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Effects of chloroquine phosphate in diabetes mellitus

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THE EFFECTS OF CHLOROQUINE PHOSPHATE IN DIABETES MELLITUS

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Introduction

The Islands of Langerhans were first recognized in 1869. In 1890, it was demonstrated by Von Mering and Minkowski that extirpation of the pancreas would produce diabetes. Immediately following this discovery attempts to isolate the active substance were begun. This was successfully accomplished in 1922 by Banting and Best. The substance proved to be valuable only by parenteral administration, however, as the oral administration subjected the protein insulin to digestion by proteolytic enzymes which inactivated it. [1]

Insulin has remained and is at present the principal therapy for diabetes mellitus. There has been however during the last thirty-five and principally the last fifteen to twenty years a constant quest for an oral agent that would control Diabetes and do away with the necessity of daily injections of Insulin. [2]

Of the many preparations that have been studied to date, the sulfonureas have received the greatest attention and have proven the most successful. The first of these was Carbutamide which has been administered to over forty thousand diabetics in Germany and some eight thousand in Canada and the United States. [3] This drug was capable of reducing blood sugar and maintaining it, however it was found to produce evidence of liver damage and death by fall in prothrombin time, and has therefore been discontinued. [4]

Another sulfonurea, Tolbutamide (Orinase) has now been in use in adult diabetics for six years and has been found useful in

70 % of patients, and has as yet not been found to be hepatotoxic. It however is of no use in brittle, or juvenile diabetics, or diabetic acidosis.[5]

The drug under discussion in this paper, Chloroquine, was first found to produce hypoglycemia quite by accident. It's use as an antimalarial agent in World War II was successful and it was noted in one ward of patients under intensive continuous therapy for acute malaria that the patients developed a symptom complex similar to hypoglycemia. This could be prevented by parenteral glucose administration.[6]

Since this first discovery of the hypoglycemic action of the drug, many researchers have attempted to use it in treating diabetic patients. To date there has been no report of complete control of elevated blood sugar with this agent.

It is the purpose of this experiment to demonstrate the clinical value of Aralen in lowering and controlling the blood sugars of diabetic patients.

Chemistry

Chloroquine (SN-7618; aralen; resochin) is one of a large series of 4-aminoquinolines investigated in connection with the extensive cooperative program of antimalarial research in the United States during World War II.[7] The objective was to discover more effective and less toxic suppressive agents than quinacrine. Although the 4-aminoquinolines had previously been described as potential antimalarials by Russian investigators, serious attention was not paid to the group until the French reported that 3-methyl-7-chloro-4(4-diethylamino-1-methylbutylamino) quinoline (SN-6911; santochin; sontoquin) was well tolerated and had high activity in human malarias. Beginning in 1943, a large number of these compounds were synthesized and tested for activity in avain malaria and for toxicity in mammals; 10 of the series were then examined in humans with experimentally induced malarias. Of these, chloroquine proved most promising and was released for field trial. When hostilities ceased, it was discovered that the chemical had been synthesized and studied under the name of resochin by the Germans as early as 1934.

Chloroquine is 7-chloro-4-(4-diethylamino-1-methylbutylamino) quinoline, the compound is generally available as Chloroquine Phosphate. It is a white, bitter, water-soluble, crystalline powder. Approximately 60 per cent of the (di) phosphate represents the base. A solution of the drug is acid to litmus (pH about 4.5). The

degree of homogeneity is less than 4 per cent. The phosphate is marketed as 0.25-gram tablets for oral use.

In general, the absorption, fate, and excretion of chloroquine and related 4-aminoquinolines are similar to those of quinacrine.[8] Chloroquine is almost completely absorbed from the gastrointestinal tract and only small amounts are found in the stools; it is absorbed somewhat more rapidly than quinacrine, the plasma concentrations of chloroquine are substantially higher on any given dose schedule. Approximately 55 per cent of the drug in the plasma is bound to nondiffusible plasma constituents. Excretion of chloroquine is quite slow; only 10 to 20 per cent is found unchanged in the urine under ordinary conditions. However, the rate and extent of renal excretion of the drug may be appreciably influenced by the concurrent administration of acid or alkali; the excretion of chloroquine is increased by acidification of the urine and decreased by alkalinization.[9]

Chloroquine is deposited in the tissues in considerable amounts. In animals, from 200 to 700 times the plasma concentration may be found in the liver, spleen, kidney, and lung; leucocytes also concentrate the drug. The brain and spinal cord, in contrast, contain only 10 to 30 times the amount present in plasma.[8] The general pattern of distribution of chloroquine thus resembles that of quinacrine.

