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Bismuth Encephalopathy: A Model of Metal Toxicity

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Abstract

In 1974 some articles in the Australian medical press raised the question of the toxicity of bismuth subgallate administered to ileostomized patients. Somewhat earlier in France, similar cases of myoclonic encephalopathy were formally linked to the oral ingestion of bismuth salts by focusing on the dosage of the metal in the blood, urine and cerebrospinal fluid (CSF). However, whereas Australia immediately banned the use of bismuth, cases of intoxication in France continued for another four years despite health warnings which eventually led to its ban in 1978. Some cases can still be observed in certain countries. An outside factor was evoked concerning the unexpected absorption of bismuth salts. About 50 years later, the origin of this phenomenon can most likely be linked to the purity - micronization of the metal and his higher degree of solubility in acid pH mineral waters. In France a geographic link can be established between the consumption of mineral water and cases of bismuth encephalopathy. The utilization of bismuth salts today is almost limited to the treatment of gastric ulcer and the association with some mineral waters should be avoided. Some others metals could be influenced by this phenomenon and perhaps take a part in brain dysfunction.

Keywords: Bismuth; metal toxicity; myoclonic encephalopathy; mineral water; micronization.

Introduction

Sometimes, in a Latin country where high level influences can delay for years the elementary precautions, a major side effect was not decisive to forbid the use of a drug. The following article relates facts dating back to 50 years or even more as retrospective cases, unnoticed at the time. Bismuth intoxication cases were then very frequent in Australia and France, almost epidemic, and are still possible elsewhere in the world today. The orally consumption of this metal had increased during the years following World War II (mostly the intake of inorganic salts for digestive disorders) but, as it was said to be insoluble after ingestion, the risk of intoxication appeared underestimate. The proof of this responsibility needs to measure bismuth concentration in body fluids (blood, urine, CSF) when happen a myoclonic encephalopathy or an unexplained change in awareness or a subacute astasia-abasia. For a mysterious reason, the real cause has never been found : why a medication used since many centuries become unforeseeable ? Does the same increasing of mineral waters consumption in these years also play a part ? Looking for the explanation of this pathology must continue because it can be a model of neurotoxicity and we should like to modestly contribute in this undertaking.

Historical Background

Let us take into consideration the retrospective study of the Australian Drug Evaluation Committee [1] concerning 24 cases with comparable clinical pictures: 1 case in 1968, 5 in 1970, 5 in 1971, 1 in 1973, 4 in 1974. Already, and as from 1972 some of these cases had been reported by the Association of Colostomies Patients of Victoria, [2] but the publication went unnoticed and anyhow unexpected. It was not the same with the article [3] of R. Burns, D.W. Thomas and V.J. Barron in the British Medical Journal of February 9, 1974 on *Reversible Encephalopathy Possibly Associated with Bismuth Subgallate Ingestion* which had fixed our attention on the reality of the toxicity. The evidence of this is what we endeavoured to disclose.

Indeed, a 62 year old female patient was admitted to the Paris Hospital La Salpêtrière on 10 January 1974 in a neurology department headed by Prof. A. Buge for an obscure case of myoclonic encephalopathy. The origin was most puzzling and the various causes systematically rejected. A brain biopsy was deemed necessary in order to discover a possible case of Creutzfeldt-Jakob disease. Meanwhile, what was discovered was the unexpected presence of a radio-opaque product under the diaphragm showing up on the chest X-ray and the abdomen X-ray without preparation. The question was thus raised on the supposed responsibility of an intestinal lining (bismuth salts ? Not known by her family) affecting a woman suffering from constipation with megadolichocolon. Used to seeking toxic elements in body fluids, it seemed judicious to inquire if there was detectable bismuth in the blood, urine and CSF of the patient. A technique was conceived for this purpose because bismuth salts via oral ingestion were then considered as insoluble and not absorbable. The laboratory there developed the method [4] and the result for the same patient on 31 January 1974 was : bismuth concentration in the blood at 135 µg/ L. It was indeed the proof of the responsibility of the metal. In comparison with the slow recovery, there was also a major consequence for the patient : bilateral osteonecrosis of the two humeral heads.

We shall not delve into the too well-known symptomatology of myoclonic encephalopathies described in a number of publications [5-6] and which enables the physician to discover further cases, reference to this being for instance new cases in 2012 [7] and 2019 [8]. Likewise, the necessity of bismuth dosage is obvious in order to determine the diagnosis, but the presence of the metal in the body fluid varies considerably from one individual to another. There is no high concentration of bismuth in the blood in order to be certain that there is no risk of future encephalopathy. The bismuth concentration in CSF is a better indicator for neurological disorders and decreases with time and favorable evolution.

