

This section looks back to some ground-breaking contributions to public health, reproducing them in their original form and adding a commentary on their significance from a modern-day perspective. To coincide with World No-Tobacco Day, Robert N Proctor reviews experimental tobacco carcinogenesis in the 1920s–1940s with special reference to the work of Angel H Roffo. One of Roffo's papers is reproduced and translated in this issue of the *Bulletin*.

# Angel H Roffo: the forgotten father of experimental tobacco carcinogenesis

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Angel Honorio Roffo of Argentina (1882–1947) was one of the first to publish detailed accounts of animal experiments demonstrating the production of tumours by tobacco tars. As founding director of the Instituto de Medicina Experimental para el Estudio y Tratamiento del Cáncer, established in 1922 in Buenos Aires, he was able to examine and treat a large population of cancer patients, from whom he had learned by the end of the 1920s that smoking was a cause of many kinds of cancer.<sup>1</sup> During the next decade and into the early 1940s he published a series of ambitious papers pioneering the field of experimental tobacco carcinogenesis, blending experimental, clinical and statistical reasoning with a strong sense that many of the world's most common cancers could be prevented. Using a number of different experimental methods, Roffo showed that cancers all along the “smoking highway” (lips, tongue, throat, cheek, bronchial passages, etc.) must be caused by exposure to tars released in the course of smoking; he was also one of the first to realize that smoking could cause bladder cancer.

Roffo's work is interesting for a number of different reasons. For one thing, there is his defence of the use of experiments to investigate tobacco carcinogenesis — as if clinical observations had already proved the point. In 1931, writing in the *Zeitschrift für Krebsforschung* (he published much of his work in German), he noted that while there were cases in which tobacco was clearly

to blame for the onset of certain malignancies (from clinical observations) it was nonetheless useful to document the phenomenon more generally by animal experiments.<sup>2</sup> Reasoning by analogy from the production of cancer using coal tars, he argued that the carcinogens in tobacco smoke must be the complex, tarry, polycyclic aromatic hydrocarbons, rather than the (chemically simpler) inorganic constituents or the alkaloid nicotine. To test this hypothesis, Roffo separated tobacco smoke into three separate distillation products, which he rubbed onto the ears of three groups of 10 rabbits each. He found that the tarry fractions produced cancers but that when nicotine alone was applied no cancers were produced, no matter how long he waited. The same (no cancerous effect) was true from the various inorganic components he had isolated from smoke, including salts such as ammonium chloride but also carbon monoxide and carbon dioxide.<sup>2</sup>

Roffo ran many similar tests using different methods of preparing tobacco extracts, different fractions of tobacco tars, and different species of test animals. He never seems to have doubted the role of tobacco, and by the end of his career was able to claim, based on hundreds of his own published papers, that tobacco was the major cause of lung cancer, that tar rather than nicotine was the primary culprit, and that polycyclic aromatic hydrocarbons were the principal carcinogenic agents. Among these

last-mentioned compounds was 1:2 benzopyrene — the subject of the paper reproduced here<sup>3</sup> — which Roffo was apparently the first to identify in tobacco smoke (on the basis of spectrographic signatures).<sup>4,5</sup> Roffo also concluded that blonde tobacco was more dangerous than black — from having higher quantities of tars — and that the most dangerous were Turkish, Egyptian, and Kentucky tobaccos.<sup>3,6</sup> He also showed that cancers could be induced in experimental animals even by using nicotine-free tobacco, meaning that it must be the *tar*, rather than the *nicotine*, that was causing cancer. Tar was not a trivial component of tobacco smoke: Roffo calculated that smokers could inhale as much as 4 kg of tobacco tar in 10 years of smoking.<sup>4</sup>

Roffo had access to a very large pool of cancer patients at his institute in Buenos Aires and used this to explore cancer causation on a statistical basis.<sup>7</sup> In 1934, he described how 302 of his 500 skin cancer patients had presented with malignancies of the nose, the body part most directly exposed to the sun.<sup>8</sup> He also directed a number of projects involving human experiments, to determine the role of skin pigmentation in protecting against X-rays, for example. Male versus female differences in cancer rates were an important source of evidence for him on the tobacco question: how else did one explain the fact that men were far more likely than women to contract cancers of the lips, tongue, gums and cheeks, while cancers of the stomach were evenly

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balanced by sex? (Tobacco use, of course, was far more prevalent among men.) This difference by sex was particularly evident for cancers of the throat and larynx: fully 5% of his male patients' cancers struck the throat, whereas among 7000 women in his clinic with malignancies only three (about 0.04%) suffered from cancer at this site — and all three were smokers. Similar patterns were evident for cancers of the lung.<sup>2</sup> This was convincing evidence for him, and the language he uses is interesting; he says the patterns were so strong as to have an “almost experimental value” (*fast experimentelle Wert*).<sup>9</sup>

Not everyone was convinced by Roffo's studies, however. Ernest Kennaway in England had pioneered animal experimental techniques for replicating occupational cancers (especially from petrochemicals), and he objected that Roffo had burned his tobacco at too high a temperature to be realistic.<sup>10</sup> Roffo's methods of chemical identification also came under scrutiny. He had used spectrographic fluorescence to identify specific components within the class of polycyclic aromatic hydrocarbons, and some critics thought the method too crude to be decisive. The tobacco industry objected to his use of a method known as destructive distillation to obtain tars for experimental manipulations, though that was actually a standard method used by the industry itself in the 1930s.

