THE DAY SAM THOUGHT WE HAD CURED CANCER

One of the projects that José was given in 1950 as a post-doctorate, in the laboratory of Sam G., was to synthesize compounds which José would consider useful in cancer chemotherapy. "What kind of compounds shall I synthesize?" José asked Sam, and the reply was, "Compounds that you think might be useful."

At that time, nitrogen-mustards were being used, with some minor success, in cancer treatment. After reading in the literature about these compounds, however, José realized that they were exceedingly toxic. Although José had little background in biochemistry at the time, and even less in cancer work, he felt that, since DNA and RNA each contain a specific sugar (ribose and deoxyribose respectively), perhaps what might work would be to substitute a different sugar for each of these, a sugar that would enter the gene and possibly "confuse" the cancer mechanisms.[1] He decided to substitute glucose for ribose (a six-carbon sugar in place of the five-carbon sugar) and informed Sam. This was to be a difficult synthetic undertaking, for none of these compounds had yet been made, so new synthetic procedures would be involved.

Sam delegated the animal work to a young physician who had just finished his training, Jerry V. (Jerry had lately been treating Sam's wife Ceil as his patient.) Jerry told Sam that he had never done research in cancer and didn't have the expertise to maintain a colony of rats. He was therefore sent to Bethesda, Maryland, for one day to learn how to transfer tumors from one diseased animal to a group of healthy rats and maintain a rat colony. The tumor selected was a sarcoma, considered by pathologists to be lethal in a short life span, such as that of rats.

Upon his return from Bethesda with one cancerous rat, Jerry obtained other rats from the animal house, and became friendly with two dieners who worked there. They promised that they would help handle the colony of diseased animals and all the work involved in this project. No controls were assigned. Neither were any healthy animals included in the study. Around this time, the animal house in the anatomy-chemistry building had been attacked by a group of anti-vivisectionists, who released most of the animals out of the laboratory. Certain security measures were now established, and the two dieners had full control of both the entrance and the handling of all animals.

José had, by now, begun the lengthy synthesis of uracil-glucose (U-G) that was to be the first compound studied. This preparation involved a seven-step

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[1] The idea was novel: there are few exceptions on this planet to the use of ribose and deoxyribose in genetic materials. One exception is the sea-star organism found in the area of the Bahamas; it contains the sugar arabinose instead of ribose. The compounds obtained from these marine animals showed some anti-cancerogenic properties when tested years later.

synthesis. Since there were many delays in the synthesis of U-G, Jerry found himself with little to do and, with Sam's permission, he accepted several part-time positions as physician in a number of children's day-camps at various summer locations near Philadelphia. Many calls would come in concerning minor accidents to children that required his precipitous dashing off to specific camps to treat sprained wrists, vomiting, diarrhea, etc. Ten weeks later, U-G was finally synthesized and recrystallized by José, and Jerry also got twelve rats, each with sarcoma that, he announced, had been successfully transferred from another sick rat. Jerry claimed that all the animals now showed tumors. José observed pustules on all the animals. He then had the U-G that he had prepared analyzed independently. The analysis confirmed its structure and, now, José wrote a paper, which he later sent out to a scientific journal. (This paper was published years later.[2])

The doses to be given to the rats, and the mode of administering these doses, were not discussed with José. Neither was the frequency of the treatment. José delivered a container with U-G to Jerry (fortunately, not all of it got used.) José then began to plan the synthesis of the next chemical to be tested. At this time, the anti-vivisectionists made another raid on the animal house, and the deiner said that he and his colleague had subsequently repaired the damage and handled the situation, and that no animals had been lost. Jerry now started to give U-G to the rats. A few weeks passed by, and Jerry reported that the tumors in the rats had all disappeared, and no scars were to be found. All of the animals were in good health and fully recovered!

Upon the arrival of this information, Sam grew ecstatic, and he suddenly became unavailable to José. Days later, Sam finally called José in and told him about the Gordon Conference in New Hampshire. He said that, next week, there was going to be a meeting there on proteins, and that Lindestrom-Lang, the famous protein chemist who had just been given the Russian Science Medal, would be presiding at many of the meetings. It would be very educational, Sam insisted, for José to attend these meetings, even though they were not in his field. José explained that he had no funds, and that usually it took a month in advance to request permission for acceptance to these meetings. Next day, Sam informed José that he had been accepted. Funds would be available, he advised, but it would only be for that particular meeting on those given dates. José then departed with Josy, then four months pregnant with their first child (Malva), and drove to New Hampshire.

In the meantime, Sam prepared a press conference with Harold Stassen, then President of the University, and several of the University scientists, among them

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[2] *J.A.C.S.* 75, 5758 (1953).

the Pathology Chairman, Dale Colman. The gist of the press conference was that this was the first time that a sarcoma had ever been successfully treated, even in a rat. Dale assured the interviewers that, in his experiences with sarcoma, never before had a tumor regressed and totally disappeared.

