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Interview with Ezra M. Greenspan, MD by Arthur H. Aufses, Jr., MD
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ARTHUR AUFSES: It's Monday, March 22, 1999, and I am sitting in the office of Dr. Ezra Greenspan at 1045 Fifth Avenue, and we're going to chat about Ezra's roles, multiple roles, at Mount Sinai, and the development of chemotherapy at the Hospital under his leadership.

Ezra, to start off, why don't you tell me a little bit about your background, so we can sort of get you up to date — your training, and all that - and up to the point where you really got involved in chemotherapy.

EZRA GREENSPAN: Well, I was strictly a Brooklyn nature boy until I went to Cornell [University], and graduated from Cornell to enter NYU [New York University] Medical School [Class of 1943], where in an accelerated program of nine-nine-nine [months] because of the war, oncoming war [World War II], we had the most intensive clinical training you can imagine. And among the outstanding faculty people at NYU, there were several Nobel Prize winners, and in addition, I had the unique opportunity of taking certain electives, and working with people like Arthur DeGraff, and [Robert C.] Batterman, who had developed Demerol and important forms of other drugs, particularly standardized digitalis into Digoxin. So I got a little bit of clinical testing experience as a third-year [telephone rings] intern—as a third-year student, rather, at NYU. And then I went to Memorial Sloan-Kettering and then achieved a lot of experience in Kaposi's sarcoma at the Lymphoma Clinic of Sloan-Kettering, which was a unique gathering place for Kaposi's sarcoma of the old-fashioned type. It was a magnificent place to study this disease.

But my real introduction to cancer, per se, came when I arrived at Mount Sinai Hospital as a lowly intern, on the Baehr service [George Baehr, MD, Chief of the 1st Medical Service]. First, I was impressed with the manner of conducting rounds, which was absolutely unique as far as I was concerned. I mean it was run like, well, like the Army, with all kinds of rules and customs and costumes and so forth. And it was dramatic; it was intense and dramatic. And as luck would have it, the very first time [telephone rings] I went out on the ward, as the lowest man on the ladder of a group of some eighteen people, around Bed 27 in a twenty-seven bed ward, the higher-ups were talking about a case they couldn't diagnose that had been sitting around for almost a year without a definitive diagnosis, apparently some form of bizarre heart failure. To make a long story short, it was a man who had a liver and a spleen and ascites and edema, and so forth, and nobody could figure it out *exactly*. When the sheet was lifted up off his legs, I saw one tiny purple patch at his instep and that told me that he had Kaposi's sarcoma, old-fashioned type. So, [telephone rings] at the end of rounds, I said, [laughs] "I think this man has systemic Kaposi's sarcoma for many, many years. And now what you see is the end stage." [P.A. page in background] Well, this automatically—yeah, I'll take it. I have to take it. That automatically set an uproar and a whole new tone of events.

[Pause in Recording]

EG: I gave Grand Rounds on systemic Kaposi's sarcoma, which was rare as hen's teeth. There were four cases in the entire Mount Sinai Hospital literature from the day they kept records of the Hospital. Two of them were—one a child, one a young adult. And subsequently, I got involved when I switched to the Snapper service [Isidore Snapper, MD was Chief of the 2nd Medical Service] in other esoterica, of which the main component was Snapper's interest, from my viewpoint, in stilbamidine as a drug that worked in kala-azar, which had high globulins, and which might work in multiple myeloma. So my job was to infuse the patients with stilbamidine. This was an extra; this was not the regular [laughs] intern's job! And at the same time, he had Schneid [B. Schneid], this woman pathologist, looking at the smears that we made from the bone marrow. At the end of the third week, all of a sudden we see granules appearing in the cytoplasm of the myeloma cells. Well, this was absolutely, as far as I was concerned, a world-shaking discovery, which turned out to have no clinical significance or at least we never could demonstrate the true clinical significance of it. But, if chemotherapy could localize into a malignant cell, this was the way of the future. So it was a naïve, simplistic visualization of something that later on became very, very important to the cancer field.

