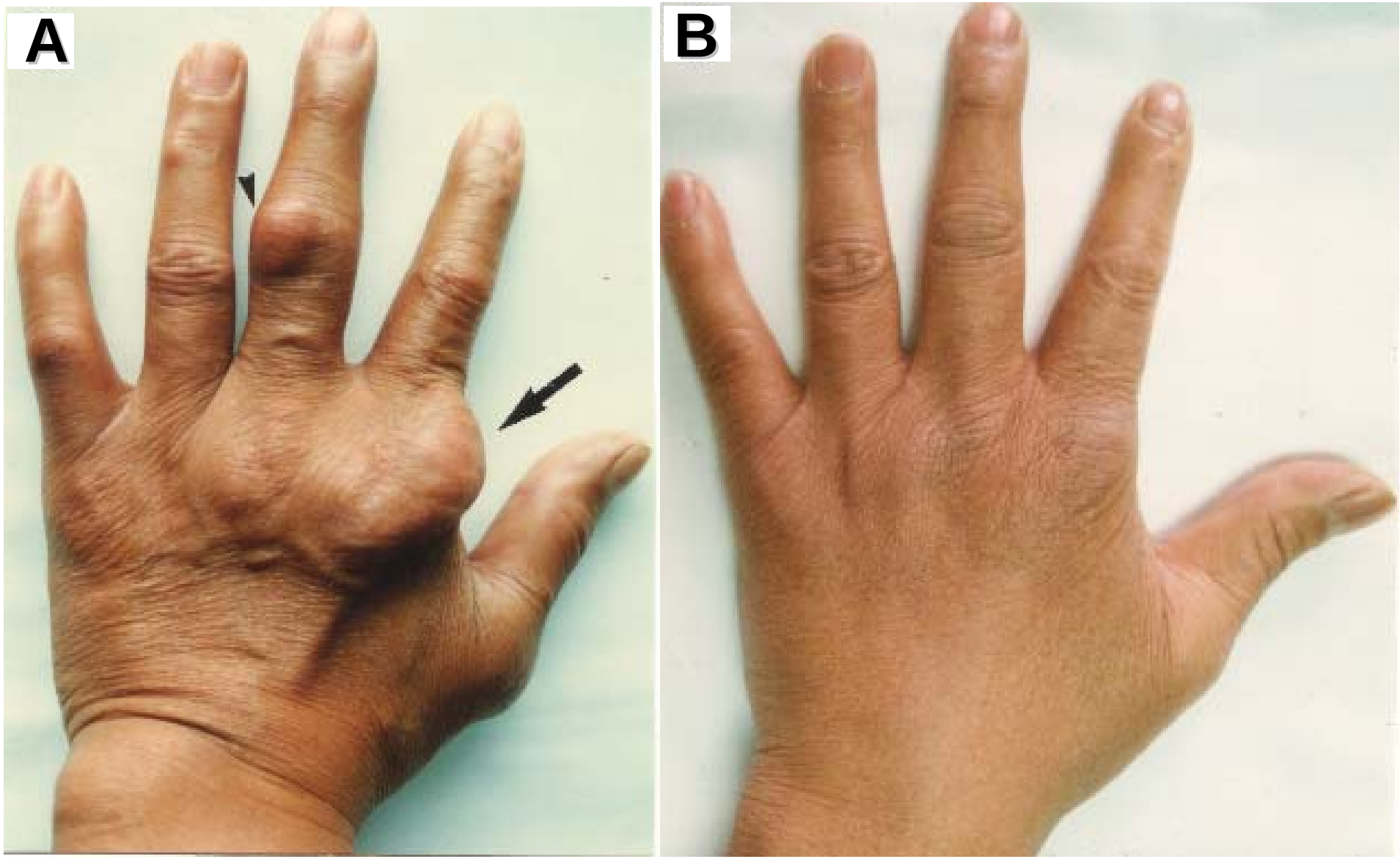
