Letters to the Editor

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To the Editor:

I am writing to express my opinion regarding two articles that attracted my attention and appeared in *Cirugía y Cirujanos*, Number 4, Vol. 77, corresponding to July-August 2009: the first article (p. 255) entitled "Modern medicine and sciences of complexity" by Emilio Arch-Tirado and Javier Rosado-Muñoz and the second (p. 341) entitled "Sciences of complexity and chaos as tools in the analysis of the proliferation of vectors and zoonosis" by the same authors.

I consider it a success publishing articles like these addressing issues that we have heard about but that physicians and surgeons almost always do not understand. The sciences of complexity with multidimensional causality gain importance and application over time. They are involved by chance intrinsic and extrinsic factors, which act not only in a specific place and at a determined time but in different places and over a period of time.

According to the chaos theory the coincidence in time and space can occur to give rise to phenomena of various kinds and whose magnitude is not always in proportion with the origin, as in the flapping of butterfly wings in the Amazon, which coincided with other factors that may lead to a storm in Chicago. This may support the Big Bang theory that 20,000 million years ago gave rise to life, the spread of diseases and epidemics such as leptospirosis, Chagas disease and the epidemic of the H1N1 virus, originating from the human influenza virus. In this respect it is noteworthy to mention the comments emanating from the World Health Organization, in which they mention sciences of complexity, chaos and chance as determinants of such epidemics, endorsing the extent and opportunity of measures taken by public health authorities in Mexico for its control.

The sciences of complexity and chaos influence social, political and economic situations that we experience and that affect us on a daily basis, suffice it to mention events such as the beginning of World War I or an assassination that for various circumstances came to be perpetrated, the Medical Movement of Mexico in 1965 initiated by the grievance and appeals from the residents of a hospital and that could have been solved with simple, inexpensive measures, the student movement of 1968 that begun with the struggle of secondary school and pre-vocational students, what happens in the social and political situation of this time as also happened in Paris and Prague.

The articles written by Drs. Arch-Tirado and Rosado-Muñoz remind us that we have passed from the linearity and reductionism of complex dynamic systems, in which space, time and chance intervene and force us to adopt a more widespread vision not specifically to our specialty. The very complexity makes it essential to the multidisciplinary approach of the current problems within and outside medicine.

The whole is not equal to the sum of its parts. At the end of the second article we are presented with the deterministic equations, the behavior of different variables over time. In reality, I did not understand the whole fractal forms, which forced me to consult with other professionals who know them, understand them, implement them and can explain them. I congratulate the authors and thank them for having made me reflect on the science of complexity, its mathematical representation and its application for health sciences, as well as social sciences and economics, which can direct policies for a more accurate and timely action in all areas of life.

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The radioactive molecule is determinant

To the Editor:
In a recent article published in *Cirugía y Cirujanos*[1] it was stated that tetrofosmin "has the same features but with less cost" and "has a similar behavior and can be used equally" when compared with the lipophilic cation MIBI. These concepts are wrong. Although most of the tetrofosmin accumulates in the cytoplasm and only a small part binds to mitochondrial protein, MIBI is sequestered in the mitochondrial matrix in response to transmembranous potentials associated with mitochondrial activity, providing information on the cellular bioenergy.[2,3] Therefore, MIBI and tetrofosmin do not have "the same biokinetic characteristics."

The literature has shown significant clinical differences between distinct radiocative molecules in the study of various types of malignant tumors of the parathyroid glands and thyroid nodules. In the latter, the negative predictive value (NPV) of tetrofosmin never reaches 100%, whereas MIBI is constantly at 100% (the absence of MIBI uptake in a nonfunctioning thyroid nodule always rules out cancer), a finding that our group reported

in 2004 in a Mexican[4] population and was corroborated in other non-Mexican studies.[5] This finding was recently reproduced prospectively by an independent group in a European population.[6]

Clinically, distinct radioactive molecules are not similar or interchangeable. Unlike tetrofosmin, MIBI does have determinant clinical value, particularly in the evaluation of nonfunctioning thyroid nodules with nondiagnostic fine needle aspiration biopsy.