So I really became an oncologist as a result of Snapper using stilbamidine and this crazy observation, which we went on at Walter Reed Hospital later on, to study high doses of stilbamidine. It didn't do very much in myeloma, but of course, we didn't study it long enough anyway. We couldn't—we may have missed something. To this day, we don't know whether we missed anything. The first drug came out at that time, the first organized drug, you might say, tested drug. It was nitrogen mustard, from the Army Chemical Warfare service. And we at Sinai were the fourth place to use it. It was at Sloan-Kettering, Walter Reed, and Yale; Yale was the first place. And we were the fourth place to use it.

AA: Who was in charge of using it at Sinai, at that time?

EG: I don't remember, but we had it on the Snapper service. But it was shortly after that I went to Walter Reed Hospital, actually.

AA: Right.

EG: I left Sinai; my two and a quarter years were up. So, from there, I was a non-Mount Sinai physician practicing internal medicine and doing odd things like using nitrogen mustard and stilbamidine! We even used the stilbamidine at Walter Reed Hospital for about a year, a year and a half. So the idea evolved during 1946 to '48, when I was at Walter Reed, that there were other drugs, mustard-like drugs, that could be used of which thiotepa was the leading contender. There was triethylamine, an oral triethylamine, TEN. But thiotepa, you could give it intramuscularly, you could give it intravenously. It was easily absorbed. It was a cinch; there was nothing to it. You could give it, even, subcutaneously, it didn't cause necrosis. So, you really had a hell of a good drug.

And it was working with thiotepa, and with methotrexate, which came along at the same time. In ’47 they started to use methotrexate, but they weren’t sure what they had; by ’48 they knew what they had. The Lederle people had given various selected institutions nitrogen-substituted derivatives of a folic acid eluate. Now, Babe Ruth, at some point between ’46 and ’47 and a half, I would say—oh, we know when it was, as a matter of fact. It was in ’47 that Babe Ruth, in desperate situations, was given a folic acid eluate, an impure mixture obtained from Subba Row [Yellepragada Subba Row], who was the Chief Chemist at Lederle Laboratories in Pearl River. Now, he had been providing Lewisohn [Richard Lewisohn, Director of Mount Sinai’s Cell Biology Laboratory – ed.] with all kinds of *gmishes*, and he called them *gmishes*, because they were impure and they were working to isolate the active ingredient. And the fact is that Babe Ruth got, I think, six shots. And he had a big mass in his neck, which went down. He had—actually, in retrospect we know he had a lymphoepithelioma, Schminke tumor, classical Schminke. And first it was missed, then they diagnosed it, then they fooled around, and so forth. Then the tragedy, to end up that part of the story, was when he relapsed they already had the pure aminopterin they did not treat him a second time when he relapsed, because had they done so, they could have—probably have responded. He may have lived a couple of years more, before—[coughs]. This was as a result of politics. Now, when you talk about politics, you don’t know exactly who was involved.

AA: You never know! [Laughs]

EG: But, [laughs] we can make a very shrewd guess as to who was involved. In the first place, Sidney Farber had moved from Brooklyn Jewish Hospital, as a pathologist, to Boston, to Dana Farber, as a clinician. He was practicing chemotherapy, on children, primarily at Children’s Hospital. And he was interested in what Subba Row had. And I’m sure that his first materials were—contained what was called teropterin. And he, Sidney Farber, [phone rings in background] wrote a big paper, three pages [laughs] long, or less, actually—but it was two columns per page—on some sixty cases, and he vaguely said he thought it did some good. But you couldn’t actually pinpoint what good, what it, what good it did. However, he was called in, Sidney Farber was called in by Sloan-Kettering that was working on the same stuff. And he told Sloan-Kettering the stuff was no good. Now, when Sidney Farber told Sloan-Kettering it was no good, they quit working with teropterin.

Now, whether that was some form of self-interest or whether it was just really relating what was really occurring, nobody will really ever know. But what is known is that within a month or two [laughs] after he wrote the manuscript, he wanted to recall the manuscript, but it was already in press. So he knew within two months or so of the time that he submitted a manuscript that the real McCoy, the real anti-cancer drug, which was a—was a pure nitrogen-substituted derivative from the folic acid eluate, was actually the ingredient that cured leukemia in children. So it was an unfortunate concatenation of events in which, I think, certain influence, political influences and certain prestige factors played a role. But Lewisohn appeared to be the fall guy, even though Lewisohn did not protest, nor did he publish. And he certainly felt, correctly so, that the drug that he was using, which was impure, was not yet ready for clinical use. But within three, four

months or five months, it was ready for clinical use, when Subba Row at Lederle Labs was able to purify the stuff.