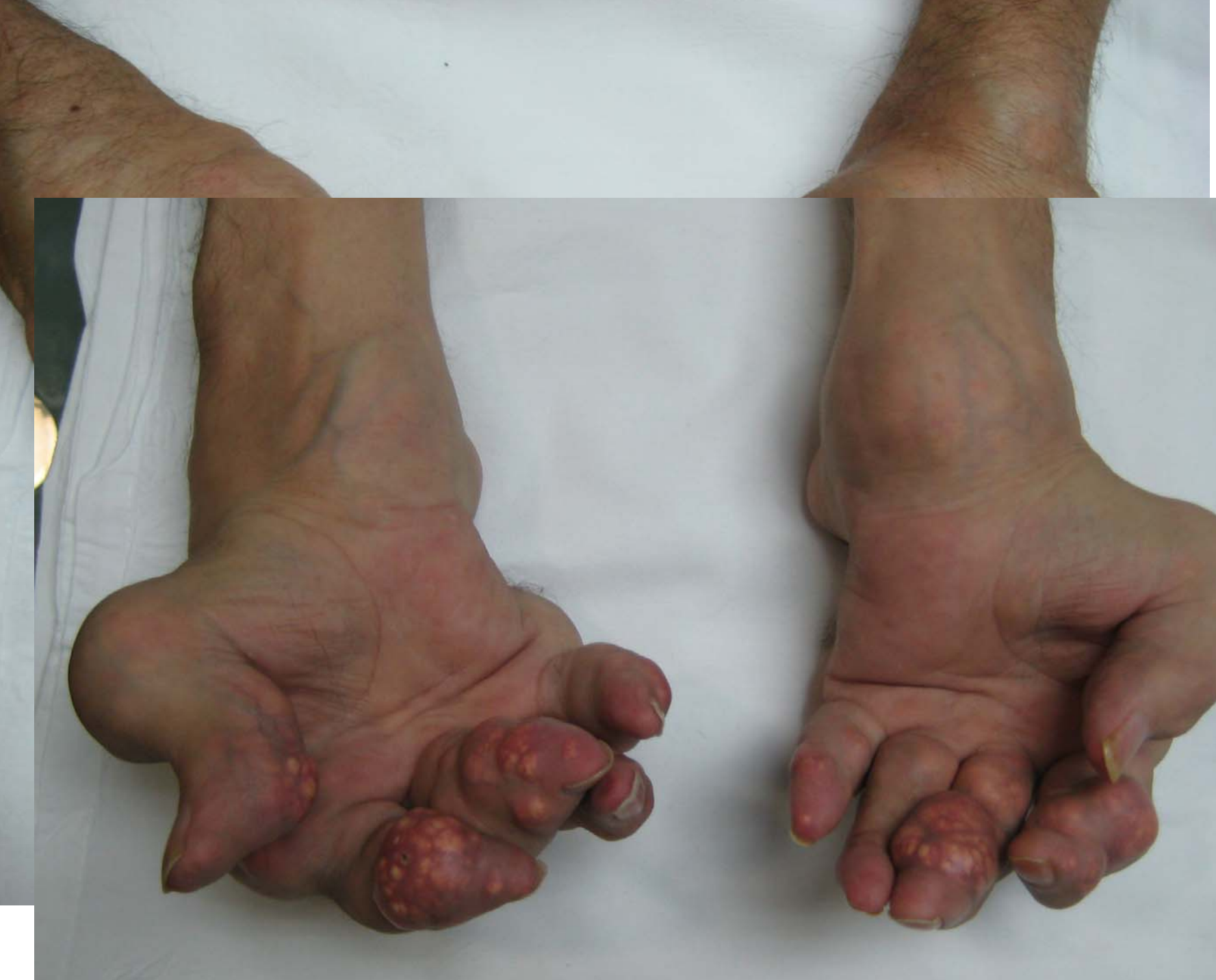
- Bien tolerado
- Cómodo
- Barato