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References

1. Gallegos-Hernández JF, Pichardo-Romero P, Esparza-Pérez H, Reséndiz-Colosia JA, Minauro-Muñoz GG, Hernández-Hernández DM. Valor de la gammagrafía con Tc-99m-tetrofosmín en el diagnóstico del cáncer bien diferenciado de tiroides. Cir Cir 2009;77:275-278.
2. Younès A, Songadele JA, Maublant J, Platts E, Pickett R, Veyre A. Mechanism of uptake of technetium-tetrofosmin. II: Uptake into isolated adult rat heart mitochondria. J Nucl Cardiol 1995;2:327-333.
3. Chiu ML, Kronauge JF, Piwnica-Worms D. Effect of mitochondrial and plasma membrane potentials on accumulation of hexakis (2 methoxyiso-butylisonitrile) technetium(I) in cultured mouse fibroblasts. J Nucl Med 1990;31:1646-1653.
4. Hurtado-López LM, Arellano-Montaño S, Torres-Acosta EM, Zaldívar-Ramírez FR, Duarte-Torres RM, Alonso-De-Ruiz P, et al. Combined use of fine-needle aspiration biopsy, MIBI scans and frozen section biopsy offers the best diagnostic accuracy in the assessment of the hypofunctioning solitary thyroid nodule. Eur J Nucl Med Mol Imaging 2004;31:1273-1279.
5. Hurtado-López LM, Martínez-Duncker C. Negative MIBI thyroid scans exclude differentiated and medullary thyroid cancer in 100% of patients with hypofunctioning thyroid nodules. Eur J Nucl Med Mol Imaging 2007;34:1701-1703.
6. Giovanella L, Suriano S, Maffioli M, Ceriani L, Spriano G. ^{99m}Tc-sestamibi scanning in thyroid nodules with nondiagnostic cytology. Head Neck 2009 Aug 19. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19693945

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It is an honor for us that our manuscript has been the subject of a Letter to the Editor sent by such distinguished professionals. The following is in response, clarifying a number of inaccuracies in the letter:

1. Nowhere in the article was it stated that tetrofosmin (TFM) has the same characteristics and biokinetic behavior as MIBI. It is stated that upon clinical evaluation they have a similar behavior as well as sharing many biological properties. This is based on existing information.[1-3]
   Both are lipophilic cationic agents used interchangeably in myocardial perfusion studies and are the most useful organotechnetium compounds in the study of various neoplasms.[4,7] Both agents, in studies performed in cell cultures,[8-10] have confirmed to be a substrate of the surface glycoprotein Pgp, and both being lipophilic cationic complexes behave as a substrate that is incorporated into the tumor cell through a pump directly dependent on the presence of Pgp in cytoplasmic membrane.[11,12]
   This implies that the outcome in the clinical evaluation of different malignancies is similar. Arbab et al.,[13] after evaluating the uptake of TFM, MIBI, and thallium on tumor cell lines, concluded that the three tracers indicate (without difference) cell viability, although the uptake of the first depends on the mitochondrial membrane potential and the second of mitochondrial accumulation. Based on their results, these authors concluded that both compounds (TFM and MIBI) can be used as "tumor imaging agents."
2. When comparing the clinical usefulness of both agents in detecting tumors, results show no difference between them, and they may be used interchangeably.[14] There is no information in the literature for concluding that the negative predictive value (NPV) of TFM is never 100% as is MIBI; however, based on current evidence we cannot conclude, as argued by the authors of the letter, that a negative MIBI rules out thyroid cancer. Although the false negative rate is very low in general, figures of 58%[14] have been reported with a specificity of 73% and NPV of 92-97%.[15,16]
3. Without basing their comments on bibliographical references, the authors assure that there are differences between the two radiopharmaceuticals in the study of various tumors, which is not true. The exceptions are parathyroid adenomas, which are excluded because the aim is to ascertain the usefulness of these compounds in order to rule out cancer. It has been shown that TFM is a radiotracer that is incorporated in various tumors such as hepatocellular carcinoma,[17] thyroid cancer,[18,19] mediastinal tumors,[20] soft tissue sarcoma and osteosarcoma,[21-24] breast cancer (where it plays an important role especially in patients with high-density mammograms that are difficult to assess and during the investigation of high-risk patients and evaluation of recurrence)[25-28] and non-small cell bronchogenic carcinoma.[29-32]

Based on this information, we can conclude that TFM has an important role in the evaluation of various neoplasms, similar to MIBI and without the high cost. Evaluation of thyroid nodule is not the exception.

Based on existing data, we may conclude that both components produce similar results. Although there are reports that the NPV with MIBI is 100%, in general it is not so, such as occurs with

TFM. This may be explained by the patient selection. It is also logical because there are well-differentiated malignant thyroid neoplasms and the only way to distinguish a follicular adenoma is complete capsular evaluation and the presence of lymph invasion in the hematoxylin/eosin analysis. Additionally, there are incidentalomas immersed in benign thyroid nodules. In both situations histopathological analysis alone confirms the diagnosis of carcinoma.