Official inquiry in France

An epidemiological study of bismuth encephalopathies by the « Institut National de la Santé et de la Recherche Médicale (INSERM) » (National Institute for Health and Medical Research) was commissioned as from 1975 to identify 945 cases, of which 72 deaths. A detailed report first published in French in 1980 [9] and in English [10] the following year made it clear that the totality of bismuth salts was concerned and that the « explosive » period 1974-1975 was not due only to higher sales (figure 1).

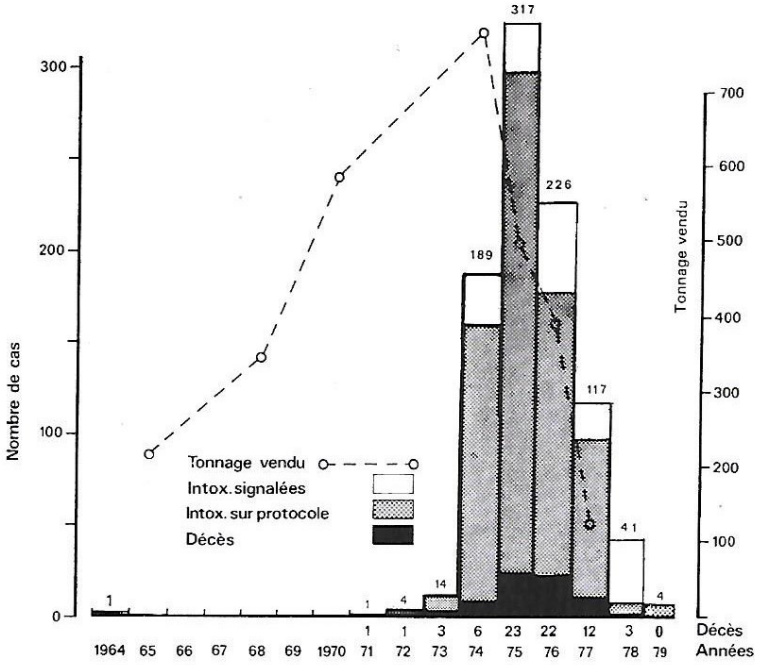

Figure 1: an indication of intoxications in time corresponding to sales of bismuth by the ton: on the left vertical scale = number of cases; on the right = sales in ton; below deaths by year from 1964 to 1979 (according to reference 10, a study of 915 cases in France for this figure).

Geographical zones localizing cases of bismuth intoxications vary from one part of the national territory to another with peaks in the central and western parts and fewer cases in the eastern and the southern parts (figure 2).

