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Use of chloroquine phosphate (aralen) as a blood sugar reducing substance in diabetes mellitus

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THE USE OF CHLOROQUINE PHOSPHATE (ARALEN) AS A BLOOD SUGAR REDUCING SUBSTANCE IN DIABETES MELLITUS

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INTRODUCTION

With the preparation of a pancreatic extract capable of inducing a reduction in blood glucose level, Banting and Best in 1921 made possible the first approach to the treatment of diabetes mellitus. Insulin, the active principle of the extract, has remained the principal pharmacologic tool in the management of this metabolic disorder. Recently a sulfonamide (N_1-sulphanilyl-N_2-n-butylcarbamide) was introduced by Franke and Fuchs[1], which resulted in a lowering of blood sugar in diabetics. Subsequent clinical trials substantiated these original observations, and the drug at first seemed to be an answer to the long sought oral treatment for diabetes. Unfortunately serious side effects were reported with the use of the drug, and it was subsequently abandoned. Another sulfonylurea (Tolbutamide, Orinase) is presently undergoing extensive study, and general experience indicates that Orinase can be used successfully in the treatment of 70% of all patients, replacing the insulin in about one-half of those using it heretofore[2].

Still another compound chemically unrelated to the sulfonylureas was found by Capriles[3] to have certain beneficial effects in diabetes. This drug is chloroquine, known for many years as an effective antimalarial and as the treatment of choice in hepatic amebiasis.

The present study was undertaken with the objective of evaluating chloroquine as a hypoglycemic agent in patients with diabetes mellitus.

HISTORY AND PHARMACOLOGY OF CHLOROQUINE

Chloroquine is 7-chloro-4-(4 diethylamino-1-methyl-butylamino) quinoline. The compound is available as Chloroquine Phosphate, U.S.P. (Aralen Phosphate, N.N.R.). It is a white, bitter, water-soluble, crystalline powder. Approximately 60% of the (di) phosphate represents the base. The phosphate is marketed as a 0.25 gram tablet for oral use.

Chloroquine is one of a large series of 4-aminoquinolines investigated under the program of antimalarial research during World War II. At the end of hostilities it was found that the chemical had been synthesized and studied by the Germans under the name of Resochin in 1934.

Absorption, Fate, and Excretion: Chloroquine is almost completely absorbed from the gastrointestinal tract with only small amounts appearing in the stools. Approximately 55% of the drug in the plasma is bound to nondiffusible plasma constitutents. Excretion is quite slow; only 10 to 20% is found unchanged in the urine. However, the rate of renal excretion is increased by acidification of the urine and decreased by alkalinization [5,6]. Chloroquine is deposited in the tissues in large quantities. In animals, from 200 to 700 times the plasma concentration is found in the liver, spleen, kidney, and lung. The brain and spinal cord contain only 10 to 30 times the amount present in plasma[4].

Dosage: For the purpose of malarial suppressive therapy, an

oral dose of 0.5 gram of the phosphate is given once weekly. The intramuscular route may also be employed.[15] For the treatment of an acute attack of vivax or falciparum malaria, an initial dose of 1.0 gram is given; this is followed by an additional 0.5 gram after eight hours and a single dose of 0.5 gram on each of three consecutive days, so that a total of 3.0 grams is given in three days. This dosage schedule is usually sufficient to cure P. falciparum infections and to terminate fever and parasitemia in acute P. vivax infections.

Toxicity: When employed in the dosage schedule for acute attacks of malaria, chloroquine may cause mild and transient headache, visual disturbances, gastrointestinal complaints, and pruritus. Prolonged chronic medication for suppressive purposes produces few untoward effects. None of the symptoms is serious, and all readily disappear when the drug is withheld. Alving, et al, undertook a study to establish whether chloroquine could be administered for prolonged periods without causing serious toxicity. Larger dosages than those necessary for suppressive treatment were administered to volunteers. One group took 0.3 gram (base) daily for 77 days and 0.5 gram (base) weekly thereafter. On the higher dosage, visual disturbances, headache, bleaching of the hair, electrocardiographic changes, and slight weight loss were observed. These changes caused no incapacity and diminished or disappeared when the dosage was decreased. The second group, which received

0.5 gram (base) weekly from the beginning of the investigations, had occasional headaches, slight weight loss, and, in two cases, a skin eruption resembling lichen planus.[13]

Pharmacological Actions: The main actions of chloroquine are against certain pathogenic parasites, including plasmodia and amebae.

In human malarias, chloroquine is not effective against the exoerythrocytic stage of the plasmodia even when massive doses are employed. However, it is extremely effective against the erythrocytic forms of P. vivax and P. falciparum. In experimentally induced human malaria in which human volunteers were tested for the prevention of mosquito-induced vivax malaria, chloroquine has been demonstrated to be devoid of prophylactic or curative activity.[7] In contrast, chloroquine proved highly effective in the termination of clinical attacks of blood or sporoqoite-induced vivax, malariae, and falciparum malarias in human volunteers.[8,14]

Field trials of chloroquine have completely substantiated and extended the above enumerated results obtained in controlled clinical studies on experimentally induced malarias. Mass prophylactic control of malaria was obtained with chloroquine in civilian populations in hyperendemic areas in Lebanon.[9] It also proved completely satisfactory for the control of acute clinical attacks of malaria caused by P. vivax, P. falciparum, and P. malariae. Chloroquine has also proved equally as effective as quinacrine in supp-

ressing relapses of vivax malaria in troops in Bataan.[11] Most and his co-workers[12] found chloroquine superior to quinine and quinacrine in military personnel with acute attacks of vivax malaria. There was more prompt control of fever, more rapid disappearance of parasites from the blood, longer interval before relapse and almost complete abolition of short-term relapses, lower incidence of toxicity, and greater ease of administration.

The mechanism of action of chloroquine as a plasmocidal agent is unknown. The drug strongly interacts with nucleates and nucleoproteins;[10] this fact probably explains the accumulation of the compound in liver, spleen, white blood cells, and parasitized erythrocytes and may be related to the mechanism of its schizonticidal effect.

Other uses: The therapeutic value of chloroquine in hepatic amebiasis in man was first reported by Conan.[16] In vitro studies with trophozoites of Endameba histolytica revealed that chloroquine has amebacidal activity superior to that of Anayodin and Carbarsone, but less than that of emetine. This observation, combined with the knowledge that chloroquine is concentrated in the liver in a concentration several hundred times that in the plasma, suggested its use in hepatic amebiasis. Clinical trials then revealed that the signs and symptoms of amebic hepatitis disappeared within a few days after the start of chloroquine therapy and that the disease was often controlled or even cured. Numerous clinical

reports soon fully substantiated the high efficiency of chloroquine in amebic hepatitis and abscess.[17,18] It was also demonstrated that the drug is relatively inactive in intestinal amebiasis. The usual course of chloroquine phosphate for extraintestinal amebiasis in adults is 1.0 gram daily for two days, followed by 0.5 gram daily for two to three weeks. This dose can be revised upward if necessary.

Haydu[19] has employed chloroquine therapy in rheumatoid arthritis. Chloroquine diphosphate was given to 28 rheumatoid arthritis patients for six months, 0.5 gram three times a week. Twenty-one patients improved considerably, one patient had complete remission, and one did not improve. These results have been substantiated by Rinehart. He found that improvement is more striking in the younger age groups, although more than half of the adults treated experienced over-all improvement with similar treatment.

A great many uses have been suggested for chloroquine in the field of Dermatology. Farber and his associates[20] treated ten cases of chronic discoid lupus erythematosus with atabrine and four cases with chloroquine for one to five months. With one exception there was objective improvement in every patient after three weeks of treatment. Pillsbury[21] treated sixteen patients with chronic discoid lupus erythematosus with chloroquine in daily doses of 0.25 to 0.5 gram with excellent results. After a period of four to ten months, no significant toxic effects from chloroquine therapy were noted.

Cahn[22] has shown that chloroquine is effective in the treatment of polymorphous light eruptions and that in most cases there is no recurrence of the disease following therapy. In a large series of cases with a similar eruption, Christiansen, et al,[23] showed that chloroquine kept 75% of the patients free from any symptoms with the majority of the remaining 25% responding favorably. Side effects of chloroquine therapy were blurring of vision and disturbance of accomodation, dyspepsia, depigmentation of scalp hair, and methemoglobinemia. The side effects were insignificant inasmuch as they could all be eliminated by reduction of the dose or suspension of treatment for a short period. It was believed that the effect of chloroquine on polymorphic light eruption is due to the ability of this preparation to restore the adaptability of skin to ultraviolet light.

Because of the efficacy of chloroquine in certain dermatoses, it was almost inevitable that it would be used in other dermatoses on an empirical basis. Ayres[24] found chloroquine effective in some cases of lichen planus and verruca, but of no benefit in psoriasis. It appeared to exert an antipruritic or anti-inflammatory effect in a few cases of pruritic and eczematous dermatoses of various types.

Brodthagen[25] has reported moderate success in treating patients with Rosacea with chloroquine, and other isolated case reports have shown good results in acrodermatitis chronica atrophicans and in vitiligo.[27]

Prompted by reports of the disappearance of a previously unmentioned itchy vaginal discharge from patients being treated for amebiasis shortly after the routine use of chloroquine in such treatment, Carpenter[28] treated eleven cases of vaginitis due to T. vaginalis with chloroquine. He followed several of these patients over a two year period and found no recurrences in this group. The dosage employed was that recommended for malaria. Swartzwelder[29] was unable to duplicate these results, and he found that any apparent suppressive influence of chloroquine on T. vaginalis was evanescent.

Recently, chloroquine has been employed in the treatment of various species of liver flukes with a resulting marked decrease in the number of ova passed.[30,31]

Arora and Sharma[32] reported chloroquine to be more effective in its antifibrillatory action than quinidine in the refractory period of isolated rabbit auricles, acetylcholine induced fibrillation in dogs, and electrically-induced auricular fibrillation in cats. In lieu of these experiments the authors suggested clinical trials in auricular fibrillation. Following these suggestions, Sanghvi[33] administered chloroquine intravenously to two patients with auricular fibrillation. Here fibrillation changed to flutter but with further injection ventricular premature beats and short periods of ventricular tachycardia appeared and further experiments were abandoned.