Chloroquine is largely degraded in the body and little is recoverable as such in the excreta. The nature of the degradation

products is not fully known. De-ethylation to the corresponding secondary amine occurs to some extent. This product is excreted in the urine of humans receiving chloroquine.[10] It is highly active against bird malaria. Metabolic products of chloroquine may be the active antimalarial agents, at least in part. Because of the avidity of the tissues for the drug and due to its metabolic alteration, a loading or priming dose is essential if effective plasma levels are to be reached and maintained. When the drug is discontinued, it slowly disappears from the tissues over a period of several weeks. With the dose of 0.5 gram once weekly, the peak plasma level varies between 150 and 250 micrograms per liter; just prior to the succeeding dose, the range is between 20 and 40 micrograms per liter.[11]

Chloroquine phosphate is administered in tablet form by the oral route, either before or after meals. The hydrochloride of chloroquine may be employed for parenteral (intramuscular) injection, if necessary.[12]

For the purpose of suppressive therapy, an oral dose of 0.5 gram of the phosphate is given on the same day of each week. For the treatment of the acute attack of vivax or falciparum malaria, an initial priming or loading dose of 1.0 gram is administered; this is followed by an additional 0.5 gram after six or eight hours and a single dose of 0.5 gram on each of three consecutive days, so that a total 3.0 grams is given in three days. This dosage schedule is usually sufficient to cure completely most P. falciparum

infections and to terminate promptly fever and parasitemia in acute P. vivax infections. Freedom from clinical attacks in vivax malarias is then maintained by suppressive doses of 0.5 gram weekly.

In animals, chloroquine is 5 to 10 times more toxic than quinine on a weight basis, and it has no advantage over quinacrine with respect to acute or chronic toxicity. Depending on the dose schedule and the species, it is slightly more or slightly less toxic than quinacrine. When rats are fed chloroquine for two years in amounts corresponding to therapeutic doses in man, the toxicity is slight or questionable; much larger doses produce a variety of pathological changes, but hematopoietic and neurological damage is minimal or absent. The relationship between chemical structure and toxicity in the 4-aminoquinoline antimalarial series has been reviewed by Blanchard and Schmidt. [13-14]

In man, however, chloroquine is less toxic and better tolerated than quinacrine. The amounts employed for therapy of the acute malarial attack may cause mild and transient headache, visual disturbances, gastrointestinal complaints, and pruritus. Prolonged chronic medication for suppressive purposes produces few significant untoward effects and only rarely must the drug be discontinued because of intolerance. None of the symptoms is serious and all readily disappear when the drug is withheld. Chloroquine does not discolor the skin, as does quinacrine. The chief untoward effects are pruritus and gastrointestinal discomfort.

Prolonged treatment with chloroquine causes a lichenoid skin eruption in a small percentage of patients; the condition is mild and subsides promptly when the drug is stopped. Similar cutaneous eruptions are observed after quinacrine. Readministration of chloroquine usually does not result in reappearance of the lesion, and the drug has been successfully employed in individuals with dermatitis caused by quinacrine.[15] Large doses given for a year to a group of normal volunteers occasionally caused some visual symptoms (blurring of vision due to difficulty in accommodation, diplopia), bleaching of the hair, diminution of T waves in some or all of the ECG (without evidence of cardiovascular impairment), mild skin eruption, headache, and slight weight loss. The observed toxic effects caused no incapacity and were reversible upon withdrawal of the drug. These findings emphasize the relative safety of chloroquine in the recommended dose range.

Clinical Reports

The first report of the use of Chloroquine in diabetes was that of Capriles.[16] This was a series of 67 diabetics 30 of whom were between the ages of 20 and 30, and 37 who were over 30. Of these patients 40 were treated for 180 days consecutively; receiving dosages of 200 mg. of chloroquine base. There was noted during therapy a gradual disappearance of glycemia, and glycosuria with reduction of diabetic symptoms. This persisted for periods ranging from three months to one year after termination of chloroquine therapy. Twenty nine of the forty patients had remissions lasting 3-6 months after termination of therapy. The other eleven received no therapy for periods of six months to one year before return of symptoms including glycemia and glycosuria which were reversable with daily administration of 400 mg. of chloroquine.