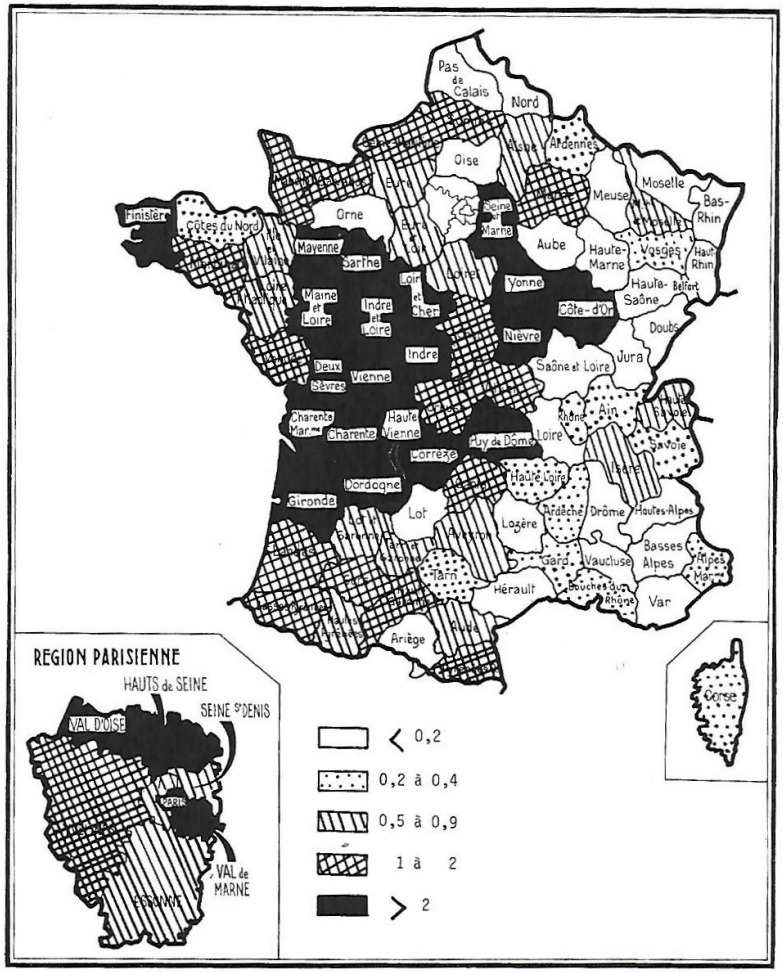

Figure 2: geographical indication of bismuth intoxications in France : in white, less than 0.2 cases/100,000 inhabitants ; in black, more than 2 cases/100,000 inhabitants ; in left corner : Paris region [according to reference 10 : morbidity rate for 100,000 inhabitants (1964-1977)].

As a comparison, the geographical distribution of sales of bismuth salts vary and are more localized in the eastern and southern regions (figure 3).

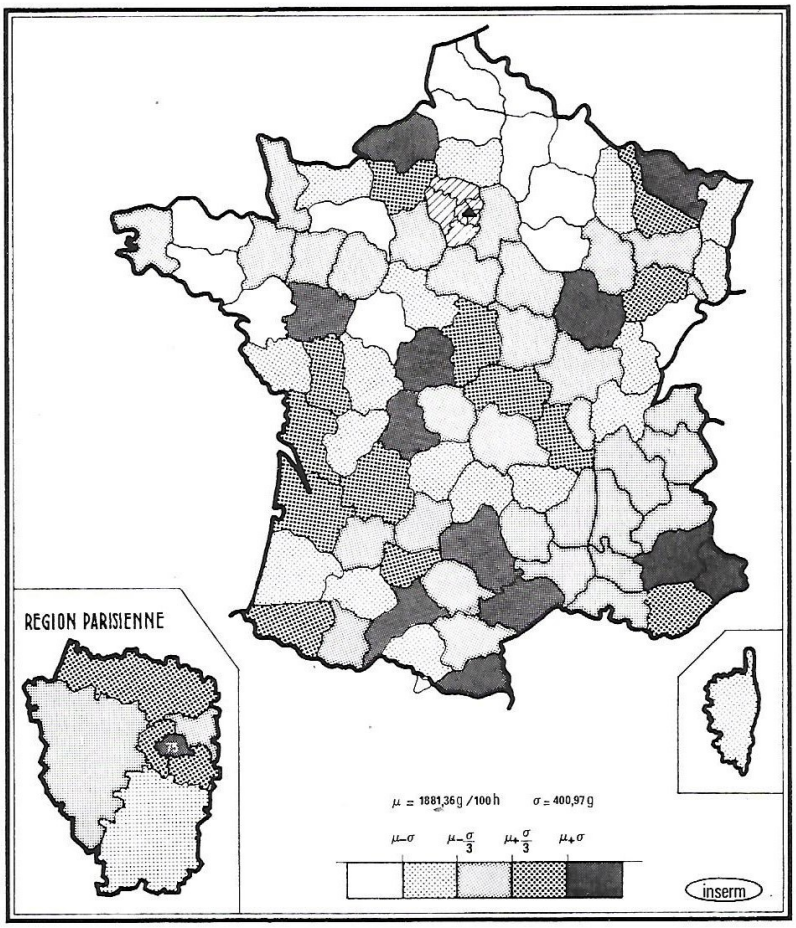

Figure 3: geographical indication for all types of bismuth sales in France for the year 1974 : white zones corresponding to minimum, dark grey to maximum (according to reference 10 : INSERM inquiry).

The authors concluded that there was no link with a fabrication error, or a modification in the presentation of bismuth salts, no relation between the quantity of bismuth consumed and the observable cases, no relation with the duration of the bismuth treatment. They suspected the effects of an outside factor (such as intestinal flora) with the capacity of modifying bismuth salts into a toxic substance, for example trimethyl bismuth. This theory did not take into account Australian ileostomized patients and not even the case of a French colectomized patient [11]. Further experiments with rats with or without various intestinal flora did not show any difference in the absorption of the metal.The extreme micronization of the very pure metal was not considered.