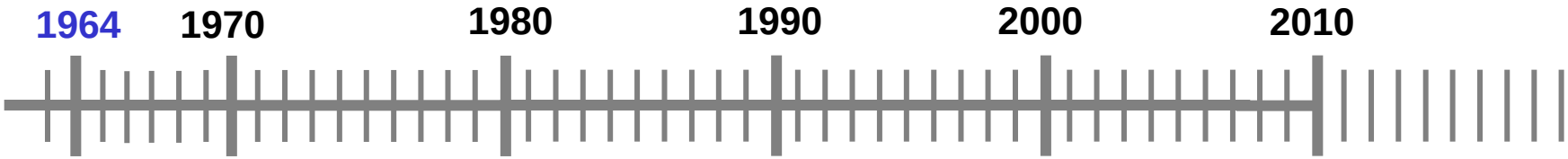
Areas de Mejora

- Crisis de GOTA ↑↑
- Reslc TOFOS ↓↓

Regresión de tofos con alopurinol (2,5 años).







¿Cuántos fármacos siguen … 45 años, sin competidores?

PROPIEDADES

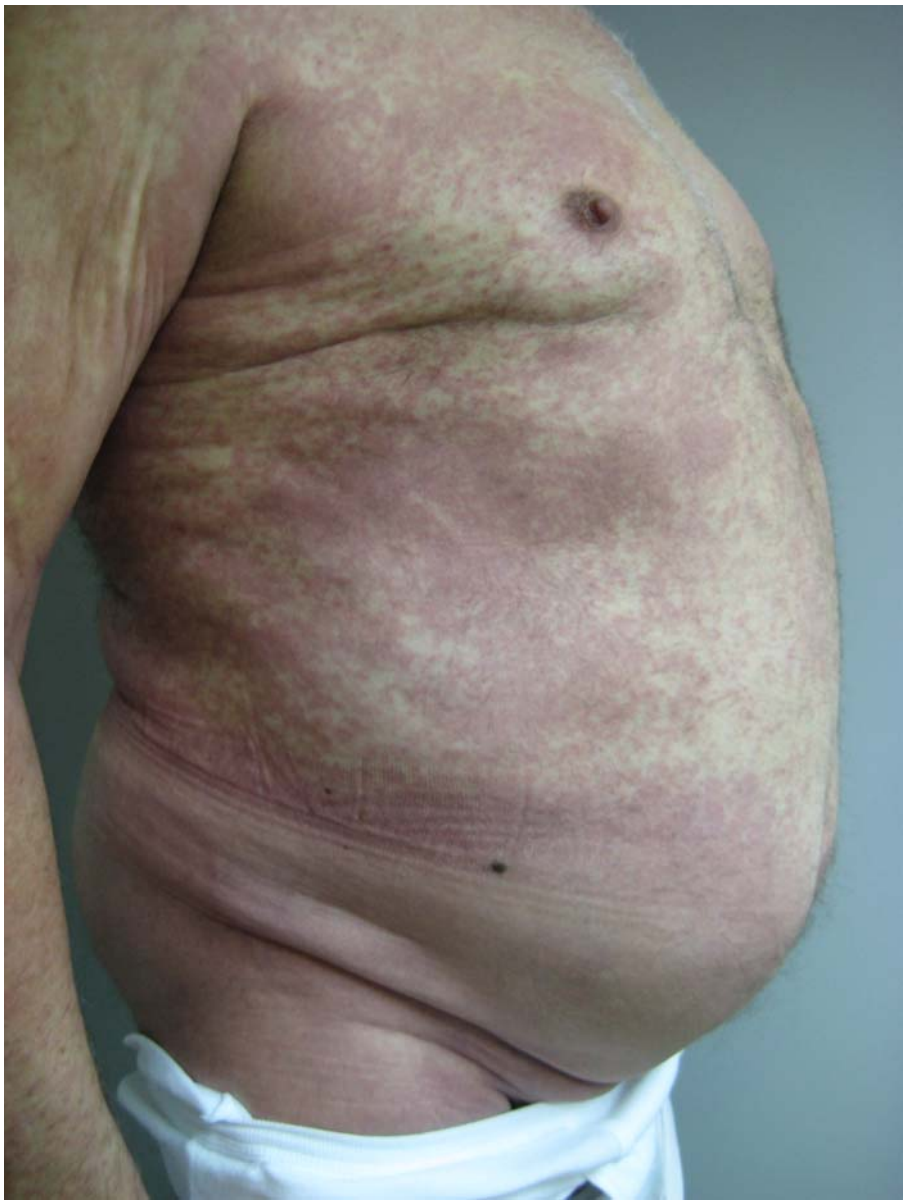
- Muy eficaz
- Bien tolerado
- Cómodo
- Barato