CASE REPORTS

The original studies of Capriles reported in February 1956 included a series of 67 cases of diabetes mellitus. Thirty patients were between the age of 20-30 years and thirty-seven patients were 30 years of age and over. Forty of his patients were treated for 180 consecutive days, with daily doses of 2 cc. of chloroquine (100 mg. chloroquine base/cc.). He noted gradual disappearance of glycemia, glycosuria, and all other symptoms. This disappearance of signs and symptoms of diabetes persisted for from three months to one year following discontinuance of therapy. Twenty-nine patients remained normal from three to six months after treatment; the remaining eleven patients did not receive any treatment between six months and one year. Diabetic symptoms returned in all cases; however, additional injections of chloroquine (4 cc. daily) resulted in a return of these patients to normal.

The remaining 27 patients in this series received more intensive treatment, i.e. 6 cc. of chloroquine daily for forty consecutive days. All these cases returned to normal, and the duration of imporvement without treatment lasted from four months to one year. The remaining twelve patients in this group did not improve in any appreciable way.

Similar results have been obtained by Alvarez in Mexico.[34] In his series of twenty cases he has had various age groups, sexes, and degrees of diabetes. Some of his cases were treated satisfactorily with 300 mg. of chloroquine base daily.

In our series, eight diabetic patients between the ages of 39 and 70 were studied. Six of these patients had previously been treated with carbutamide (BZ 55) giving us the opportunity to compare the effects of carbutamide to those obtained with chloroquine therapy. Blood carbutamide levels were taken, and Aralen therapy was not started until these levels were zero. The dosage of chloroquine employed was equivalent to the highest dosages employed by Capriles[3] in his series. Most patients received four tablets of chloroquine di-phosphate (Aralen) daily which is equivalent to 600 mg. of chloroquine base. Those patients showing toxicity to the drug were placed on lower dosages. Treatment in most cases was continued for at least forty days. Serial liver function studies were carried out on all patients because of the concentration of this drug in the liver and the prolonged course of therapy.

The following are examples of the effects of chloroquine in diabetes:

Figure 1 shows a case of a 66 year old woman who was a known diabetic for eleven years. She had been on 15 units of protamine insulin in 1951 and ten units of protamine insulin from 1952 to 1956. During a course of therapy with BZ 55, her insulin requirement dropped to zero, and her fasting blood sugar during therapy fluctuated between 100 and 140 mg.%. Thirty days after cessation of treatment with BZ 55 her blood BZ 55 level had dropped to zero and she was started on Aralen at a dosage of 1.0 gm./day. Approxi-

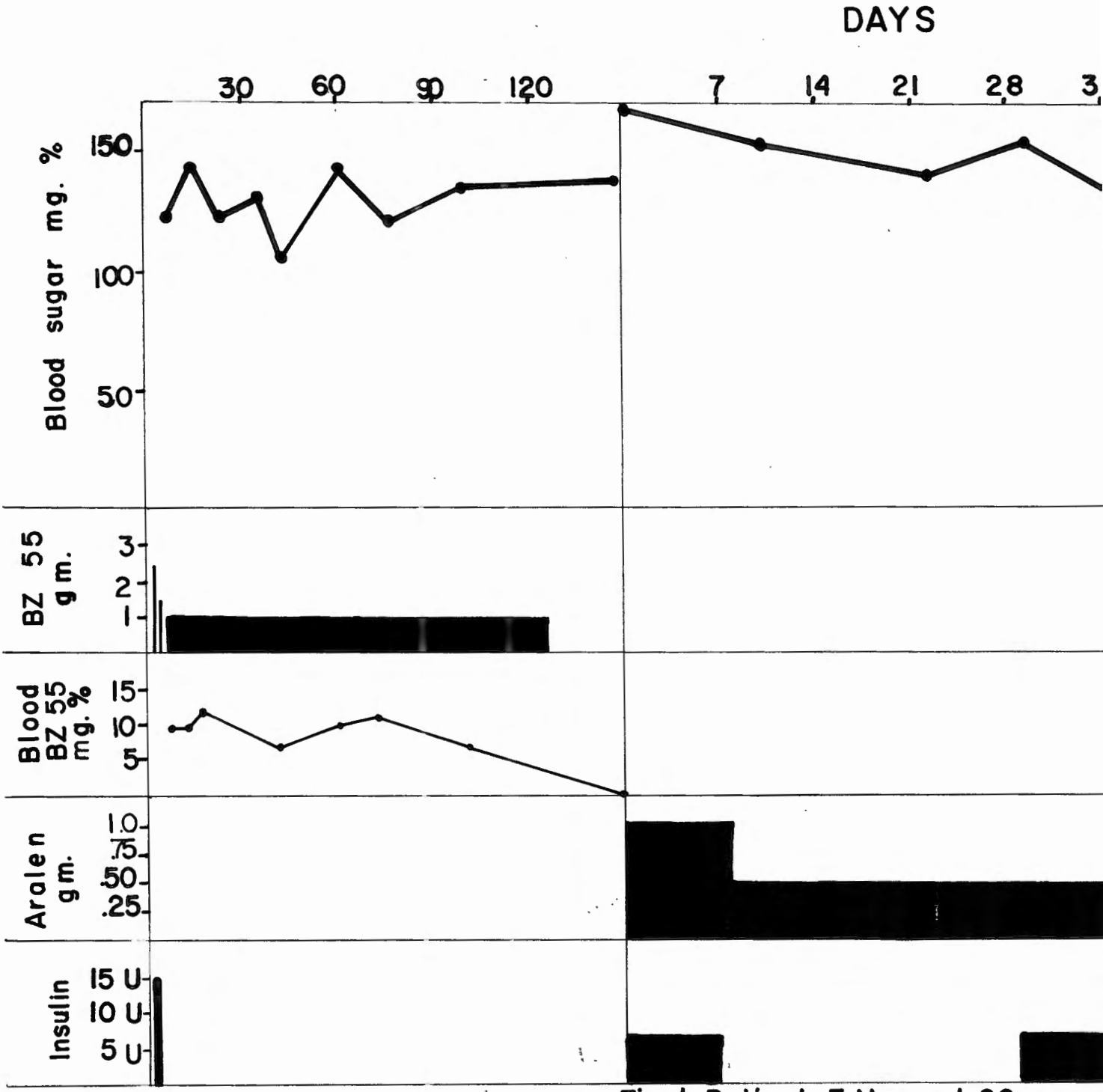

Fig. 1 Patient E.M. aged 66 years

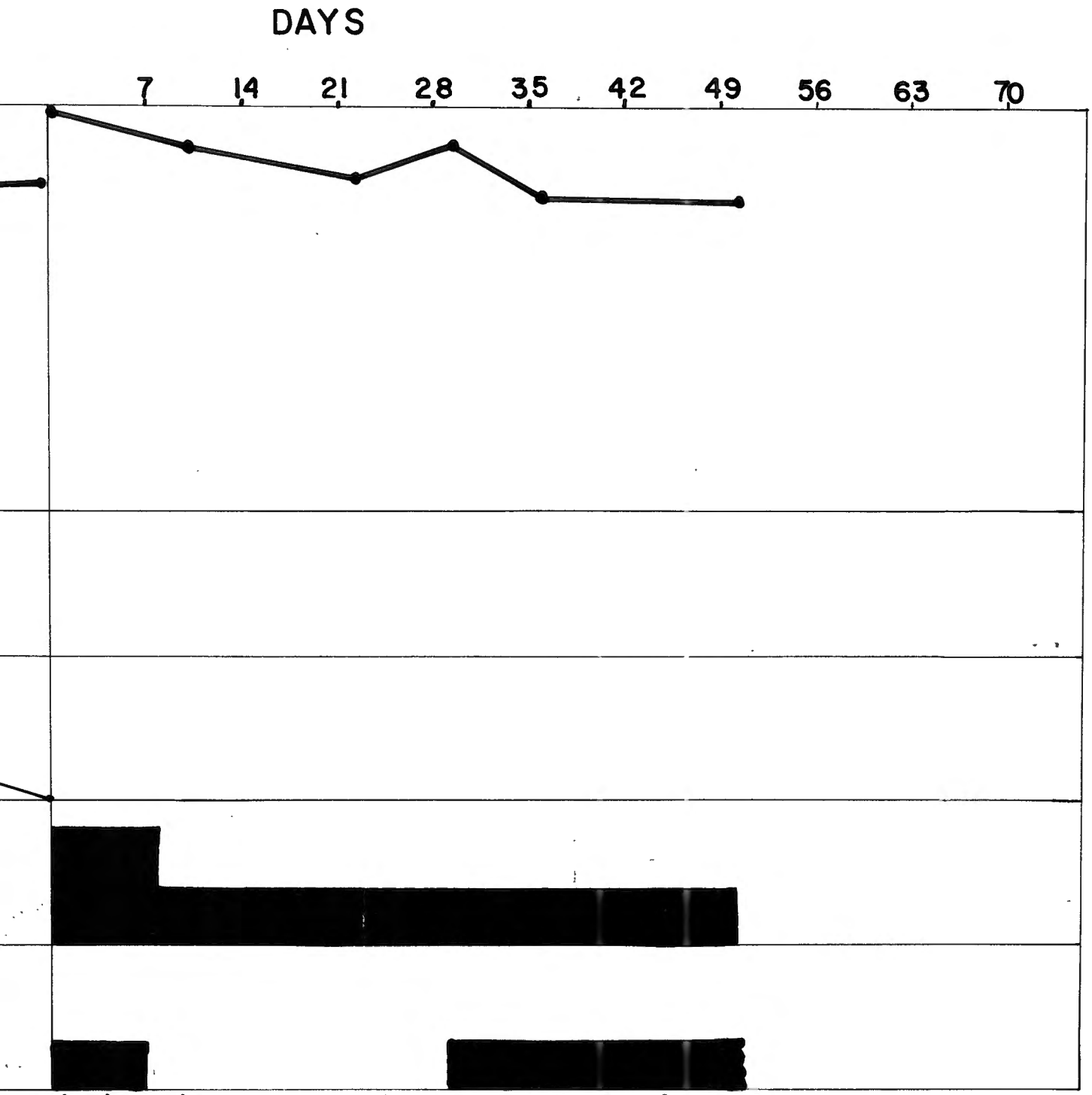

Fig. I Patient E.M. aged 66 years

mately one week after beginning Aralen therapy the patient developed nausea, and became light headed and shaky. Aralen was reduced to 0.5 gm./day, and no further signs of toxicity were noted. The patient was treated with Aralen for a total of 50 days during which time her fasting blood sugar remained between 129 and 150 mg.; insulin requirements dropped to zero for 21 days during Aralen therapy and then was reinstated at a level of six units per day.