For all the above reasons and as mentioned in our manuscript, evaluation of a thyroid nodule with MIBI/TFM is subject to clinical and ultrasound findings and outcome of fine needle aspiration biopsy and directed to those patients in which none of above parameters indicate surgery. Surveillance is an alternative within the diagnostic and therapeutic schema of the thyroid nodule.

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Referencias

1. Choi JY, Kim SE, Shin HJ, Kim BT, Kim JH. Brain tumor imaging with 99mTc-tetrofosmin: comparison with Tl-201, 99mTc-MIBI and 18F-fluorodeoxyglucose. J Neurooncol 2000;46: 63-70.
2. Pauwels EK, McCready VR, Stoot JH, Van Deurzen DF. The mechanism of accumulation of tumor localizing radiopharmaceuticals. Eur J Nucl Med 1998;25:277-305.
3. Schomäcker K, Schicha H. Use of myocardial imaging agents for tumor diagnosis; a success story? Eur J Nucl Med 2000;27:1845-1863.
4. Kostakoglu L, Kiratli P, Ruacan S, Hayran M, Emri S, Ergün EL, et al. Association of tumor washout rates and accumulation of technetium-99m-MIBI with expression of P-glycoprotein in lung cancer. J Nucl Med 1998;39: 228-234.
5. Nosotti M, Santambrogio L, Gasparini M, Baisi A, Bellaviti N, Rosso L. Role of ^{99m}Tc-hexakis-2-methoxy-isobutylisonitrile in the diagnosis and staging of lung cancer. Chest 2002;122:1362-1364.
6. Dadparvar S, Chevres A, Tulchinsky M, Krishna-Badrinath L, Khan AS, Slizofski WJ. Clinical utility of Tc-99M methoxisobutylisonitrile imaging in differentiated thyroid carcinoma. Comparison with thallium-2O1 and I-131 Na scintigraphy, and serum thyroglobulin quantitation. Eur J Nucl Med Mol I 1995;22:1330-1338.
7. Basoglu T, Sahin M, Co kun C, Koparan A, Bernay I, Erkan L. Technetium-99m-tetrofosmin uptake in malignant lung tumors. Eur J Nucl Med Mol I 1995;22:687-689.
8. Piwnica-Worms D, Chiu ML, Budding M, Kronauge JF, Kramer RA, Croop JM. Functional imaging of multidrug-resistant P-glycoprotein with an organotechnetium complex. Cancer Res 1993;53:977-984.
9. Ballinger JR, Muzzammil T, Moore MJ. Technetium-99m-furifosmin as an agent for functional imaging of multidrug resistance in tumors. J Nucl Med 1997;38:1915-1919.
10. Ballinger JR, Bannerman J, Boxen I, Firby P, Hartman NG, Moore MJ. Technetium-99m-tetrofosmin as a substrate for P-glycoprotein: in vitro studies in multidrug resistant breast tumor cells. J Nucl Med 1996; 37:1578-1582.
11. Hendrikse NH, Franssen EJ, van der Graaf WT, Vaalburg W, de Vries EG. Visualization of multidrug resistance in vivo. Eur J Nucl Med Mol I 1999;26:283-293.
12. Sun SS, Hsieh JF, Tsai SC, Ho YJ, Kao CH. Technetium-99m tetrofosmin mammoscintigraphy findings related to the expression of P-glycoprotein mediated multidrug resistance. Anticancer Res 2000;20:1467-1470.
13. Arbab AS, Koizumi K, Toyama K, Araki T. Uptaker of technetium-99m-tetrofosmin, technetium-99m-MIBI and thallium-201 in tumor cell lines. J Nucl Med 1996;37:1551-1556.
14. Klain M, Maurea S, Cuocolo A, Colao A, Marzano L, Lombardi G. Technetium-99m tetrofosmin imaging in thyroid diseases: comparison with Tc-99m-pertechnetate, thallium-201 and Tc-99m-methoxyisobutiylisonitrile scans. Eur J Nucl Med 1996;23:1568-1574.
15. Kresnik E, Gallowitsch H-J, Mikosch, Gomez I, Lind P. Technetium-99m-MIBI scintigraphy of thyroid nodules in an endemic goiter area. J Nucl Med 1997;38:62-65.