Suggested Hypothesis

The responsibility of all types of bismuth salts orally ingested could be retained for the future: their purity is guaranteed at 99,99 %. Some salts are micronized as a powder with a grain size between 1 to 5 μ and it exists a polymorphism crystalline which can interfere with it dissolving. Neuropathological and toxicological studies in deceased patients revealed a high level of bismuth in the brain like in the neocortex, cerebellum, thalamus and hippocampus [12] (from 2-8 mg/kg to 25 mg/kg), focal areas of bismuth in the leptomeningeal space and a lymphocytic periveinulaire infiltration. These lesions are identical to those provoked in a mouse by an intraperitoneal injection of bismuth subnitrate with, observable by electron microscopy, an expansion of extracellular spaces [13].

In a study on the absorption of bismuth with six different salts, five healthy volunteers were used to find a serum concentration of bismuth [14] of 0.6 μg/L up to 9.1 μg/L during a time span of 20 to 60 minutes with major variations from individual to individual.

After an ingested dose, colloidal bismuth subcitrate provokes the highest concentration in the blood during the first six hours, as much as basic bismuth gallate. The elimination of bismuth in urine in 48 hours reflects with a very good correlation serum bismuth concentrations during the six hours following the ingestion.

This rapid absorption was confirmed by an examination [15] by electronic microscope of the mucus membrane of the stomach via biopsy 30-60 minutes after 5 patients had orally taken tripotassium dicitrato bismuthane (De-Nol tab®): a transmucosal penetration of bismuth particles was observed but went unnoticed with bismuth salicylate with 5 other patients.

It is clear that the presence of low pH in the oesophagus and the stomach can influence this phenomenon and a concomittant consumption of mineral waters containing acid pH rather than tap water would favour the solubility of bismuth salts.

As it was pointed out as from 1976, a suspension of 2 grammes of bismuth subnitrate in 100 cubic centimetres of water agitated for 3 continuous hours leads to a deposit [16] using a Millipore membrane with diameter pores of 0.2 µ. The bismuth is rendered soluble with a concentration varying from 0.54 mg/L in tap water with pH varying from 6.5 to 8.1 to over 200 mg/L in various mineral waters with low pH.

In an article on the consumption of mineral waters in France [17] one observes a tripling of the quantity during the period 1961-1971 (figure 4) as well as the geographical locations of this consumption (figure 5) somewhat corresponding to cases of bismuth encephalopathies (figure 2).

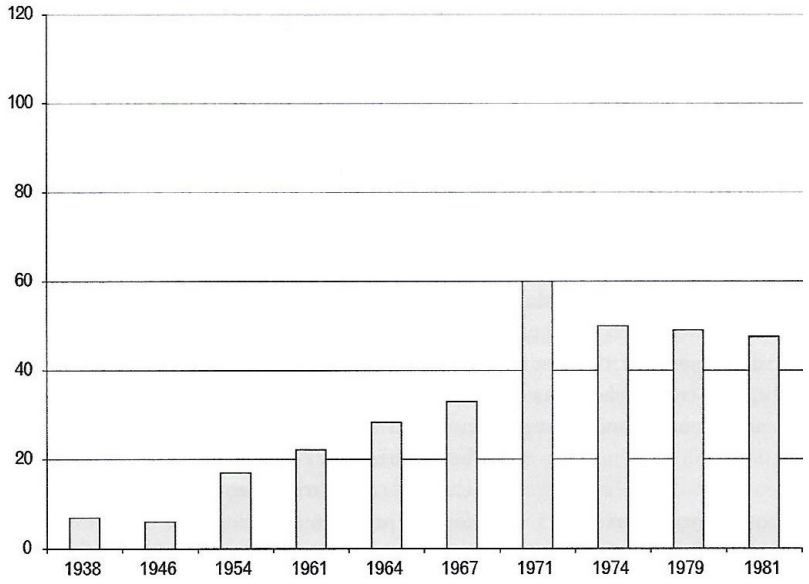

Figure 4: the tripling of mineral water consumption in France (1961-1971) : in ordinate : litres per year by inhabitant ; in abscissa : time in years from1938 to 1981 (according to reference 17 : mineral water consumption by litre/ inhabitant and per annum).