AA: Mm-hm.

EG: So it was a—that is the way the field evolved. In the meantime, I was totally disaffiliated from this since I was working at Walter Reed Hospital.

AA: Sure, you were in the Army.

EG: I was away. So I was doing my own work there. And at Walter Reed we had a wonderful drug, thiotepa, which is still [laughs]—still being used, long after Lou Wasserman [later Director of Mount Sinai's Dept. of Hematology] pronounced it a platelet poison, by the way. And we had methotrexate, which was made available to us. So between the combination of thiotepa and methotrexate, two drugs acting by totally different mechanisms, I was able to start treating patients with cancer. And then I left the Walter Reed to become a special cancer fellow at the National Cancer Institute and I had to actually run the pilot plant of the new hospital. I ran the pilot plant for about three, two and a half years. I was a fellow for a year, and then two and a half years, so I—

AA: That's the Clinical Center?

EG: Yeah, before the new buildings. The old buildings—they were all wooden, big old wooden buildings. So I had three and a half years of government support, and I had the most magnificent set up! I was just lucky to be in the right place at the right time. And for example, Snapper came to visit me, after a year I was there or so, when he came and said, "Greenspan, you'll never have it better in your whole life!"

AA: [Laughs]

EG: I said, "You're right, Dr. Snapper. You're right!" I had a budget of about $20 million for an outfit that would today cost about $250 million to run it, plus fifteen beds that we didn't have to pay for. So we were able to do clinical research, real clinical Phase I, II research, and we introduced combination chemotherapy there. Then, at Mount Sinai when I came back, I had the experience to use the drugs simultaneously, and to get the most mileage out of them.

AA: Mm-hm.

EG: But at Sinai, nobody knew anything about this! Because it was a practicing hospital without a medical school and without basic scientists, and there was nobody who understood what I was doing, or—if they understood it, they only understood it in theory. They couldn't believe in the practice component of it. So that at Sinai, I achieved a number of nicknames, like Lucrezia Borgia Greenspan, the Poison King, things like that.

But we were able to do a great deal of work at Sinai and were able to do work in other fields because the laboratory that the Cancer Institute gave me permitted so much leeway that we were able to stumble into a number of new observations. We were able to develop the dysproteinemic analysis of diseases with the serum mucoprotein and the serum alpha-1 and alpha-2 glycoproteins, so that I was both a protein chemist as well as a chemotherapist. And this was possible because Adolph Lewisohn gave me $70,000 the first, the moment I entered Mount Sinai Hospital's walls, the very first day I came there from the—

AA: After you came back from the Army?

EG: After I came back, yeah. Lewisohn—but he gave it to me because Snapper said, "Give it to him!" [Laughs] It was a combination of Snapper and Lewisohn that was responsible for it. So we set up the first lab, but it was a lab based on protein studies, not on cancer studies, because we didn't have the facilities to do the animal work that we were able to do in Baltimore at the Public Health Service Hospital. So, it was sort of a bit of a mongrel. They used to call me Greenspan, Muco-puke-oh Greenspan because of the mucoprotein, or else, Lucrezia Greenspan. But at the same time, I kept reporting the clinical observations and the papers, and so forth. So, it took about eight years at Mount Sinai Hospital before most of the people at the hospital began to think that maybe I wasn't crazy, or a money-grubber, or self-interested, or whatever. They didn't look at me as a queer duck. It took about eight years. But I remember very well, Bill Hitzig telling me, "Ezra, I've never seen a case of chemotherapy response." I said, "You haven't? Well, that's your fault." [Laughs] I said, "What about your friend '['s]' wife?" "Oh!" [Laughs] He forgot about her completely! I had to go to New York Hospital to treat her. She had cerebral metastases from breast cancer and she responded brilliantly to methotrexate-thiotepa.

So, it was an odd set of circumstances at the hospital—while the hospital encouraged research, there was a certain type of freedom, there was cantonization in the hospital. I call it the greatest cantonized hospital—clinical cantonization. I mean, I said to myself that only at Mount Sinai could I have been—worked there. And I worked there for fifteen years before we had a medical school! And interesting thing, I did all the work on the mucoprotein and differential diagnosis of jaundices, and for a while it looked like very big stuff, because there was so much liver disease in Africa and other places like that. But then, electrophoresis, quantitative electrophoresis came along and sort of put it out of business. Sheila Sherlock put it out of business, too.