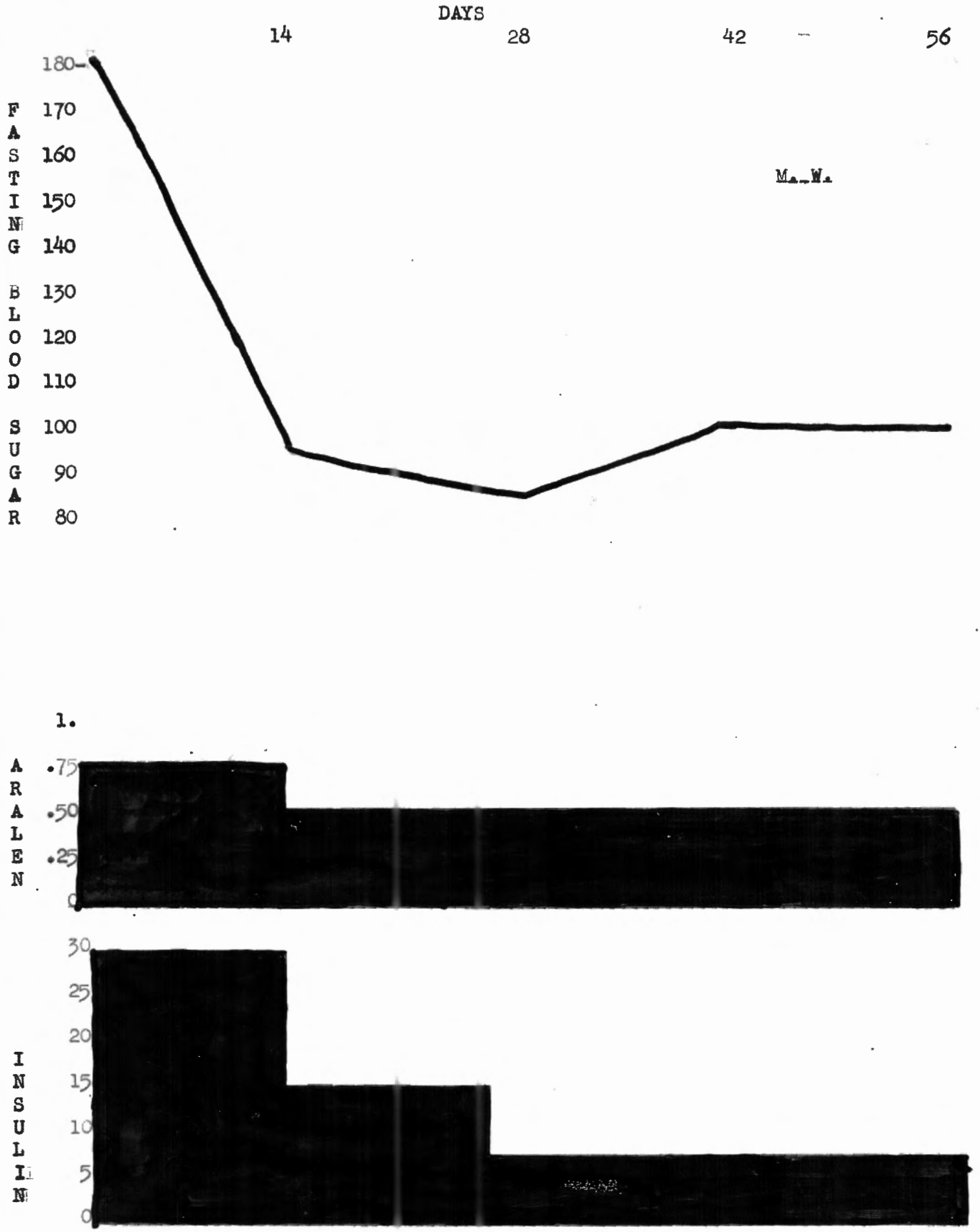
The other group of 27 patients in the series received a greater initial dosage of chloroquine; 6 cc. ie. 600 mg. of chloroquine base daily for 40 consecutive days. Fifteen of these patients showed a response by lowered blood sugar, absence of glycosuria and subsidence of symptoms. These patients remained in remission from four months to one year. Twelve of these patients showed no response to therapy..

The following reports are of nine patients studied by us and will be discussed individually.

Patient M. W. is a 80 year old white female, her weight was 147 pounds. She has been a known diabetic for twenty years receiving from 20-30 units of Insulin daily with good control. She was initially started on three tablets, 750 mg. Aralen daily and was continued on her previously established Insulin dosage of 28 Units. Her Aralen dosage had to be reduced because of visual disturbances, however during her 62 days on Aralen she was maintained on gradually reduced insulin requirements. She was well controlled at termination of experiment of 8 Units of Insulin and 500 mg. Aralen daily, see Figure 1.