16. Sathekge MM, Mageza RB, Muthuphei MN, Modiba MC, Clauss RC. Evaluation of thyroid nodules with technetium-99m MIBI and technetium-99m pertechnetate. Head and Neck 2001;23:305-310.
17. Ding HJ, Huang WT, Tsai CS, Chang CS, Kao A. Usefulness of technetium-99m tetrofosmin liver imaging to detect hepatocellular carcinoma and related to expression of Pglycoprotein or multidrug resistance associated protein¾a preliminary report. Nucl Med Biol 2003;30:471-475.
18. Kosuda S, Yokoyama H, Katayama M, Yokokawa T, Kusano S, Yamamoto O. Tc-99m tetrofosmin and Tc-99m sestamibi imaging of multiple metastases from differentiated thyroid carcinoma. Eur J Nucl Med Mol I 1995;22:1218-1220.
19. Nemec J, Nyvltová O, Preiningerová M, Vlcek P, Racek P, Novák Z, et al. Positive thyroid cancer scintigraphy using Tc-99^m-tetrofosmin (myoview). A preliminary report. Nucl Med Commun 1995;16:694-697.
20. Ishibashi M, Fujimoto K, Ohzono H, Meno S, Hayabuchi N. 99m-Tc tetrofosmin uptake in mediastinal tumours. Br J Radiol 1996;69:1134-1138.
21. Karanikas G, Köstler WJ, Becherer A, Wiesner K, Dudczak R, Krainer M, et al. Technetium-99m-tetrofosmin scintigraphy in patients with metastatic soft tissue sarcoma. Oncol Rep 2002;9:1009-1013, 139.
22. Rodrigues M, Chehne F, Kalinowska W, Zielinski Ch. Comparative Tc-99m-MIBI, Tc-99m-tetrofosmin and Tc-99m-furifosmin uptake in human soft tissue sarcoma cell lines. Eur J Nucl Med Mol I 2000;27:1839-1843.
23. Schillaci O, Spanau A, Scopinaro F, Montelone F, Masala S, Tarantino U, et al. Technetium-99m tetrofosmin scintigraphy in pediatric osteogenic sarcoma. Oncol Rep 2003;10:605-608.
24. Söderlund V, Jonsson C, Bauer HC, Brosjö O, Jacobsson H. Comparison of technetium-99m- MIBI and technetium-99m-tetrofosmin uptake by musculoskeletal sarcomas. J Nucl Med 1997;38:682-686.
25. Schillaci O, Buscombe J. Breast scintigraphy today: indications and limitations. Eur J Nucl Med Mol I 2004;31(suppl1):S35-S45.
26. Spanu A, Farris A, Schillaci O, Chessa F, Solinas ME, Falchi A, et al. The usefulness of Tc-99m tetrofosmin scintigraphy in patients with breast cancer recurrences. Nucl Med Commun 2003;24:145-154, 144.
27. Rambaldi PF, Mansi L, Procaccini E, Di Gregorio F, Del Vecchio E. Breast-cancer detection with Tc-99m tetrofosmin. Clin Nucl Med 1995;20:703-705.
28. Mansi L, Rambaldi PF, Procaccini E, Gregorio FD, Laprovitera A, Pecori B, et al. Scintimammography with technetium-99m tetrofosmin in the diagnosis of breast cancer and lymph node metastases. Eur J Nucl Med Mol I 1996;23:932-939.

29. Tabuenca MJ, Vargas JA, Varela A, Salas C, Ramón y Cajal S, Durántez A, et al. Inverse correlation between Tc-99m tetrofosmin uptake and P-glycoprotein in non-small cell lung cancer. J Nucl Med 1999;40:1223-1224.
30. Tabuenca MJ, Vargas JA, Varela A, Salas C, Durántez A, Ortiz-Berrocal J. Technetium-99m-tetrofosmin scintigraphy, P-glycoprotein and lung cancer. J Nucl Med 1998;39:1830-1831.
31. Fuster D, Viñolas N, Mallafre C, Pavia J, Martin F, Pons F. Tetrofosmin as predictor of tumour response. Q J Nucl Med 2003;47:58-62.
32. Basoglu T, Bernay I, Coskun C, Canbaz F, Talu A, Erkan L. Pulmonary Tc-99m tetrofosmin imaging: clinical experience with detecting malignant lesions and monitoring response to therapy. Clin Nucl Med 1998;23:753-757.