For many of his contemporaries, however, Roffo was a force to be reckoned with. Schairer & Schöniger in 1943 cited Roffo's experiments as evidence of the carcinogenicity of tobacco tar, as did Franz Hermann Müller in 1939 and Fritz Lickint in his great *Tabak und Organismus*.<sup>11–13</sup> Roffo was the key prompt for Leonard Engel's widely read “Cigarettes cause cancer?” in 1946,<sup>14</sup> and was crucial also for Edwin J Grace's 1943 article in the *American Journal of Surgery*, which cited the Argentine's discovery of benzopyrene in cigarette smoke.<sup>15</sup> James Ewing in his 1940 textbook, *Neoplastic diseases*, devoted several admiring paragraphs to Roffo's work.<sup>16</sup> Argentina's foremost cancer institute today, in Buenos Aires, is named after him.

Roffo was also taken seriously by scientists employed by the American tobacco industry. A 1950 memorandum to the president of the American Tobacco Company (AT) reviewing the “alleged causative relation between cigarette smoking and bronchiogenic carcinoma” cited Roffo as “the chief protagonist of the theory that there is a causal relation between smoking and cancer of the respiratory organs”; it also noted Grace's “echoing” of Roffo's opinion and conceded that cancer authorities had been dissenting from Roffo's view “until recently”.<sup>17</sup> Claude E Teague at R J Reynolds in his revealing (but unpublished) 1953 *Survey of cancer research* cited nine separate studies by Roffo, including his “isolation of a benzopyrene from a pyrolytic distillate of tobacco” and his observation that the compound was “highly carcinogenic in animal tests”.<sup>18</sup>

Cigarette manufacturers had actually been keeping a close watch on Roffo since his first published work on this topic in the early 1930s. Indeed, it is in responding to Roffo that we find some of the earliest industry denials of tobacco as a possible cancer hazard. In the 1930s and 1940s many people wrote to the tobacco companies, asking whether Roffo was right in claiming that cigarettes were carcinogenic. On 11 May 1939, for example, AT Research Director Hiram R Hanmer replied to one such enquiry: “We have been following Roffo's work for some time, and I feel that it is rather unfortunate that a statement such as his [implicating smoking in cancer] is widely disseminated.” Hanmer claimed that the positive response to Roffo's work had kept the literature on tobacco “in a very beclouded condition” and reassured his correspondent — a New York physician — that “the use of tobacco is not remotely associated with the incidence of cancer”.<sup>19</sup> It was partly in response to Roffo that the industry started hiring translators; indeed, the only known English translation of his publications prior to the article published here is one commissioned internally by the Lorillard Company in the 1980s in preparation for litigation.<sup>7,20</sup>

It is unfortunate that we do not have a good biography of Roffo. We need to know more about his earlier work in the 1920s, and how scholars and tobacco men in his native Argentina viewed his research. We need to know more about how he first came to realize that tobacco was causing cancer, and how he faded somewhat from the public theatre in the wake of Wynder et al.'s experimental carcinogenesis<sup>21</sup> and the epidemiology of Doll & Hill<sup>22</sup> and others. Was the language gulf a problem? Did his German ties taint him? And what role did professional jealousies or industrial defamation play in the reception of his ideas?

Prior to 1950, Roffo was arguably the single greatest scientific threat to the tobacco industry. After the Second World War, however, German-language medical literature fell into a kind of oblivion; international efforts to exploit German science concentrated almost exclusively on science that could be used for military purposes (tropical medicine, rocketry, biowarfare agents, aviation medicine, etc.), and most of the work on preventable chronic diseases was ignored.<sup>23</sup> Roffo's contributions fell further into neglect in the 1950s, when English and American scholars improved upon his methods, sometimes without giving him much in the way of credit.

Cigarettes kill an estimated 5 million people annually worldwide, a figure expected to grow to 10 million by the year 2025. A billion people could die from tobacco disease in the present century.<sup>24</sup> Enough cigarettes are smoked every year to circle the earth 13 000 times, or to make a continuous chain from the earth to the sun and back with enough left over for several round trips to Mars. The Argentine we honour today gave us the correct diagnosis, but tobacco mortality is still on the rise worldwide, and will be for another couple of decades. Roffo would probably be saddened to learn how little we have done to grasp this bull by the horns. ■

**Competing interests:** I have served as an expert witness for plaintiffs in tobacco litigation in the USA.

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