The second patient, B.W., a 75 year old white male, weight 205 pounds has been a diabetic for twelve years. He has been controlled with dosages of 5-15 Units NPH Insulin. He was initially started on one gram Aralen daily and also continued on his present Insulin dosage of 15 Units daily. He sustained a marked drop of fasting blood sugar from 245 to 74 mg.%, and suffered no side effects. He was taken off of insulin and was well controlled on Aralen, 500 mg. daily for the duration of the experiment, see Figure 2.

The third patient, B.R., is a 48 year old female who had been a diabetic for two years. Her weight was 165 pounds. She had previously been treated successfully with Carbutamide following which she received Aralen therapy for one year with good control. She initially received one gram Aralen daily, and through gradual


DAYS
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FASTING BLOOD SUGAR
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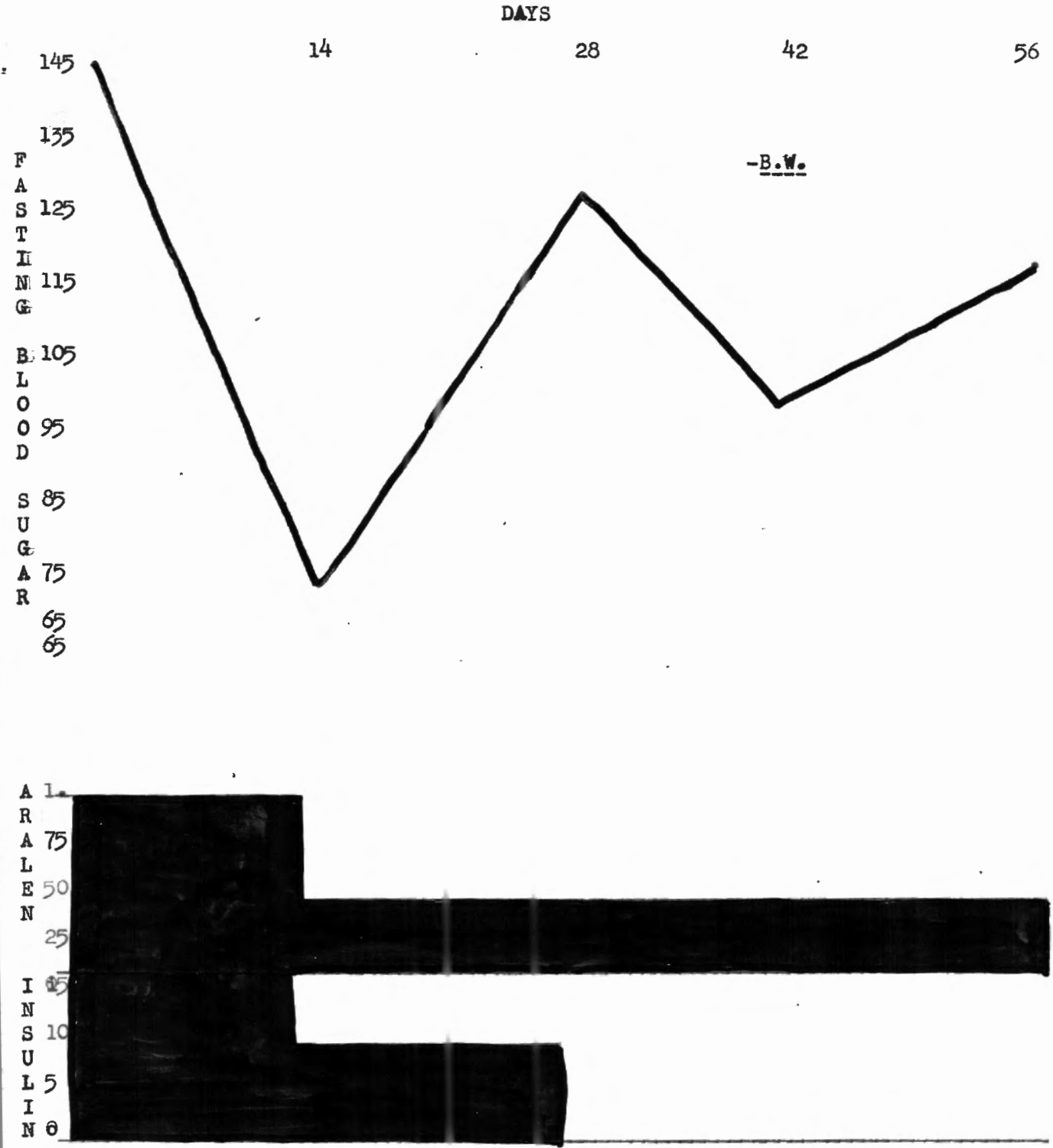
INSULIN