Areas de Mejora

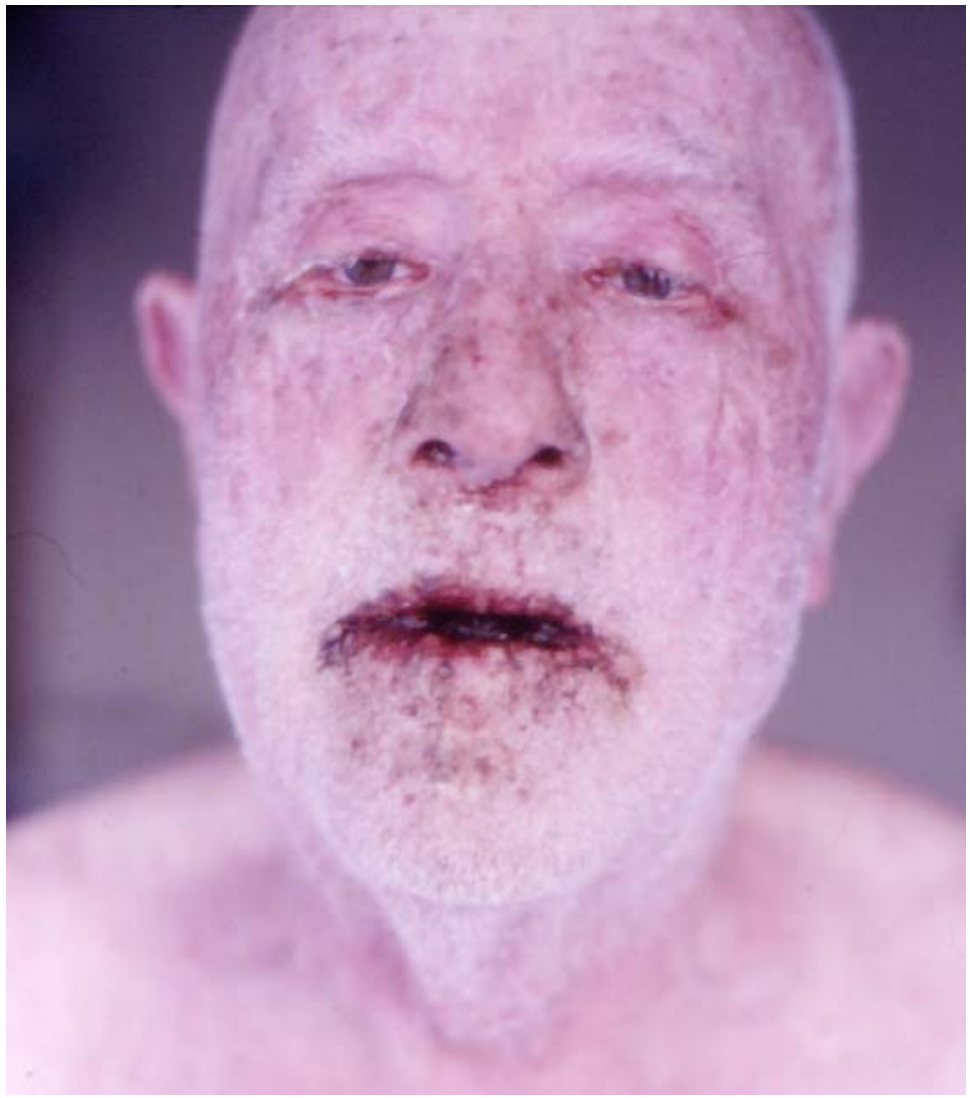
- Crisis de GOTA ⇑⇑
- Reslc TOFOS ⇓⇓

- *Reacc. cutáneas*
- *S. Hipersensib.*
- *Litiasis Xantina*
- *Metab. hepático*
- *Ajuste en IR*

Exantema cutáneo por alopurinol.



S. Hipersensibilidad alopurinol.



THE ALLOPURINOL HYPERSENSITIVITY SYNDROME

Unnecessary Morbidity and Mortality

Arthr Rheum, 1986;29:82-7.

JOYCE Z. SINGER and STANLEY L. WALLACE

Patients receiving allopurinol are at risk of developing the allopurinol hypersensitivity syndrome, an immunologic reaction to the drug, characterized by multiple abnormalities such as fever, rash, decreased renal function, hepatocellular injury, leukocytosis, and eosinophilia. The records of 8 patients with the allopurinol hypersensitivity syndrome evaluated at the Downstate Medical Center hospitals and an additional 72 patients described in the literature were reviewed. All were seriously ill. Three of the 8 patients at the Downstate Medical Center hospitals died as a result of allopurinol hypersensitivity; 19 of the 72 previously described patients also died from consequences of taking the drug. Only 1 of our 8 patients with allopurinol hypersensitivity was given allopurinol for an appropriate reason. Eight of the 59 previously described patients on whom there was adequate information had legitimate indications for allopurinol therapy. Severe, often fatal iatrogenic disease occurred unnecessarily in the others.