Upon returning from the Gordon Conference, José, in a meeting with Sam and Jerry, inquired whether the findings had been double-checked. Since there was enough U-G left, it would involve only a matter of getting some more animals and repeating the procedure. When this was told to Dale Colman, he announced that the healed animals were now being sectioned from head to tail at close distances, that slides were being prepared to see if there was any internal damage left, and that there was no need to repeat the testing at this time. After two weeks, Dale invited Sam and José out for lunch and announced that all the animals in all their sections showed no trace of cancer. This was a remarkable achievement! Additional press conferences were planned.

Meanwhile, Jerry left the project to take a clinical position elsewhere. José insisted on a repeat experiment as soon as possible. New animals were brought in. Dale now took charge of the testing. Shortly, every single animal to which a tumor had been transferred died of a sarcoma tumor, in spite of having been treated with U-G from the same bottle. Immediately there were accusations that this U-G must have been impure and heterogeneous, that the original U-G had contained a very potent anti-cancer compound and, since the U-G in the bottle had not been homogeneous, Jerry must have removed **his** U-G from the top, U-G which must have been different from that at the bottom of the bottle. José explained that the preparation of U-G had been in a single batch, that it had been recrystallized as a unit, and that analysis sent out for carbon, hydrogen, and nitrogen had indicated a purity of over 99.9%. The remaining contents of the bottle were now put into a safe, and José was ordered to make a new batch of the material, following as closely as possible the same procedures employed in preparing the first batch. Representatives of Merck, Dupont, and other pharmaceutical companies were brought in by Sam and given small amounts of the original U-G. The information on the steps in the preparation was also given to them. Months later, all the companies reported that the U-G of Batch 1 was pure and, after careful drying, they reported the purity to be 99.95%.[3] Batch 1 was shown to be identical to batches made later on. Mixed material from Batch 1 and other batches chromatographed as a single spot.[4]

Sam continued to have José make new batches, and Dale continued to test them. No curative effect whatsoever was found. A conference was now held

[3] A Dr. Jane Gordon of M.S.D. was one of those who repeated parts of the synthesis.

[4] Dr. Cecil Cooper at U. of P. confirmed this.

involving scientists from the different pharmaceutical houses (to which José was not invited). Here, they declared that the compound was non-toxic and, therefore, could not possibly show any anti-cancer properties.

From these conferences, Sam came out with a new theory, the "Impurity Theory". There must have been a trace, he concluded, of something in the U-G that did the curing. Sam managed to get from the National Institute of Health (N.I.H.) a large and special grant. José's salary was increased, and he now got two technicians to assist him. The project consisted in preparing all possible side-impurities that could conceivably be present and/or formed during synthesis. It also involved biological testing on the sarcoma-infected rats, as well as the testing of every single reagent, solvent and, even, all physical containers involved in the synthesis. Hundreds of samples were prepared and sent to Dale, and hundreds of rats with sarcomas were injected with each one of the new preparations. No anti-carcinogenic effects were observed. Dale, Sam, and José again met, and José tried to explain that the total amount of impurity that could have been present was so infinitely small that it could not possibly show any effect. In spite of these discussions, however, José repeated the experiments several times.

Six months later, after the funding was used up, the project was finally dropped. José was then assigned a totally different project, one in the field of cholesterol biosynthesis, for which he was very thankful. Dale, on any occasion when he saw José, would again try to discuss what impurities could possibly exist in U-G and mentioned that, if José could think of some of these, he would be rewarded.

For many years, Sam did not discuss the matter again with José. Sam eventually became Dean of the Medical School and, later, he left Philadelphia for many years. He eventually retired to a community called Pine Run in Doylestown, on the outskirts of Philadelphia near the well-known Polish shrine of Our Lady of Shestakova.

One day, forty-two years after he had first started working on the cancer project (and long after Sam had retired), José got a phone call. It was Sam, inviting both José and Josy to come have lunch with him at the retirement center where he was now living. José accepted, and they met again after many years apart. Lunch with Sam and his wife Ceil (by then married for sixty-four years) was most pleasant. Afterwards, Sam pulled Josy over to the piano and, together, and they played four-handed arrangements of Mozart's *Fortieth Symphony* and Schubert's *Trout Quintet*. When the music was over and they had all sat down together again in the living room, Sam reopened the discussion of the day that he thought "we had cured cancer." Sam still believed in the "impurity theory", and that it is possible for a few molecules present as impurities in some preparations to stop a tumor. José was unable to dissuade him. José again pointed out to Sam that two unusual

circumstances had been going on at the time that they had done the work such a long ago. The first was the real lack of security in the animal house, so that anti-vivisectionists did repeatedly enter. For this reason it was quite possible that the animals treated were not the same as those that had been injected with the sarcoma. Second was the fact that Jerry had been too busy with his part-time jobs and depended completely on the two unsupervised animal dieners for the many steps of the testing. And that is how the matter stands to this day.