[Pause in Recording]

EG: The fascinating thing, from my viewpoint, was that I had this freedom to work at Mount Sinai Hospital, and I had the greatest respect for the Hospital. I knew that there were a lot of smart people at the Hospital, but they really had such a limited knowledge of the things that I was doing, that I had to be, not sarcastic, but you had to be indulgent to—actually, is what it boiled down to. And it came to the realization, after a while, to people like Al Gutman [Alexander Gutman, Chairman of Medicine, 1952-1967], who was

always a very fair guy, but who was—and this is a personal thing. When I first met him, the minute I arrived back from the Cancer Institute, his office was right next to Snapper's. He had just lost his wife from leukemia! And here I am [laughs] this young kid. I can imagine what it must have looked like or felt like to Al: this whippersnapper is talking about killing leukemia, controlling leukemia, and his wife has just died! I mean, he must have really been boiling inside, but he never should display that.

But he never helped me one bit; never did anything! But he also didn't say anything! He never criticized me. In fact, [laughs] once I wrote an article for the *Mount Sinai Journal* on the mechanism and action of folic acid antagonists. I wrote a very—it was a very beautiful, extensive write-up. At the time, it was really important. Gutman says it's the best paper—he returned it, saying to me it's the best paper he ever read on this kind of a subject, which I really took as a great compliment! Anyway, at the end, nineteen years later—he kept me in the same rank, by the way—never gave me a promotion! [Laughs]

AA: What else is new?

EG: No, wait, listen to this. But at the end, when he retired, and he had to write up a grant for the medical school in cancer, he calls me in! So I said [laughs]—so I go into his room, and there he is, puffing away at cigarettes! [Laughs] And his first thing out of his mouth was, "Greenspan, I'm not shitting you!" Now, there's a word, I mean, he would never use! He's the—this man would never! He says, "I'm not shitting you. We didn't believe a word you said." "Oh," I said to him, "Dr. Gutman, don't worry about that. Come on, that's unimportant!" At this late date, we're going to worry about what--? [Laughs] But he had to apologize for ignoring me for nineteen years!

AA: But he never forgot that he hadn't apologized?

EG: Oh, absolutely! Oh, no, no, he was a quality guy all the way!

AA: Sure he was.

EG: Listen, the work I did on mucoprotein was right up his alley and the other stuff. He knew that was interesting, but he knew that wasn't my main interest, though. But he never forgave our—I can imagine what he must have felt. His wife had just died, and he was madly in love with her, I'm sure. And I come in to his office, [laughs] introduced by Snapper, and I start talking about treating leukemia, and curing the animals as well as patients.

AA: When you first started treating patients at Sinai, they were mainly breast, and ovary, and leukemia? [Telephone rings]

EG: And lymphomas.

AA: And lymphomas.

EG: Yeah, there were very few GI, no lungs, no—

AA: Well, that maybe came along later, didn't it--?

EG: Yeah.

AA: When you had more drugs?

EG: Yeah, yeah, yeah. No, they were—the initial was leukemia, lymphoma, breasts, and ovary. But the reason why the breast cases were my main interest and why they were, from my viewpoint, the most successful was very simple. The reason was simple: because in those days, most breast cancer that I saw was out-front disease. In other words, it was either chest wall disease, recurrent disease, or they had palpable disease that you could—

AA: And you could follow.

EG: I could not only follow—the patients could follow!

AA: Sure.

EG: That was the important point. The patients themselves could follow it. So, if I pushed the methotrexate, pill by pill, you know nine tablets, eleven tablets, twelve tablets—whatever it was that each—it varied from patient to patient of course. If I titrated them with methotrexate and with thiotepa, they could see the disease melt away!

AA: Sure.

EG: And once a woman saw that happen, they were hooked. They were happy to continue. And of course, they all recurred, with maybe one to two percent exceptions. They all recurred within two to three years, and most of them recurred by the end of the second year, with thiotepa-methotrexate. But then in '57, fluorouracil came along, with Charlie Heidelberger, and in '58, Cytoxan, Endoxan, from Europe. So we have two more different drugs, two couplets that would not cause resistance. So I introduced the combination of the other two drugs, and then made some of them three drugs or four drugs, or two and two.