Allopurinol (4-hydroxypyrazolo[3,4-d]pyrimidine) was developed in 1956 (1). Initially, it was tested as an adjuvant to increase the therapeutic effectiveness of 6-mercaptopurine in the treatment of leukemia (2). Incidentally, allopurinol was shown to diminish serum uric acid levels by interfering with conversion of hypoxanthine to xanthine and xanthine to uric acid (3).

The results of these early studies led to the release of allopurinol in 1963 as a uric acid–lowering agent. Allopurinol rapidly became widely prescribed. In 1978, the National Prescription Audit reported allopurinol to be the sixtieth most frequently dispensed drug by community pharmacies (4). This drug is also commonly prescribed to hospitalized patients. According to the Boston Collaborative Drug Surveillance Program, of 29,524 patients hospitalized in 22 different hospitals from 1966–1980, 1,835 (6.2%) had received allopurinol (5).

Reports of side effects appeared soon after allopurinol was released. In 1970, the first death directly related to allopurinol was reported (6). In general, harmful effects from allopurinol have been ascribed to toxicity (bone marrow suppression [7,8]), hypersensitivity (rash, hepatic injury, renal injury, eosinophilia, leukocytosis [5,6,9–43]), drug interactions (with ampicillin [44], coumadin [45], and certain cytotoxic agents [46]), idiopathic reactions (icthyosis [47] and retinal lesions [48]), and to dire consequences resulting from the normal therapeutic effects of the drug (xanthine stones [49,50] and increased frequency of gouty attacks [51]).

Sixty-five (3.5%) of the 1,835 hospitalized patients in the Boston Collaborative Drug Surveillance Program who had received allopurinol had harmful reactions which their attending physicians attributed to the drug (5). Seven (11%) of these patients with side effects had reactions considered to be life-threatening. Thus, 1 of every 260 patients treated with allopurinol in these hospitals had a life-threatening reaction as a

Presented in part at the VIII Pan-American Congress of Rheumatology, Washington, DC, June 1982.

From the Divisions of Rheumatology and Internal Medicine, Department of Medicine, State University of New York, Downstate Medical Center, Brooklyn.

Joyce Z. Singer, MD; Stanley L. Wallace, MD, FACP.

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Submitted for publication October 16, 1984; accepted in

MEDICAL INTELLIGENCE

URINARY XANTHINE STONES – A RARE COMPLICATION OF ALLOPURINOL THERAPY*

MARTIN L. GREENE, M.D.,
WILFRED Y. FUJIMOTO, M.D., AND
J. EDWIN SEEGMILLER, M.D.

SINCE its clinical introduction in 1964, allopurinol (4-hydroxypyrazolo-[3,4-d]-pyrimidine) has been increasingly used for the treatment of hyperuricemia of gout,[1,2] many neoplastic diseases and other metabolic disorders. Allopurinol and its principal metabolic product, oxipurinol (alloxanthine, oxoallopurinol), inhibit the enzyme, xanthine oxidase, that normally converts hypoxanthine to xanthine, and xanthine to uric acid. The concentration of these oxypurine precursors of uric acid in blood and urine thus increases in patients treated with allopurinol.

Although the formation of urinary xanthine stones has been anticipated as a possible complication of allopurinol therapy, to date this occurrence has not been documented in the clinical use of allopurinol in recommended dosage in the treatment of gout. This complication of allopurinol therapy would be most likely to occur in a patient with a markedly excessive production of purines. A fivefold to sixfold increase in purine excretion is characteristic of the hereditary disorder of purine metabolism with oxypurines. Administration of allopurinol (Zyloprim), 50 mg 4 times daily, lowered the serum urate concentration to 2.5 mg per 100 ml, with a decrease in 24-hour urinary uric acid to 0.857 mmoles (144 mg) and an increase in the oxypurines to 4.636 mmoles (42 per cent xanthine, 58 per cent hypoxanthine). Subsequent studies demonstrated virtually complete deficiency of hypoxanthine-guanine phosphoribosyl-transferase (PRT) in the patient's erythrocytes, white cells and cultured fibroblasts.[4]

The patient was maintained on allopurinol, 50 mg 4 times daily, multiple vitamins and diazepam (Valium). During February, 1968, he passed several small urinary stones, which were reported by another laboratory to contain uric acid. Because of repeated passage of urinary gravel and chronic urinary infection, cystoscopy was performed on July 1, 1968, by Dr. Charles H. Hemminger, of Northampton, Massachusetts. Three fragments of urinary calculi were recovered from the bladder and submitted for analysis.