Figure 2 represents the record of a 56 year old man who was diagnosed as a diabetic a few months before these experiments. At the time of the initial diagnosis his fasting blood sugar was 220 mg.%, and a glucose tolerance test showed blood sugar levels of 289 mg.% at ½ hour, 390 mg.% at 1 hour, 444 mg.% at 2 hours, 460 mg.% at 4 hours and 240 mg.% at 5 hours. He was subsequently placed on a 1200 calorie diet, and his insulin requirement adjusted at a level of 20 units daily. Six months later he was placed on BZ 55 1.0 grams daily for 90 days. During this course of therapy his fasting blood sugar remained between 98 and 128 mg.%, and he did not require any insulin. At the termination of therapy with BZ 55 his fasting blood sugar was 100 mg.%. Twenty-one days later his fasting blood sugar had risen to 175 mg.%, and his blood BZ 55 level had dropped to zero. At this point he was placed on Aralen therapy, and his fasting blood sugar dropped to levels between 130 and 145 mg.% during the period of treatment. He was restarted on six units of insulin fourteen days following the termination

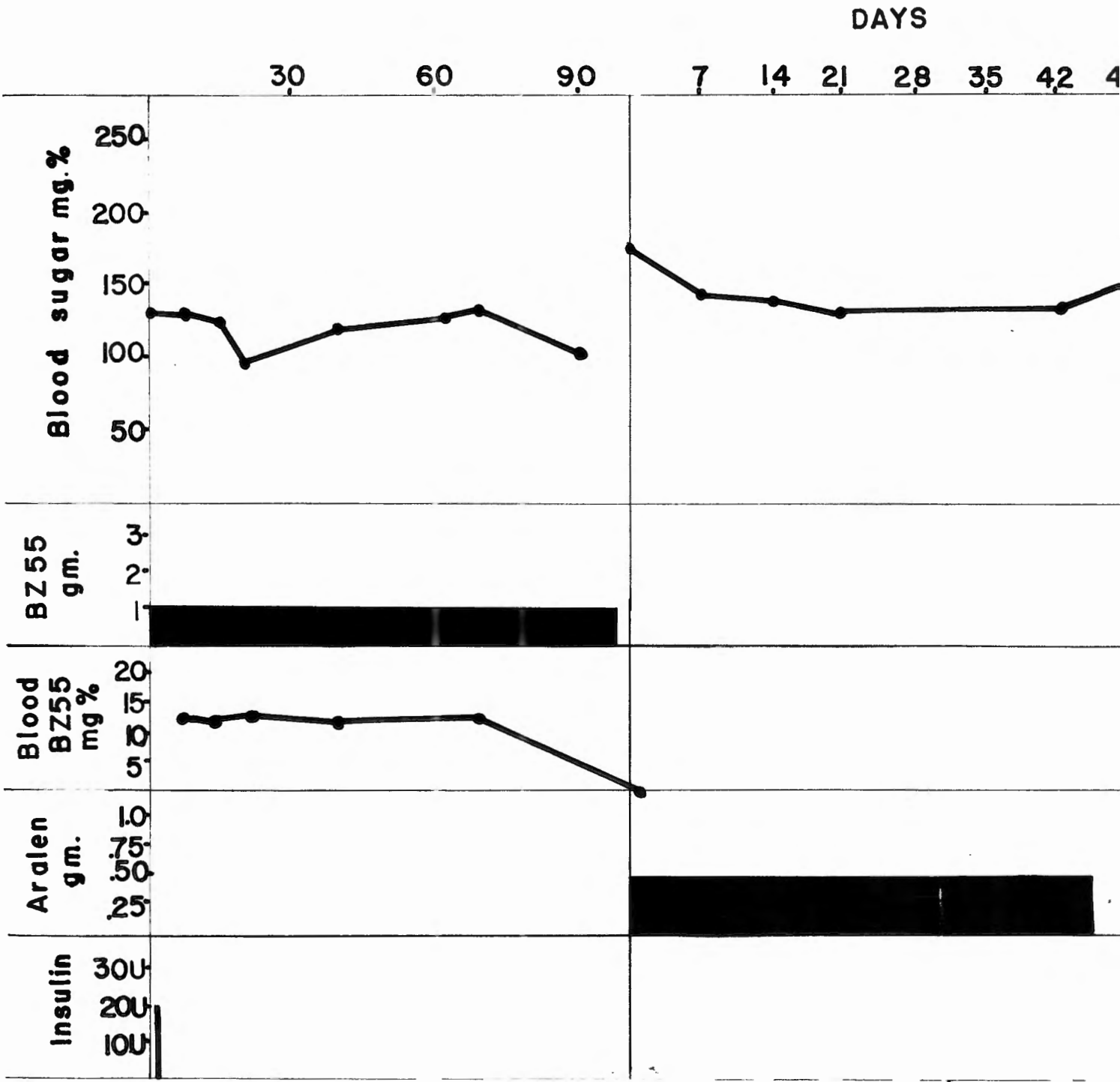

Fig. 2 Patient H.G. aged 56 years

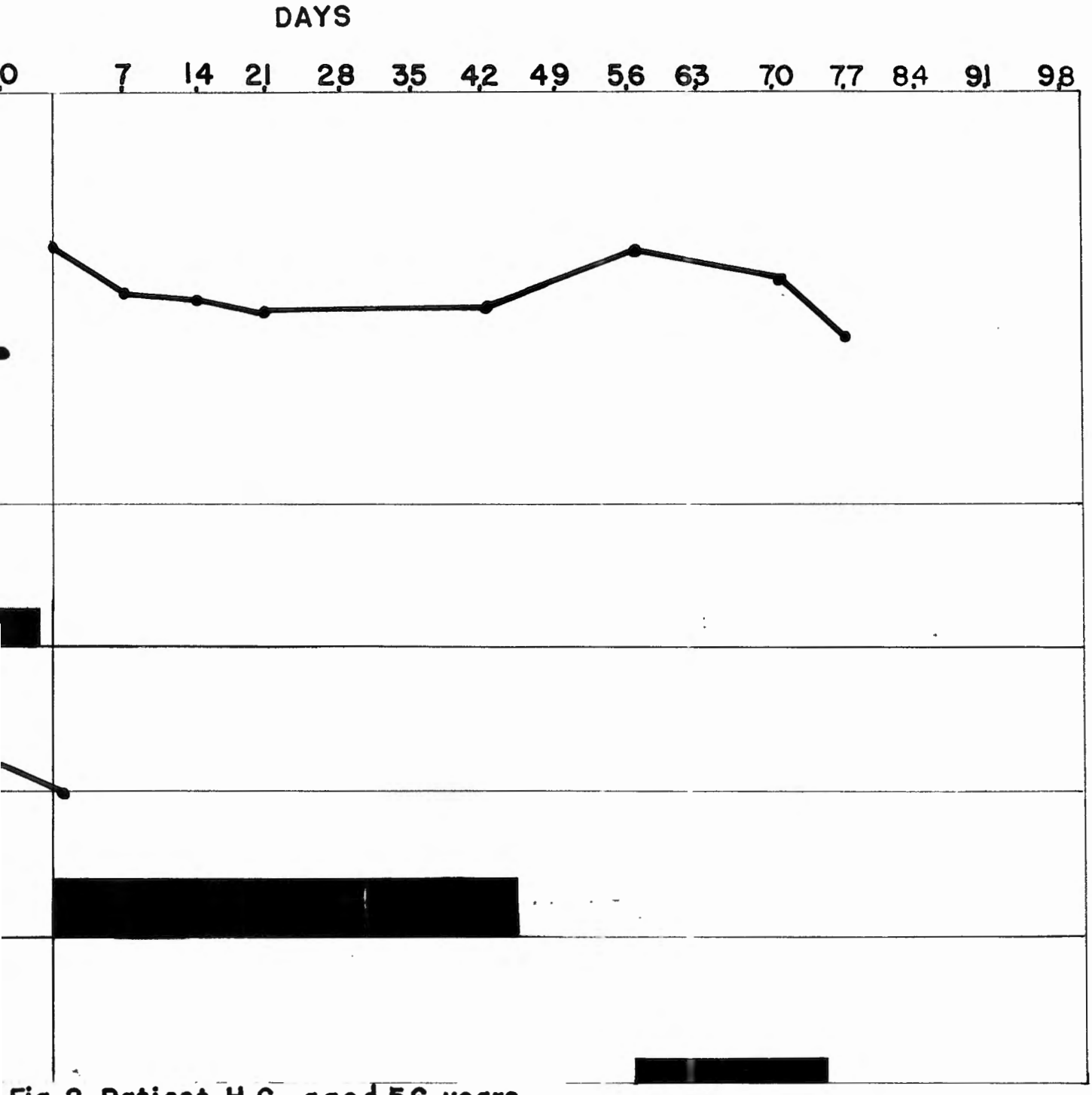

Fig. 2 Patient H.G. aged 56 years

of Aralen therapy and has been maintained on this lower dosage to the present in contrast to his higher insulin requirements before these experiments.