AA: Mm-hm.

EG: So I really introduced the whole subject.

AA: What's the longest people will go now? Are they cured?

EG: Oh, yes, there were lots of people who are apparently cured, if you consider fifteen years disease-free to be cured.

AA: I'd consider it.

EG: Well, but we realize that fifteen years is no guarantee!

AA: Yeah, I know. I know. We've had recurrences after twenty or more.

EG: But the point is, you see, I think the true—if you ask my opinion, the clinical cure rate, using—in a broad sense, let's say fifteen years. The clinical cure rate for breast cancer is probably in the realm of fifteen percent.

AA: Mm-hm.

EG: In other words, you get a certain percentage of them who for reasons—and we know now some of the reasons, but we didn't know it then. It's immunological. It has to do with factors that are immunological, of which we had no inkling until the mid-60s. It was actually, the first one who introduced the concept of immunity at a practical level was a Frenchman--er, I'm showing my age—who introduced BCG. He worked mostly in pediatrics, with leukemia. And he was the first—he came to Mount Sinai in 1971, the first meeting of the Chemotherapy Foundation Symposium.

AA: I want to talk to you a little bit about the Foundation. Let me switch this.

[End of Side 1]

AA: You had just started to talk about the Foundation, and I wanted to talk about it. When did you start that?

EG: I started the Foundation when Berson, Sol Berson came to the Hospital, and shortly after I had that meeting with Gutman. [Solomon Berson, MD was Chairman of Medicine at Mount Sinai from 1968 until his sudden death in 1972. He followed Gutman.]

[Phone call; Pause in Recording]

EG: Okay. I started the Foundation knowing Sol was the Chief, and [I was] planning, actually, to move into the Hospital. Back into the Hospital, I should say, back into the Hospital, because when I first came to Mount Sinai in 1951, I was the first one in on the ground floor of Klingenstein [Pavilion] there! But I found I couldn't get a chest x-ray or a blood count or anything—you couldn't practice medicine! It was impossible!

AA: I remember. I was there, too.

EG: It was a wonderful location, but it did me no good whatsoever. So I left there after a year and a half. And incidentally, Gutman sent me the first case of myeloma [laughs] just as—the day I'm leaving the Mount Sinai headquarters there. And that's a separate story which I don't want bore you with. It was quite a story. Well anyway, the point is, I

formed the Foundation because there was a public—I felt there was a public need for a foundation for dissemination of information to physicians and involved patients, and sophisticated patients. The subject was too complex for unsophisticated, but very sophisticated patients could follow it. So the idea was to form the Foundation, and the second purpose in forming the Foundation was to act as a vehicle to set up a cancer institute at Mount Sinai Hospital.

And when Sol Berson died [in 1972], that was the end of my plans to move back in. I was already fifty-three or fifty-four at the time, and it never dawned on *me* that I was too old, or that anyone had even mentioned the fact that I was too old, but that was a factor. But the real factor in me not getting the job [as head of a Mount Sinai cancer institute] was very obvious, and it was honestly expressed by Lou Wasserman, who said, when Emil Frei and [James] Holland were the choices, "Well, either one will be able to bring cancer money, and will be very conspicuous public figures," because they had worked, along with DeVita, they were—and Freireich—the four horsemen. They had worked at the Cancer Institute when the new buildings were formed, were erected, which was in '56.

AA: Right.

EG: So they had from '56, lead time to build up their work and their reputation, and they had the lab facilities, they had everything. And they had lots of money. And more and more money was coming. Now, what clinched it, of course, was very simple: that in theory, it's very nice to have a Mount Sinai man, but if you can get a man from the Cancer Institute, who can bring tons of money, you're much better. But the man who really did it was Richard Nixon because he started the War on Cancer and with it, tons of money. The politicians got involved because Senator Vandenberg died of lung cancer, and that really set them on their ears, because they never—I think he was the first important politician to die of cancer. And so from that time on, it was big business and it was a different business. So I stayed in private practice. The result is that I'm [laughs] an anachronism! At the present moment, I think I'm the oldest practicing oncologist in the country, [telephone rings] maybe with one exception, but he's not really practicing.