DAYS
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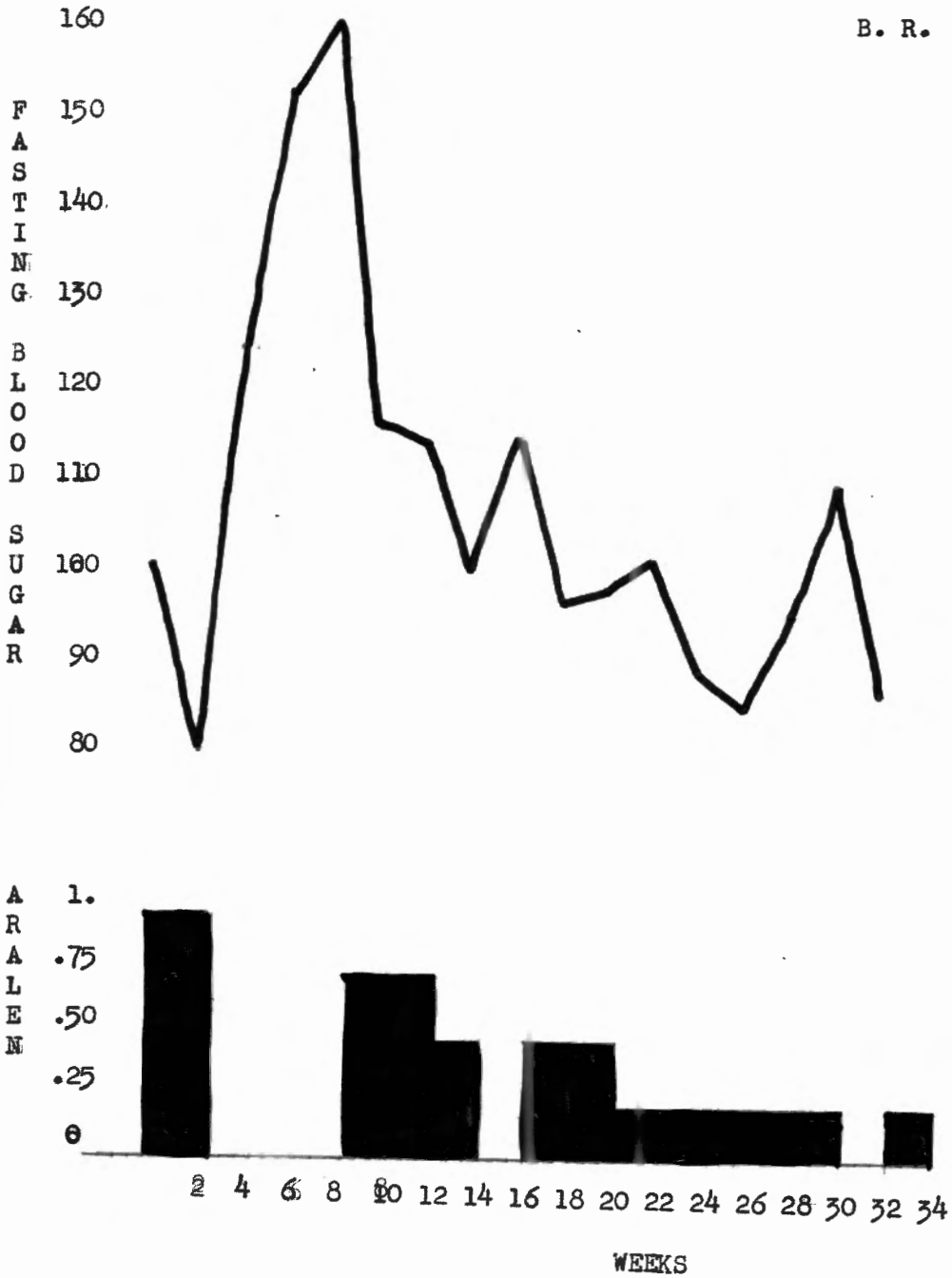
B. R.
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ARALEN