Figure 3 illustrates results in a patient who developed a generalized maculo-papular pruritic rash after 15 days treatment with carbutamide. This patient has been a known diabetic for 15 years requiring from 65 to 70 units of insulin daily. After the patient became stabilized he was started on Aralen therapy, one gram daily for 42 consecutive days. Due to a misunderstanding the patient stopped taking insulin at this time, but in spite of this his blood sugar level remained stable on aralen alone. Following Aralen therapy the patient would take 30 units of insulin for 2 or 3 days when he showed some glycosuria and then would take none until he again showed glycosuria which was usually at weekly intervals. He is currently stabilized on 20 units of insulin daily, which represents a lapse of 72 days since the termination of Aralen therapy.

Figure 4 presents a 58 year old woman with diabetes mellitus of one and one-half years duration. Following a course of BZ 55 therapy she was started on 1.0 grams of Aralen daily, but because of nausea and vomiting, the drug was withdrawn. The patient had shown some response, however, in this short period of therapy; her fasting blood sugar had dropped from 200 mg.% to 163 mg.% after 13 days treatment, and her insulin requirement had dropped

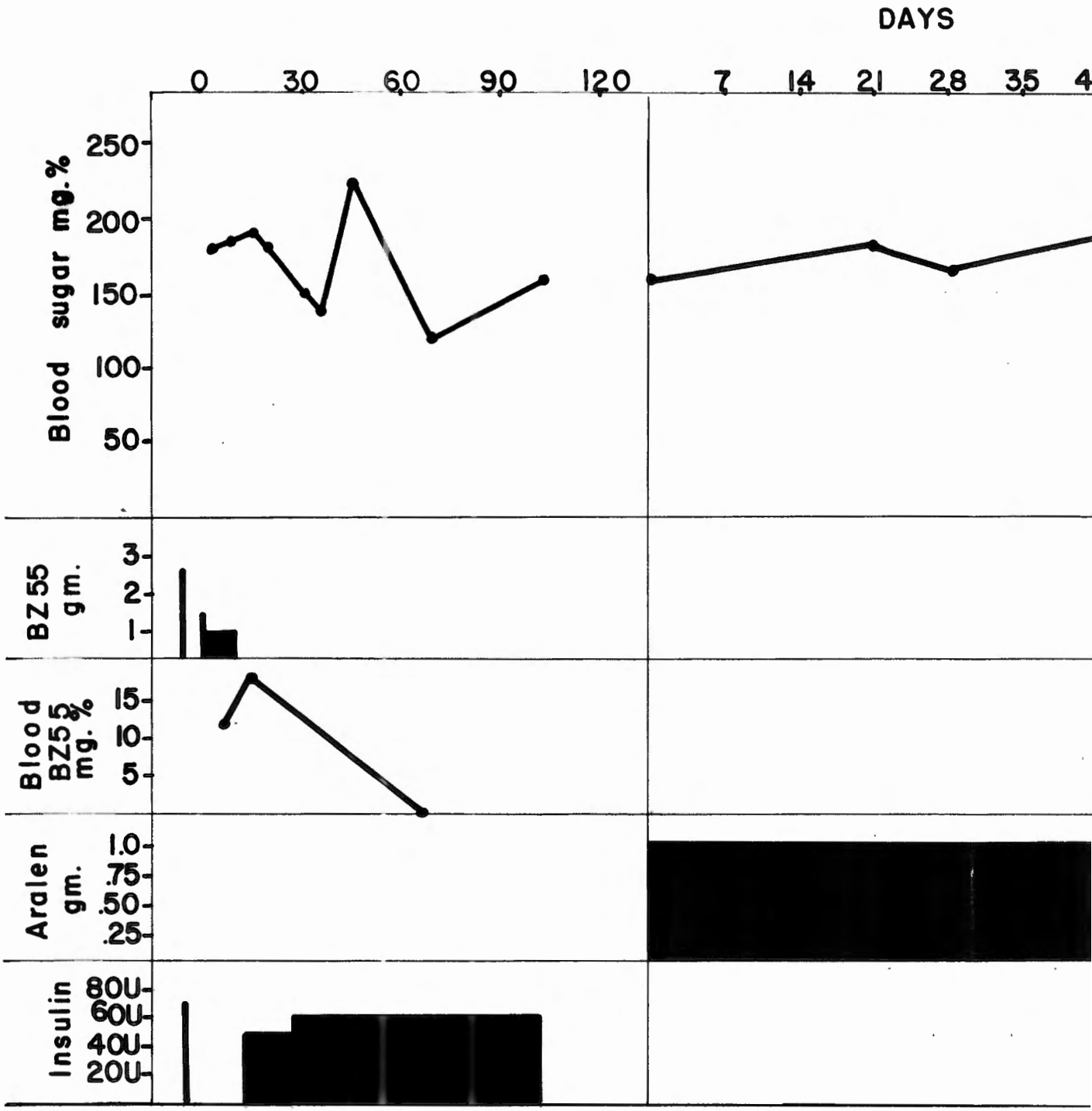

Fig.3 Patient A.F. aged 70 ye

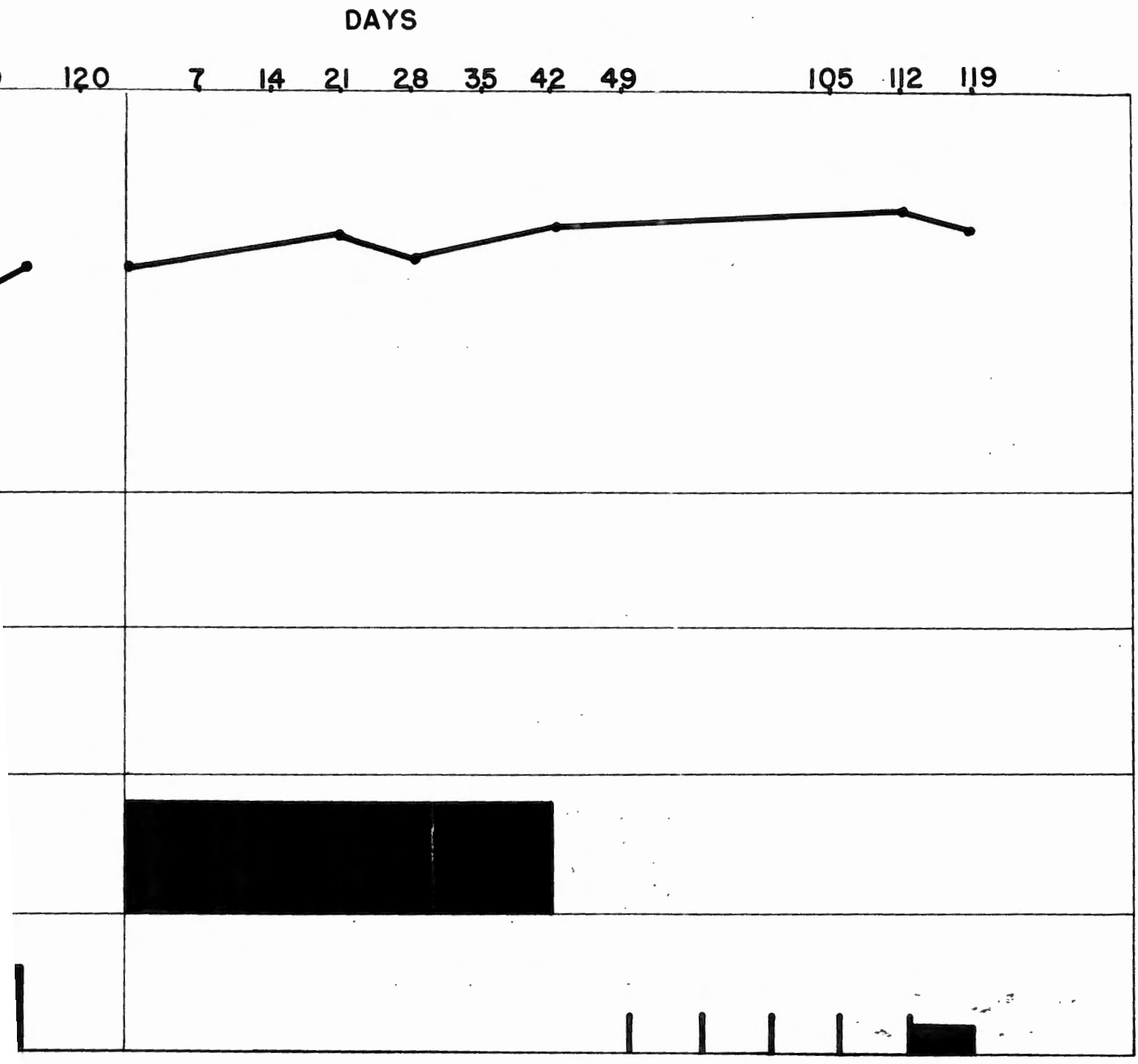

Fig.3 Patient A.F. aged 70 years

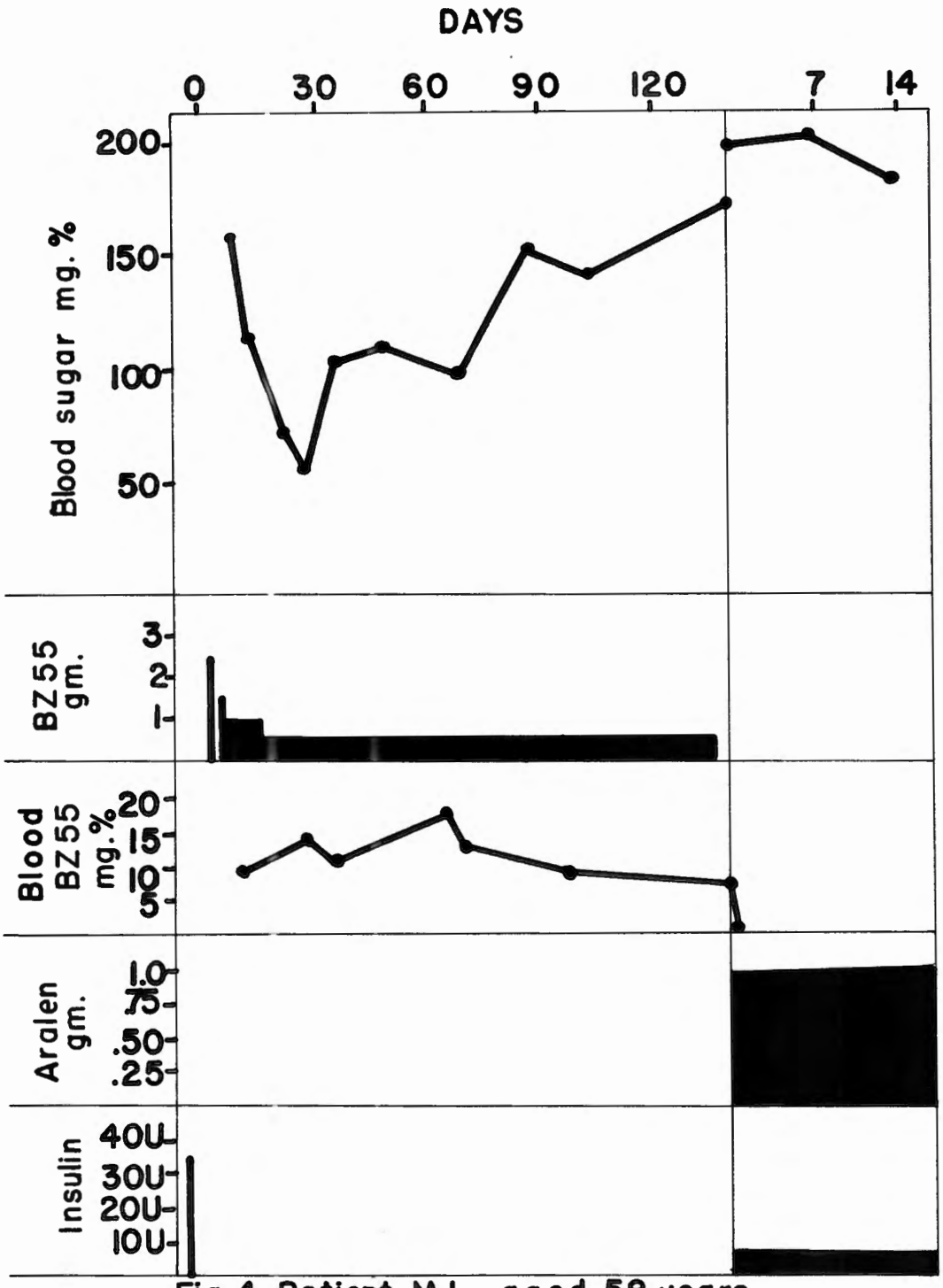

Fig.4 Patient M.L. aged 58 years

from 35 units/day to 8 units/day.

Figure 5 shows a case of diabetes mellitus in a 39 year old woman who had been a freshly discovered diabetic with a fasting blood sugar of 265 mg.%. She was controlled initially on 20 units of PZI insulin daily and then started on BZ 55 therapy. After 111 days of BZ 55 the patient was followed until BZ 55 blood levels were zero, and then she was started on a course of therapy with Aralen, 1 gram daily for 42 consecutive days. During Aralen therapy the patient did not require any insulin, and her fasting blood sugar levels remained between 85 and 110 mg.%. At this writing the patient has had no Aralen for over one month and has not required any insulin; fasting blood sugar levels have never been over 100 mg.%.

Figure 6 represents a similar case where a freshly discovered diabetic with a fasting blood sugar of 285 mg.% was started on BZ 55 therapy and maintained without insulin for 159 days. After BZ 55 blood levels returned to Zero and her fasting blood sugar had risen to 160 mg., she was started on Aralen therapy, with fasting blood sugar levels dropping to 96 mg.% and no insulin required.

Figure 7 illustrates a known diabetic for 30 years who entered the hospital in diabetic coma after having been previously controlled on 42 units of insulin daily. At the time of her admission, fasting blood sugar was 450 mg.%, and her insulin requirement gradually adjusted at 80 units daily.