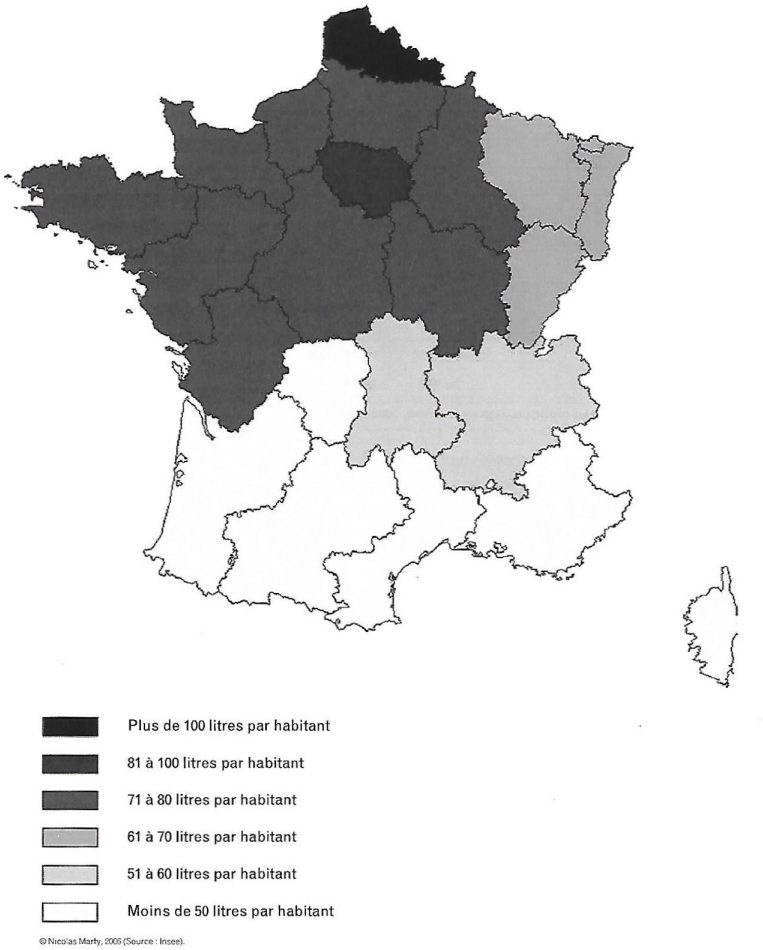

Figure 5: geographical locations for the consumption of mineral waters : white, less than 50 litres/year/inhabitant, black, more than 100 litres/year/inhabitant (according to reference 17 : consumption of bottled water in 1989).

The people in the southern part of France consumes much more tap water than mineral water.

It would be interesting to know how the consumption of mineral waters has spread in Australia with over 1,000 brands, especially during the epidemic of bismuth encephalopathies some 50 years ago. What did Australian patients then drink, pH acid mineral water or not ?

The last case in France was published in 1987 [18] and it concerned a 58-year-old man who took 10 grammes of bismuth subnitrate (purchased in a foreign country) twice a day ; bismuth concentration in blood was 550 µg/L. He told the authors of this article at his Paris home in March 2021 (our gratitude to Prof. B. Wechsler who arranged the meeting) that he drank mineral water 4 times a day, corresponding to 1.5 litres of sparkling Perrier® mineral water (pH=5.5) during the bismuth intoxication period … which he continues to do up to this day … without bismuth, and today at 91 he is totally compos mentis!

The phenomenon could also happen for the digestive absorption of aluminium or copper. It is necessary to be sure that it is safe to associate them with sparkling mineral waters.

Conclusion

The spread of bismuth encephalopathy cases in the 1970s remains a mystery for the investigators [19] despite a number of hypotheses evoked over the years, especially an intestinal outside factor rendering bismuth toxic in the form of trimethyl bismuth. An increase in the consumption of bismuth salts with daily ingestions and an improvement in the metal purety, better « micronized » for certain salts, could explain in part the phenomenon responsible for these cases. But upon reflexion, the rapid absorption of the metal could possibly depend more on the upper part of the digestive tract than on the intestine. The influence of a lower level pH in the oesophagus and the stomach by sparkling mineral or spring water is a debatable subject. Anyway, it must be stressed that the geographical location of the intoxications in France approximately corresponded to the regional sales of mineral waters

Today, the trend is to promote bismuth in quadritherapy to overcome the resistance of Helicobacter Pylori [20]. Patients should be warned of the dangers in associating bismuth with pH acid mineral waters. It must also be stressed that the tracking down of bismuth concentrations in body fluids is not sufficient to prevent the danger of brain toxicity. The fact must also be made clear that sporadic cases of myoclonic encephalopathies observed in recent years were linked to bismuth sales on the internet. The open access to bismuth purchase by internet to the general public needs to be seriously re-examined.

Acknowledgment

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