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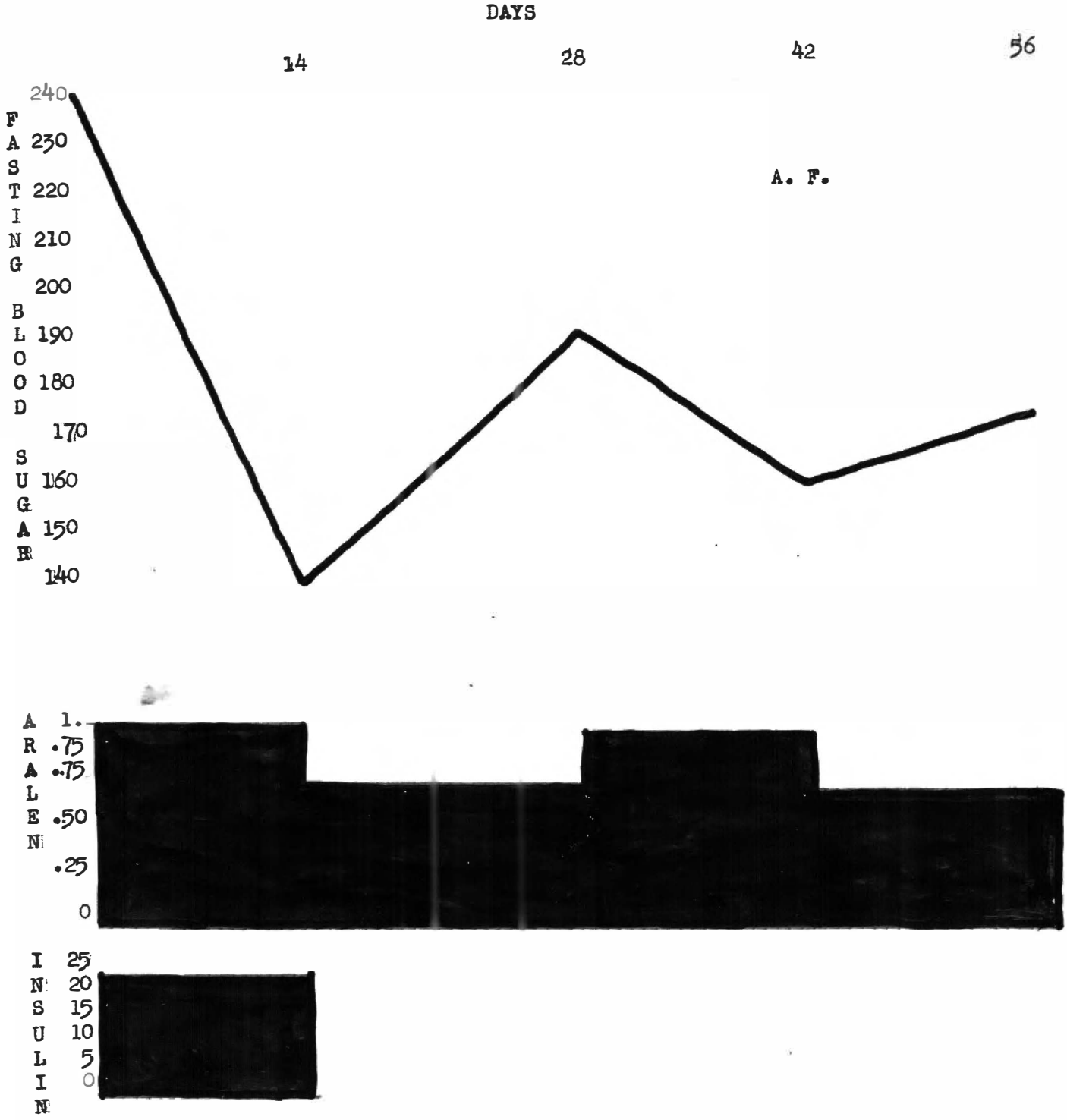
2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34
WEEKS