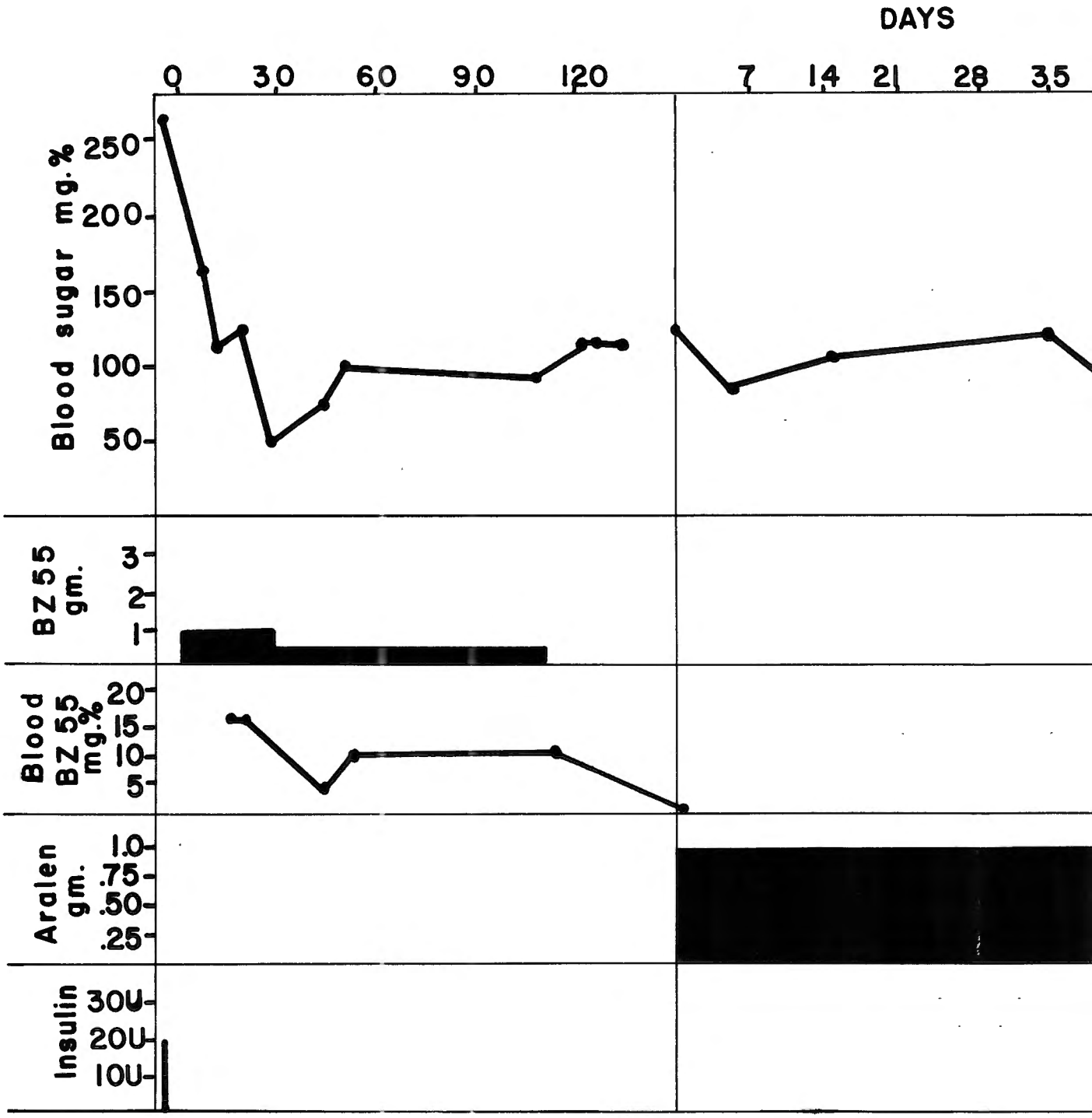

Fig.5 Patient L.W. aged 39 ye

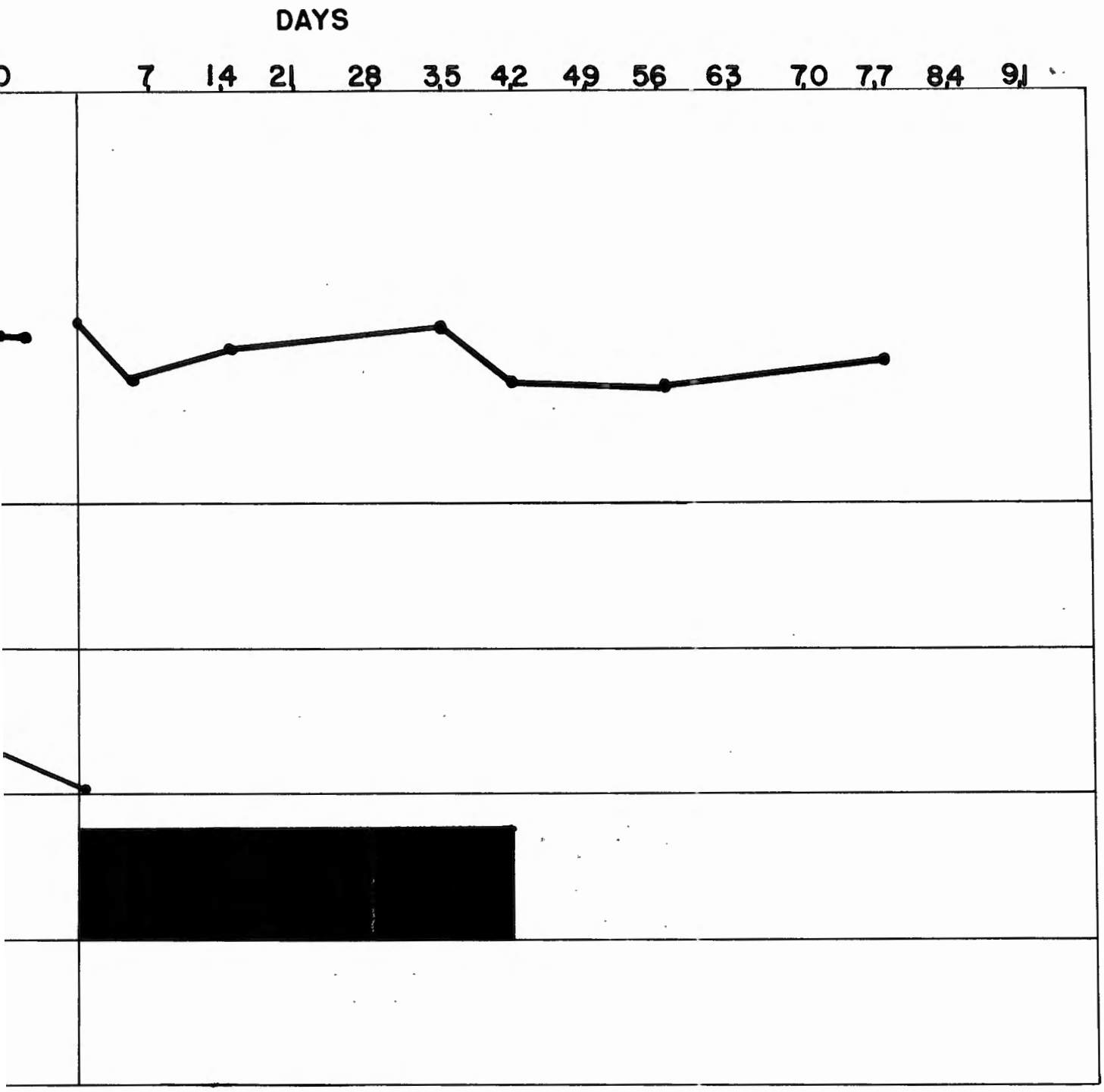

Fig.5 Patient L.W. aged 39 years

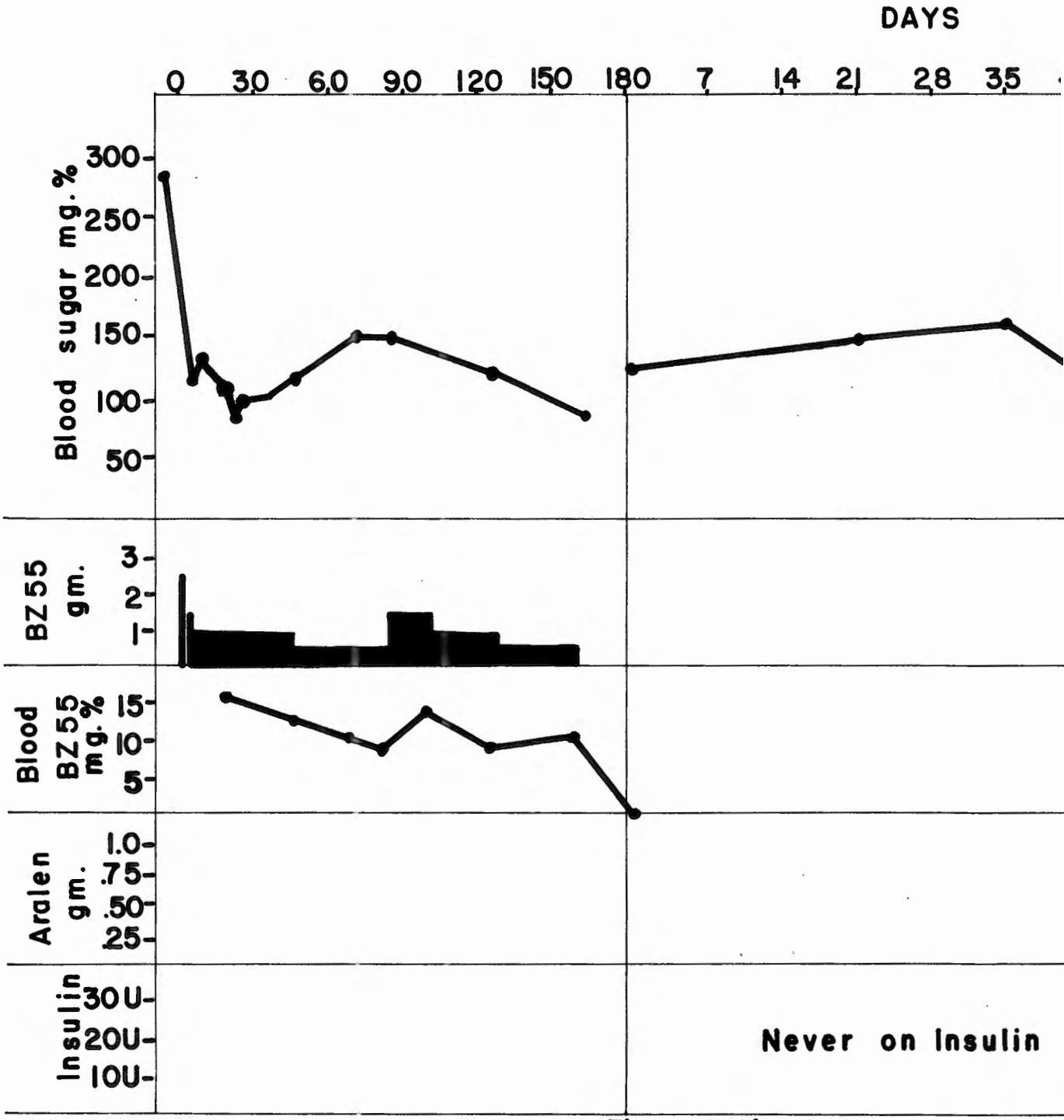

Fig.6 Patient B.R. aged 48

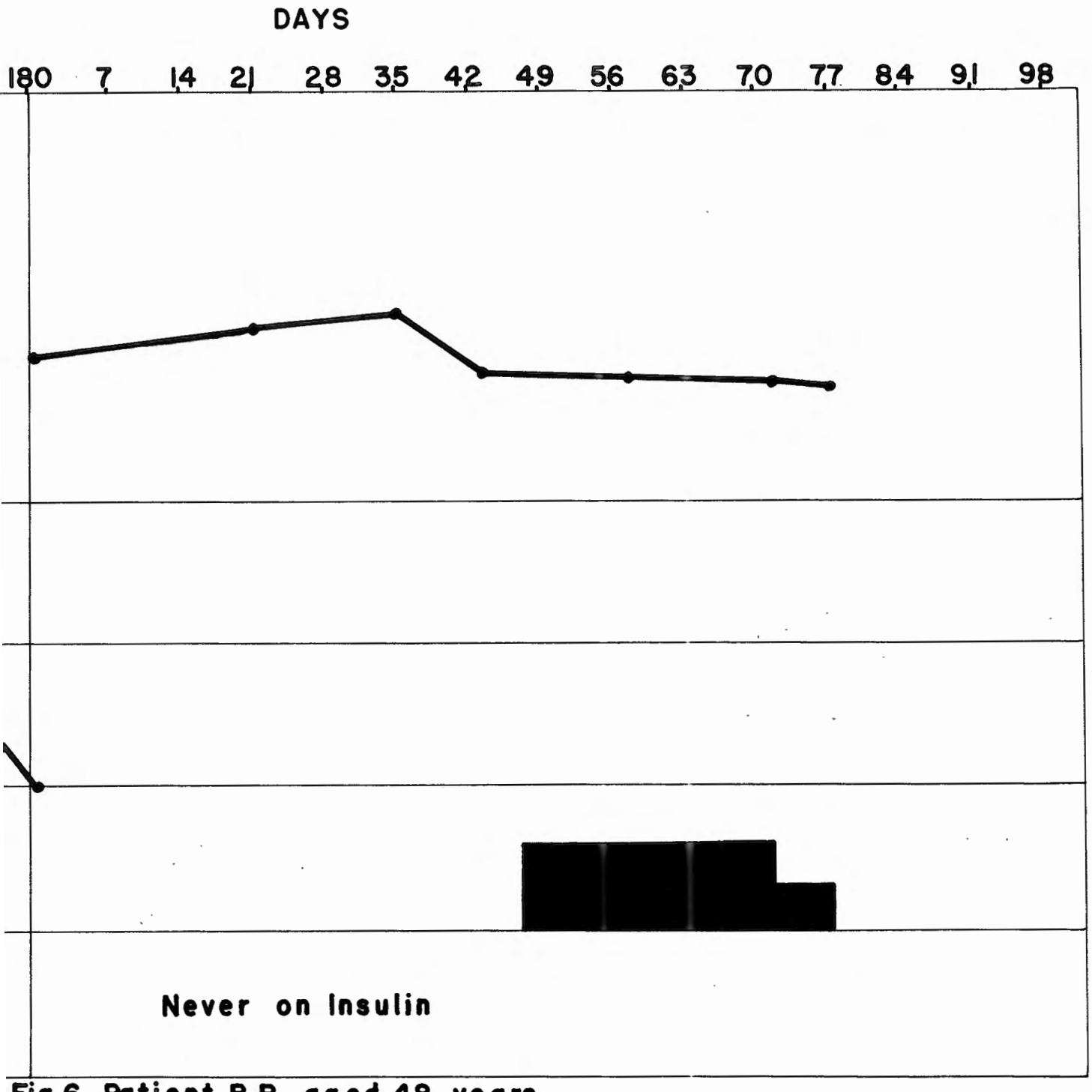

Fig.6 Patient B.R. aged 48 years

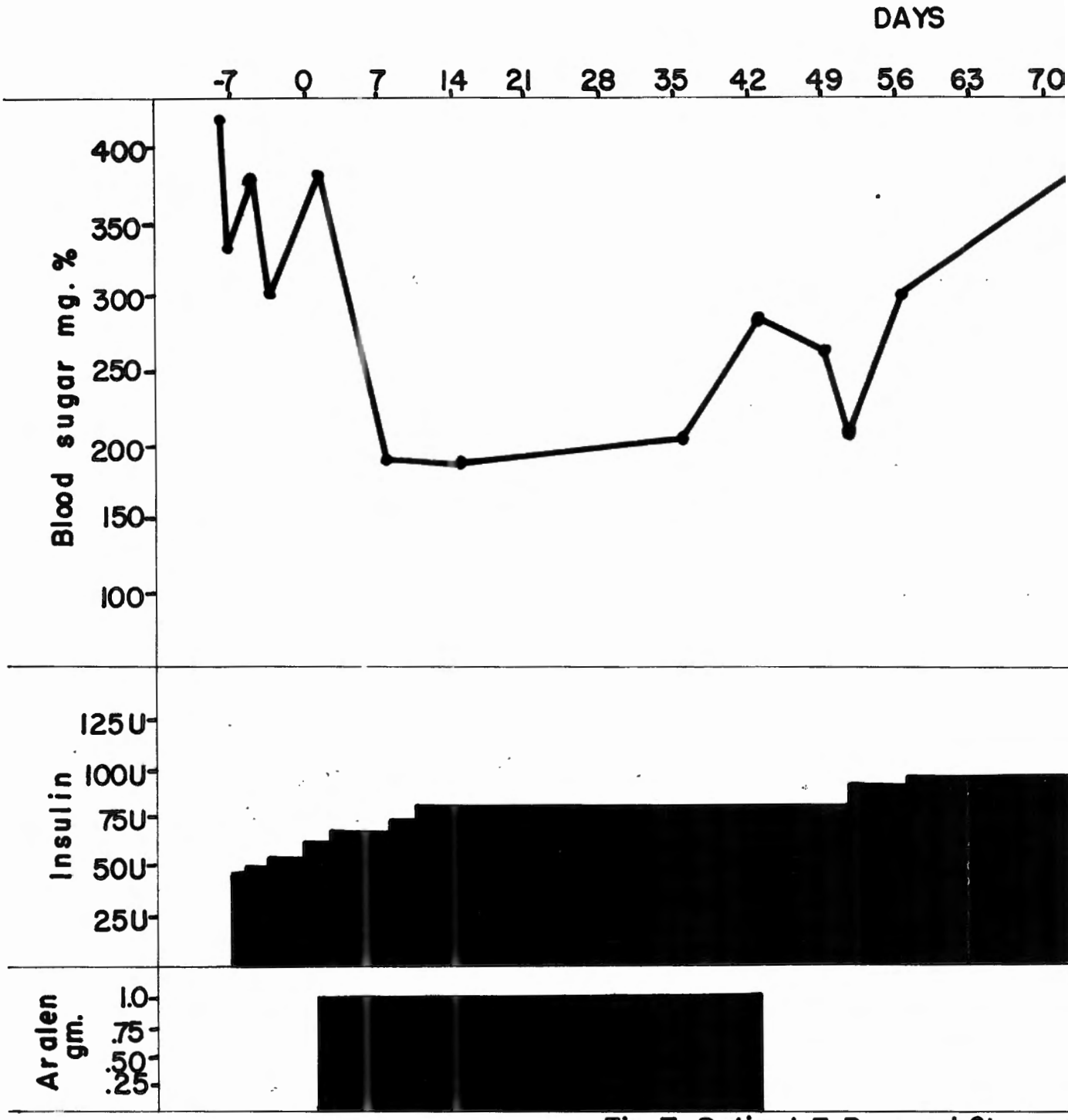

Fig. 7 Patient E. R. aged 61 yea

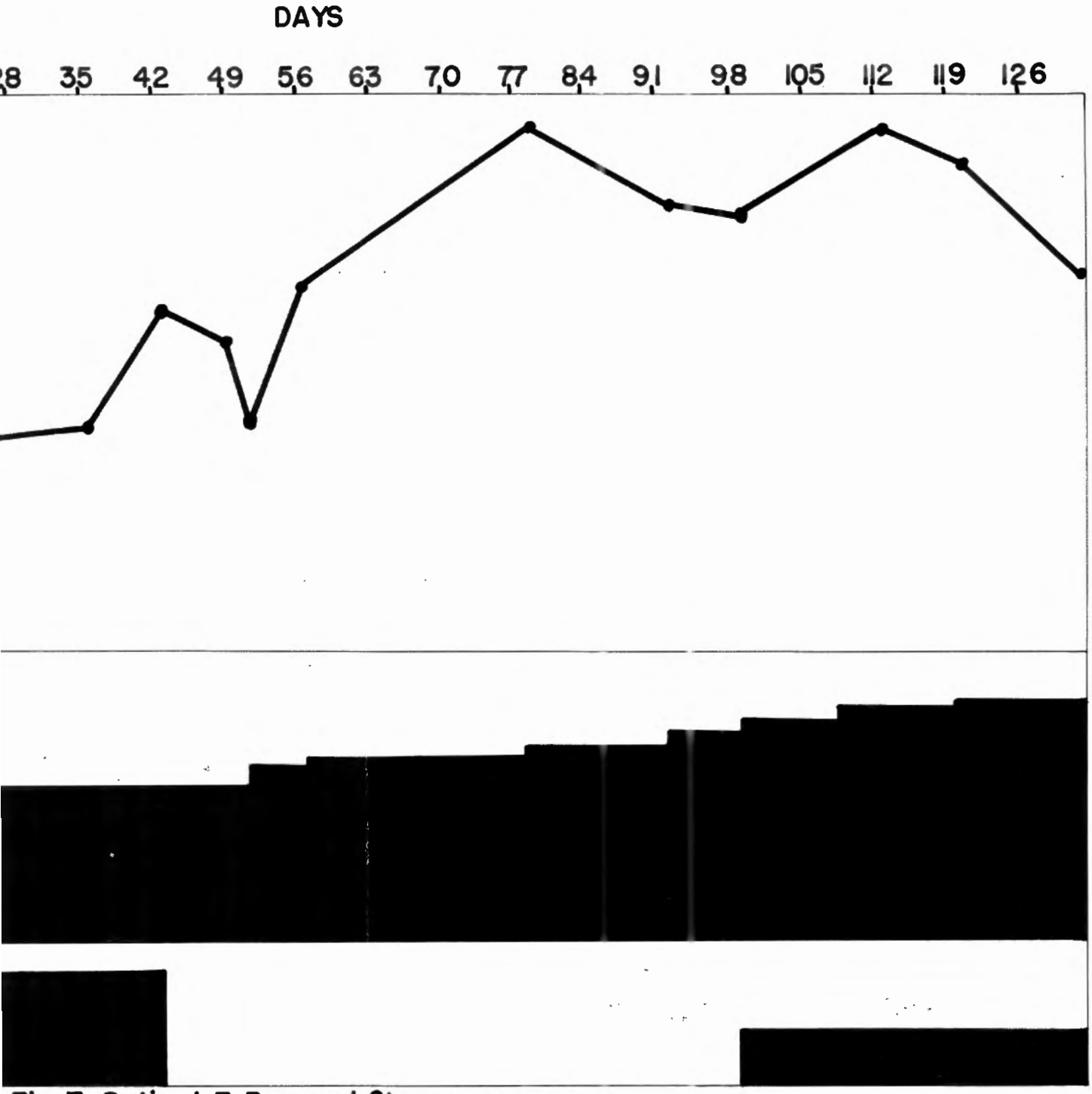

Fig. 7 Patient E.R. aged 61 years

The patient was placed on Aralen (1.0 gram daily) for 43 consecutive days; during this time her insulin requirements remained stable, and fasting blood sugar levels also stabilized. Following withdrawal of Aralen therapy the patient began requiring periodic increases in insulin, and fasting blood sugar levels rose in spite of attempts to control her with higher daily doses of insulin. The patient was started on another course of Aralen therapy on the 99th day of the experiment when insulin requirements had reached a level of 112 units daily and fasting blood sugar was 354 mg.%; however, not enough time had elapsed to evaluate this second course of treatment with Aralen.

Figure 8 represents a case of a known diabetic for 14 years. He had been hospitalized 4 or 5 times when he got out of control and has had two toes amputated because of infection and gangrene. When the patient entered the hospital out of control, his fasting blood sugar was 350 mg.%, and he had been taking 30 units of insulin daily. Insulin requirement became stabilized at 42 units daily, and the patient was then started on Aralen therapy, 1 gram daily for 44 consecutive days. Fasting blood sugar levels at the termination of Aralen therapy were 100 mg.%. Insulin was reduced to 30 units/day, and the patient remained stable with blood sugar levels gradually rising and reaching a level of 212mg.% 128 days after the onset of aralen therapy. At this point he was restarted on another course of Aralen (0.5 gm./day) but not enough time has elapsed