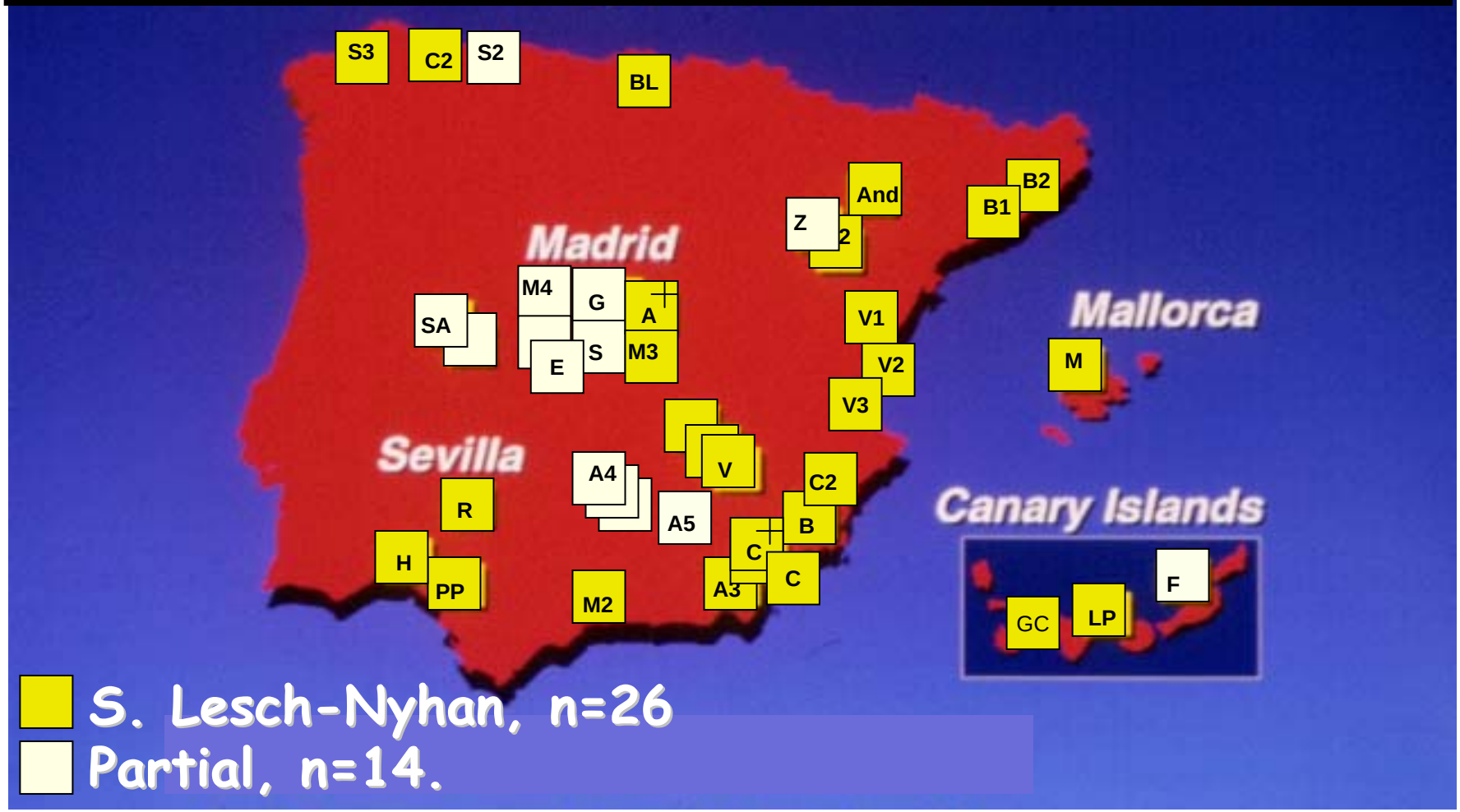
METHODS AND RESULTS

Three yellow-brown stones, weighing a total of 1.0 mg, were dissolved in 10 ml of 0.1 N sodium hydroxide. High-voltage electrophoresis in sodium borate buffer, pH 9.0, indicated the presence of xanthine and a trace of hypoxanthine, as compared with authentic standards. Analysis of the solution for oxypurines by the enzymatic method of Klinenberg et al.[5] indicated that the stones were 85 per cent oxypurines and less than 4 per cent uric acid, by weight.