trial reduction on the basis of fasting blood sugar values, has been controlled for the past five months on 250 mg. of Aralen daily, see Figure 3.

The fourth patient A.F., is a 72 year old jewish male who weighs 140 pounds, and has been a diabetic for nineteen years. He has been receiving dosages of Insulin ranging from 60-20 units daily. He had previously been treated for five weeks on chloroquine, this however was discontinued because of severe skin reaction. He had been placed on Insulin 20 Units daily and was controlled at this dosage level when he began Aralen therapy. This patient refused to co-operate and did not take his Insulin as prescribed. During the forty days he received Aralen his blood sugar was maintained at levels from 139 to 190 mg%, see Figure 4. This patient received dosages from .75 grams to 1 gram daily as he took an extra 250 mg. if he spilled sugar. He at no time had any side reaction that could be ascribed to Aralen therapy.

The fifth patient, L.W., is a 41 year old colored female who has been a Diabetic for only two years. She had never previously been on Insulin therapy. This patient had previously received Carbutamide for four months and since has been on Aralen a total of one year. She initially received one gram a day however recently has been well controlled on one tablet 250 mg. daily every other week. After 37 days of Aralen therapy it was possible to discontinue the drug for a 4 month period, during


DAYS
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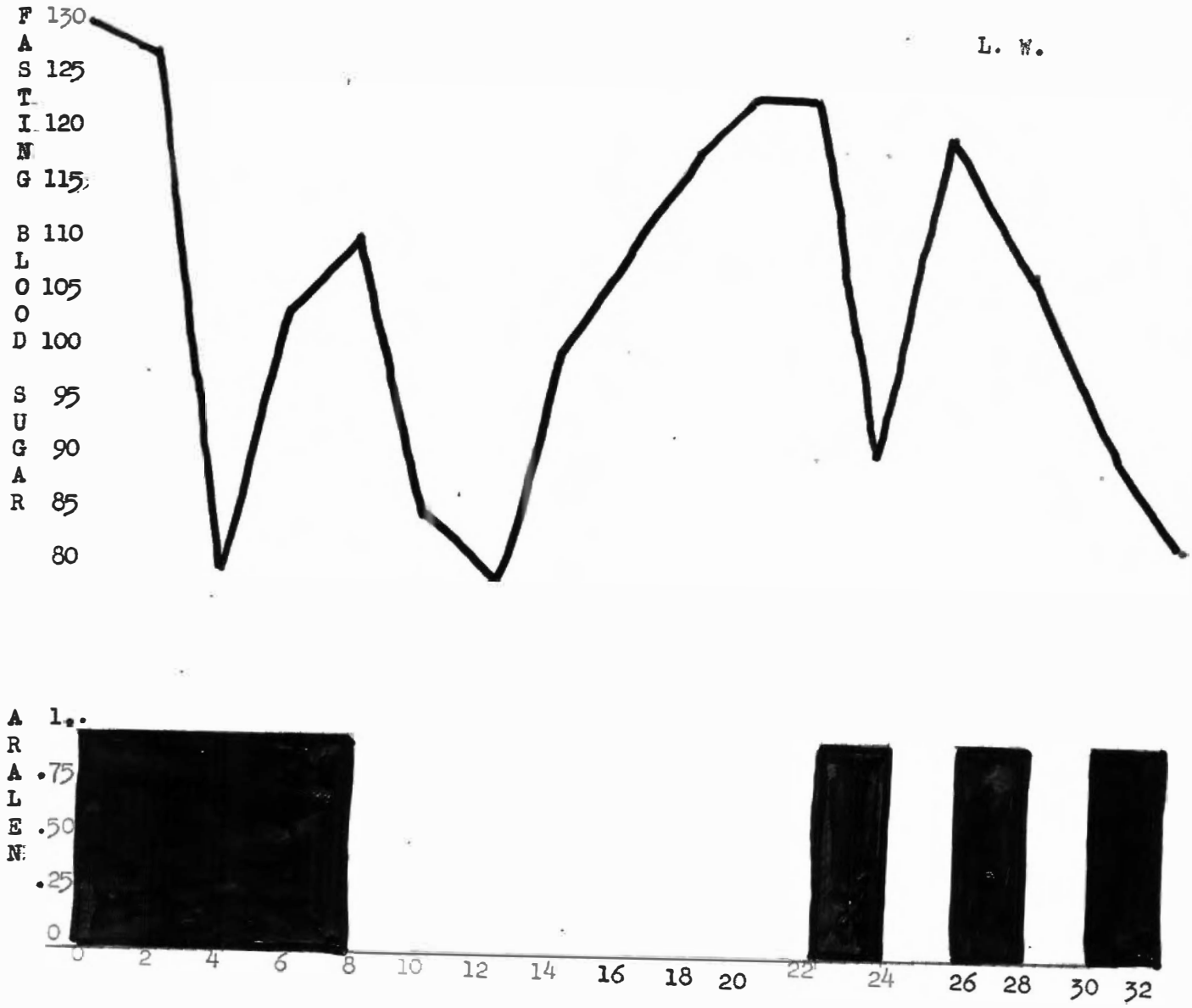
INSULIN