AA: [Laughs]

EG: No, that's true. It's true.

AA: What do you see as the major benefits of the medical school, in your field of chemotherapy?

EG: In my field?

AA: Yeah.

EG: Well, the major benefits could be tremendous, but I don't think have yet been realized.

AA: Where should the school be heading, from your point of view, in cancer?

EG: Well, the problem is cancer is so complex now. It's a logistical problem in management of patients, and in getting the medications into the patients. In other words, the treatment regimens and the patients; it's all a logistical problem, and so the institutions with the largest amount of money and publicity are the ones that are going to succeed, or with the tightest organization. Now we have, as I said, this tradition of cantonization at Sinai, which has worked out well because it permits certain individuals to do their own work undisturbed. We're a very liberal institution, Sinai is, even though people don't realize—they don't realize it. But I realize it; I realized it all along, from the day I set foot back in Sinai, I realized it. Anyway, so in order to compete, who are you competing against? You're competing against Sloan-Kettering, M.D. Anderson Hospital, Pittsburgh Center.

AA: Boston.

EG: Yeah, Boston, Seattle, maybe San Diego. But the point is, it brings you around to the question of competition for new agents and the quick application of these new agents. So, unless the hospital is set up to be fully mobilized, quickly, on whatever basis they're going to do their studies, they can't compete! And this is the real problem at Sinai, as far as I'm concerned.

AA: The wheels of progress ride very slowly is what you're saying.

EG: The wheels of general progress.

AA: Yeah.

EG: Yes, you have to say that. Yes, I think that that is the major problem with the institution.

AA: Right.

EG: It becomes worse as time goes on, because the HMOs are involved in one angle of it, and you've got the groups like Saleck and company, and they're very efficient in their way. And you've got groups like Sloan-Kettering, who will spend millions of dollars on publicity just to bring patients in. And I don't necessarily think that any one of these approaches is ideal, or is even, you know, or even necessarily high quality. But it will take away resources—money and manpower, both. So, we've got a complex problem here. We have to create an identity, and the identity is hard to define. I used to think the best identity for the institution was hematologic, as we started out with Rosenthal, and with Wasserman—

AA: And Ottenberg before them, and Rosenthal, sure.

EG: Well, I said Rosenthal; I mentioned that.

AA: Sure, sure.

EG: Sure! And don't forget, Lewisohn was the first to try the transfusion. [In 1915, he developed the minimum safe level of sodium citrate in blood to preserve it outside the body.]

AA: That's right.

EG: You know, people don't—they don't know any medical history!

AA: I know that.

EG: No history. But it's interesting. Those were sort of individuals who were here. They functioned as individuals, you see.

AA: Absolutely, absolutely.

EG: That was the whole secret.

AA: It was, each individual was his or—and it was his only; there were no hers in those days! [Laughs]

EG: That's right.

AA: It was all his own thing.

EG: Not only no hers, you couldn't even be married [as a Resident] 'til 1937!

AA: I know. I know that from home. That's why I'd be older, probably [Laughs] except my father wasn't allowed to get married!

Okay, well this has been a lot of fun. What do you see as the future of chemotherapy?

EG: Well, by itself it has limitations, but when you're talking about biomodulation, when you're talking about immunotherapy, and they're talking about gene therapy, and they're talking about angiogenesis—the whole *gestalt*! Oh, I think it has an excellent future. But conventional new cytostatic agents or cytotoxic agents by themselves? No single—the whole idea of looking for a single magic bullet is wrong. I mean, that's how I introduced my own work, really.

AA: Sure, certainly.

EG: In fact, my textbook that I wrote, that was one of the first things [laughs] that I brought out, was the fact that there is no single magic bullet. [Greenspan, EM. *Clinical Cancer Chemotherapy*, New York, N.Y. : Raven Press, 1975.]

AA: Sure.

EG: Ehrlich had the idea. [Ehrlich developed Salversan for syphilis, drug #666 that he tested – Ed.] It was an old-fashioned idea: that with the right number—the right number from the shelf, we'd get the right drug. That's….

AA: Okay, well thank you very much. I'm going to turn off the tape, and then I want to talk to you a little bit about some of your papers, okay?

EG: Okay, yeah.

[End of Interview]