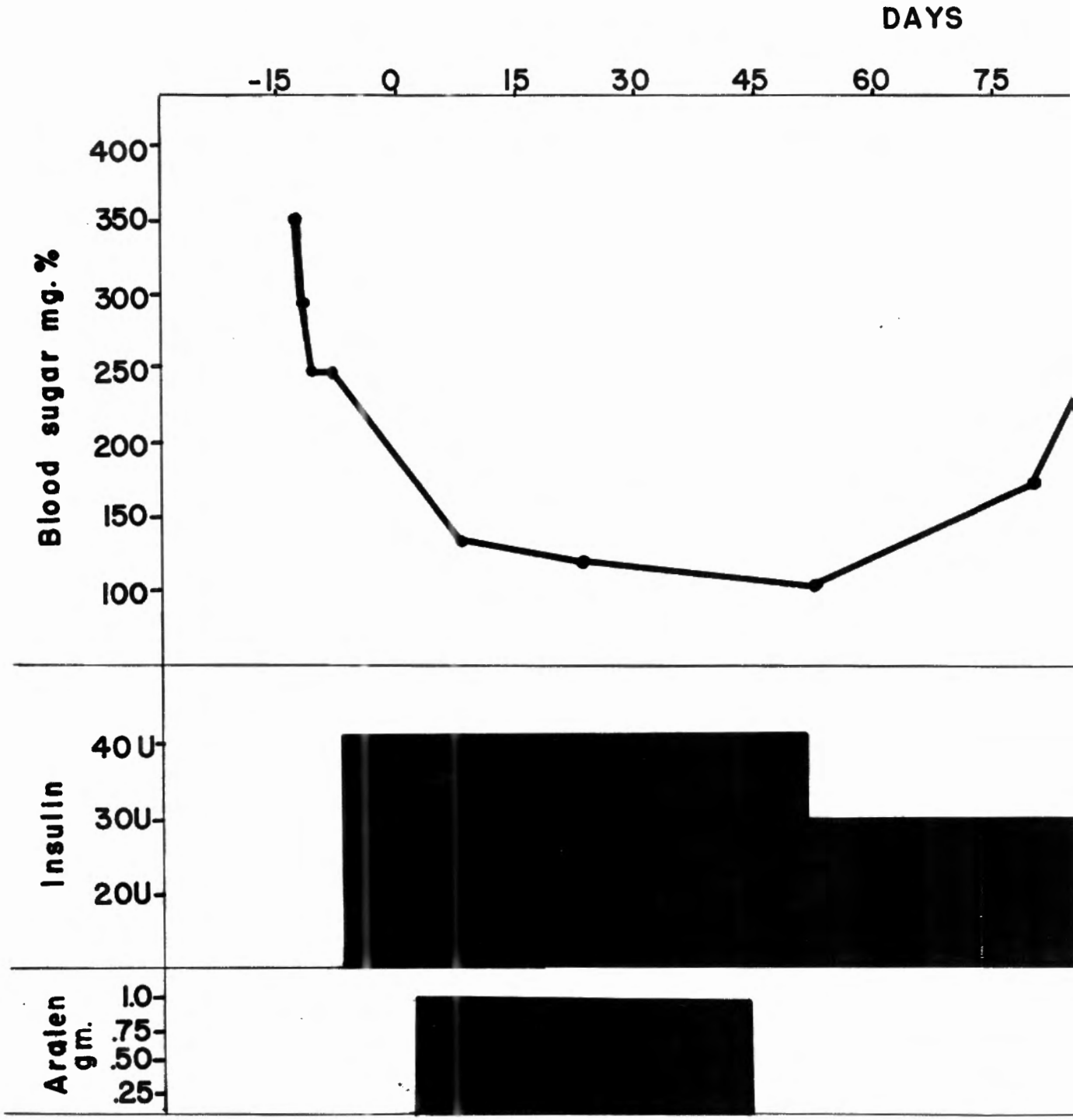

Fig. 8 Patient P.R. aged 57 ye

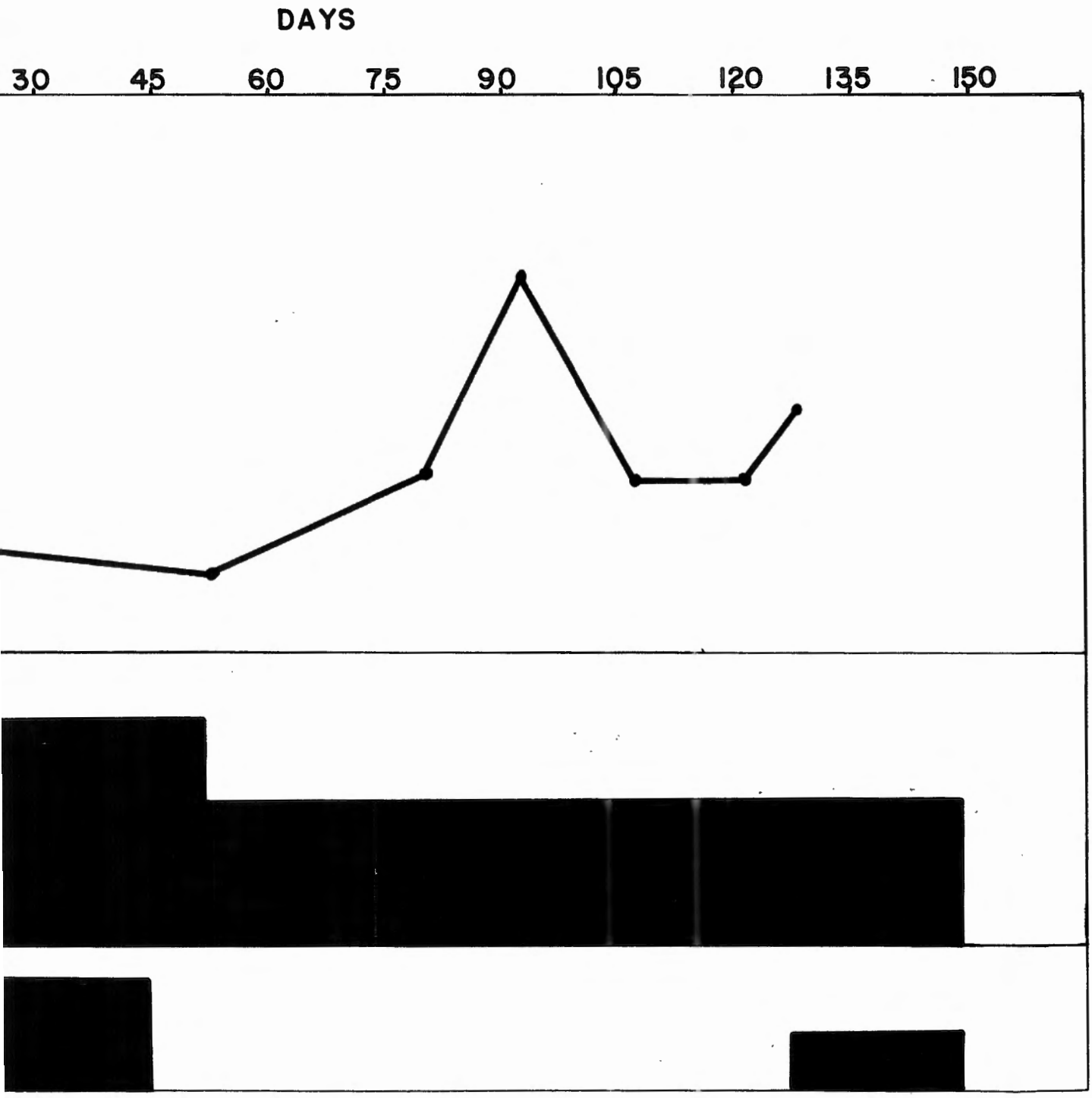

Fig. 8 Patient P.R. aged 57 years

since this second course to evaluate any effects.

DOSAGE AND TOLERANCE

Capriles[3] recommended a daily dose of 6 cc. of Aralen (100 mg. chloroquine base/cc.) as a potent anti-diabetic medication which he found to be innocuous and of prolonged action. As has been previously stated, chloroquine is almost completely absorbed from the gastro-intestinal tract, and for this reason we employed the oral from of the drug in dosages of 1.0 gram of chloroquine di-phosphate daily which contains 600 mg. of chloroquine base. At this dosage one patient tolerated the drug poorly, and treatment was abandoned after 18 days because of several bouts of nausea and vomiting. One other patient who has taken 1.0 gram of chloroquine di-phosphate daily had some upper abdominal discomfort associated with nausea and vomiting but not severe enough to discontinue therapy. A third patient complained of mild abdominal discomfort. Three patients exhibited signs of mild visual disturbances, and three showed no signs of toxicity to chloroquine.

Our experience with chloroquine demonstrated that when a patient shows a good response to the drug, smaller dosages may be employed with equivalent results. In two cases in which 0.5 gram of Aralen/day was used, the clinical response was equally as good as with the higher dosages.

SUMMARY

Oral administration of Aralen (chloroquine di-phosphate) to diabetics, some of whom had previously been treated with BZ 55 (carbutamide), resulted in a lowering of fasting blood sugar levels and a decrease or elimination of insulin requirements. Duration of improvement following treatment with Aralen will require further follow-up studies. In several cases, insulin requirement following termination of Aralen therapy has been markedly reduced or eliminated, and fasting blood sugar levels have remained much lower than pre-experimental levels.

Of the six patients who had been on carbutamide therapy prior to receiving a course of Aralen, all sustained a rapid reduction of blood sugar levels to the normal range. This rapid response was measured at the first blood sugar determination following the onset of therapy. Since fasting blood sugar determinations were done at weekly intervals it is not known if the response to Aralen occurred sooner than one week following the onset of therapy.

In the two patients who had never received carbutamide prior to Aralen therapy, a rapid response to Aralen therapy was also observed. In both cases fasting blood sugar levels remained depressed during the course of Aralen therapy; however, it is difficult to evaluate the Aralen effect in both patients because of the lability of their diabetes when these observations were made. Both patients had been out of control and were started on Aralen therapy

toward the end of hospitalization. For these reasons an evaluation of Aralen should be repeated in diabetic patients who have not previously been on other oral anti-diabetic drugs and who are well controlled and stable in the course of their disease.

Speculation would suggest that a good response to Aralen would be expected in such a patient. In the six patients who had previously been treated with carbutamide, blood levels of carbutamide were zero in all cases before Aralen therapy was instituted and any alteration in the course of the disease should be ascribed to Aralen; however positive establishment of this supposition could only be proven in the previously untreated patient.

In view of some mild toxic effects noted on doses of 1.0 gram of Aralen daily, it appears that lower doses will be necessary if this drug is to be used clinically. Since we obtained good results on doses of 0.5 gram daily without any untoward side effects, we feel that lower dosages of Aralen should be used.

Our main objective in this clinical study has been to report our observations in order to encourage further research to elluci-date the mechanism by which this remarkable drug reduces blood sugar in the diabetic patient.

CONCLUSIONS

1. Aralen (chloroquine di-phosphate) used orally appears to be effective in lowering blood sugar levels in diabetes mellitus.

2. With the use of Aralen, insulin requirements may be lowered and in some instances may become unnecessary.

3. Treatment need not be continuous because clinical remission in diabetes usually follows termination of Aralen therapy.

4. In the higher dosages used there were no severe toxic sequele other than the mild episodes of nausea and vomiting and visual disturbances. On a lower regimen the drug proved innocuous.

5. The mechanism by which Aralen reduces blood sugar levels in the hyperglycemia of diabetes mellitus remains to be ellucidated.

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