Xanthine was isolated by column chromatography on Dowex 50, H^+ form, 200-400 mesh, cation-exchange resin with a hydrochloric acid gradient elution. This yielded spectrophotometrically pure xanthine equivalent to 72 per cent of the weight of the dissolved urinary stones. Hypoxanthine (7.4 per cent by weight) was detected in other fractions. Uric acid was less than 1 per cent of the weight of the stones by this technic, and no oxipurinol was detected.

30 Mayo, 2008: Asociación de enfermos con Lesch-Nyhan

HPRT Deficiency
Spanish patients 1984-2010; n=40

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Efficacy and safety of allopurinol in patients with hypoxanthine-guanine phosphoribosyltransferase deficiency

Rosa J. Torres[a,*], Carmen Prior[a], Juan G. Puig[b]

[a]*Division of Clinical Biochemistry, La Paz University Hospital, Madrid, Spain*
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Received 28 October 2006; accepted 5 April 2007

Abstract

Hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency is a genetic disease of purine metabolism resulting in uric acid overproduction. Allopurinol, which inhibits the enzyme xanthine oxidase and reduces uric acid synthesis, is widely used for the treatment of gout and uric acid overproduction. The aim of the study was to analyze the long-term efficacy and safety of allopurinol in patients with HPRT deficiency. Nineteen patients (13 with Lesch-Nyhan syndrome and 6 with partial HPRT deficiency) were treated with allopurinol (mean dose, 6.4 mg/kg body weight per day; range, 3.7-9.7 mg/kg body weight per day) and followed up for at least 12 months (mean follow-up, 7.6 years). The efficacy of allopurinol was evaluated by serial measurement of purine metabolic parameters and renal function as well as by clinical manifestations. Safety was assessed by recording adverse events. Treatment with allopurinol normalized serum urate level in all patients and resulted in a mean reduction in serum urate of 47%. Allopurinol treatment was associated with a mean 74% reduction in urinary uric acid-to-creatinine ratio. In contrast, allopurinol treatment increased mean hypoxanthine and xanthine urinary excretion rates 5.4- and 9.5-fold, respectively, compared with baseline levels. The decrease in uric acid excretion in complete and partial HPRT-deficient patients was not accompanied by a stoichiometric substitution of hypoxanthine and xanthine excretion rates. Allopurinol-related biochemical changes were similar in patients with either complete or partial HPRT deficiency. Renal function remained stable or improved with treatment. Three patients had urolithiasis during allopurinol treatment. In 2 patients, xanthine stones were documented and they required allopurinol dose adjustments aimed at reducing excessive oxypurine excretion rates. No allopurinol hypersensitivity reactions occurred. Neurologic manifestations were not influenced by allopurinol therapy. In conclusion, allopurinol is efficacious and generally safe for the treatment of uric acid overproduction in patients with HPRT deficiencies. Xanthine lithiasis, developing as a consequence of allopurinol therapy, should be preventable by adjustment of allopurinol dose.

Allopurinol Hepatotoxicity

Report of Two Cases and Review of the Literature

F. H. AL-KAWAS, M.D.; L. B. SEEFF, M.D.; R. A. BERENDSON, M.D.; H. J. ZIMMERMAN, M.D.; and K. G. ISHAK, M.D.; Washington, D.C.

Allopurinol hepatotoxicity occurred in two patients. Data from the literature suggest that allopurinol can occasionally cause liver injury, particularly in persons receiving diuretic drugs or with compromised renal function. Clinical and laboratory findings are consistent with hepatocellular injury mediated by a hypersensitivity reaction. Most patients recover when the drug is withdrawn; the possible benefits of corticosteroid treatment remain to be established.

ALLOPURINOL is a xanthine oxidase inhibitor that has been widely used since 1963 to treat patients with symptomatic and asymptomatic hyperuricemia. Approximately 10% of patients who receive allopurinol have minor side effects, such as gastrointestinal distress, diarrhea, fever, and headache (1, 2). More serious side effects, including Stevens-Johnson syndrome (3) and massive hepatic necrosis (4), have also been reported, although far less frequently. Indeed, there are several reports of hepatic injury attributed to allopurinol, but the characteristic pattern remains to be defined (3-14). Two recently encountered instances of hepatic injury apparently caused by allopurinol prompted us to review the relevant literature.

Case Reports

CASE 1

A 66-year-old black man was admitted to the Veterans Administration Medical Center, Washington, D.C., on 15 April 1980 because of fever and skin rash. Medical history included hypertension for 7 years treated with hydrochlorothiazide, 50 mg daily. In February 1980 swelling and severe pain had developed in the right big toe and was diagnosed as gout. Indomethacin, 50 mg three times daily, led to symptomatic improvement. Later his private physician had substituted ibuprofen, 400 mg three times daily.

On 22 March 1980 treatment with allopurinol, 300 mg daily, had been started because the uric acid level was elevated. Three weeks later he developed frontal headache and a skin rash that began on the shoulders and progressed to involve the face, trunk, and extremities. He had continued to take allopurinol, hydrochlorothiazide, and ibuprofen. On admission the temperature was 38.3 °C; blood pressure, 170/100 mm Hg; and pulse, 100/min. A maculopapular rash was noted on the face, trunk, and extremities. Cardiac and pulmonary findings were normal. The liver was not demonstrably enlarged, and there was no adenopathy. Relevant clinical data and initial laboratory data are shown in Tables 1 and 2. The test result for hepatitis B surface antigen (HBsAg) was negative.

On admission all three medications were withdrawn, but fever continued and levels of serum enzymes worsened. "Fever work-up" was negative. Skin biopsy showed perivascular infiltration with mononuclear cells and eosinophils. A presumptive diagnosis of allopurinol hepatotoxicity and persistence of fever and rising enzyme levels led to initiation of treatment with prednisone 6 days after admission. On the following day temperature became normal, and the patient felt better. A liver biopsy done that day showed necrosis involving centrizonal areas, with "drop-out" of cells, collapse of reticulum, and mild infiltration with neutophils and eosinophils. A few sinusoidal acidophilic bodies and foci of ballooning degeneration were seen in several central zones. Kupffer cells were hypertrophied and contained traces of hemosiderin. Portal areas showed moderate inflammation, most cells being eosinophils.

The patient continued to improve, and the prednisone dose was decreased progressively and discontinued on 1 June 1980. On 7 June his aspartate aminotransferase and alanine amino-

▶ From the Veterans Administration Medical Center, Walter Reed Army Medical Center, Armed Forces Institute of Pathology, and the Georgetown University and George Washington University School of Medicine; Washington, D.C.


IQNet
CERTIFICATE

BIOQUIMICA GENERAL

SUERO

SODIO	141	mEq/L
POTASIO	4,7	mEq/L
CLORO	106	mEq/L
GLUCOSA	**151 ***	mg/dL
COLESTEROL TOTAL	104	mg/dL
COLESTEROL HDL	**31 ***	mg/dL
TRIGLICERIDOS	**208 ***	mg/dL
PROTEINAS TOTALES	7,2	g/dL
CALCIO TOTAL	9,7	mg/dL
FOSFATO	4,1	mg/dL
LDH	210	UI/L
ASAT / GOT	**57 ***	UI/L
ALAT / GPT	**81 ***	UI/L
GGT	**80 ***	UI/L
FOSFATASA ALCALINA	76	UI/L
COLINESTERASA	8240	UI/L
URATO	5,4	mg/dL
CREATININA	1,1	mg/dL
BILIRRUBINA TOTAL	0,85	mg/dL

Indice

Indice

1. Acido úrico y Síndrome Metabólico.
   - Hiperuricemia en SM.
   - Marcador de obesidad abdominal.
2. ¿Hiperuricemia asintomática deletérea?
   - NO en población general.
   - Cuidado!! en pacientes con FRCV.
3. Alopurinol: Un gran fármaco!! …..
   - Sin duda … con posibles áreas de mejora.

GRUPO
M A P A
(1993 – 2010)

Grupo MAPA-MADRID (1993-2010).

Reunión, 25 Octubre 2010. nº 174