L. W.
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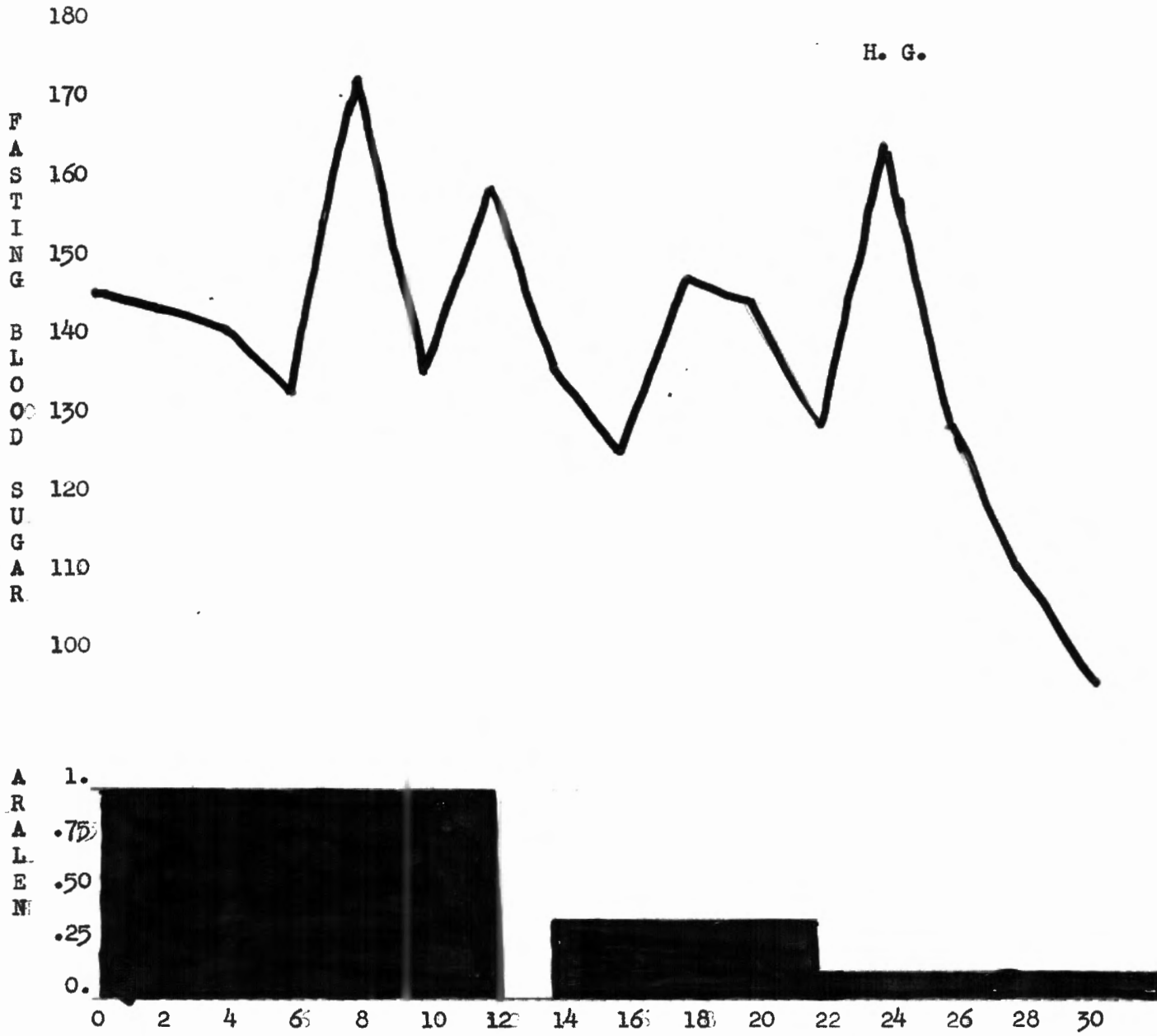
this time the patient showed a gradual return of diabetic symptoms. As was reported by Capriles[16] in his patients, this patient showed immediate response to reinstitution of therapy.

The sixth patient in our series, H.G., is a 57 year old white male, who weighs 180 pounds. He is a recently discovered diabetic who was controlled on 10-20 Units of Insulin. He received Carbutamide therapy prior to Aralen therapy. It was possible in his case to maintain him on 250 mg. of Aralen daily without Insulin. His control was not good however as his fasting sugars ranged over 160 on four occasions in the twelve months he was followed, see Figure 6.

Our seventh patient, M.K., is a 75 year old white female who has been a diabetic for six years. She has received 12-20 Units of Insulin daily prior to Aralen. This patient was started on 750 mg. daily. This dosage was reduced to 500 mg. daily and we were able to reduce her Insulin requirements in half during the 35 days she participated in the experiment, see Figure 7.

Our eighth patient, M.A., is a 66 year old white female and has been a diabetic for seven years. She had required from 10-75 Units of Insulin for control. At the time of our experiment, she was taking 62 Units daily for control. It was possible in her case to gradually reduce her Insulin requirement until she now requires only 15 Units plus 500 mg. Aralen daily. Although this patient suffered from epigastric distress and visual distur-


H. G.
FASTING BLOOD SUGAR
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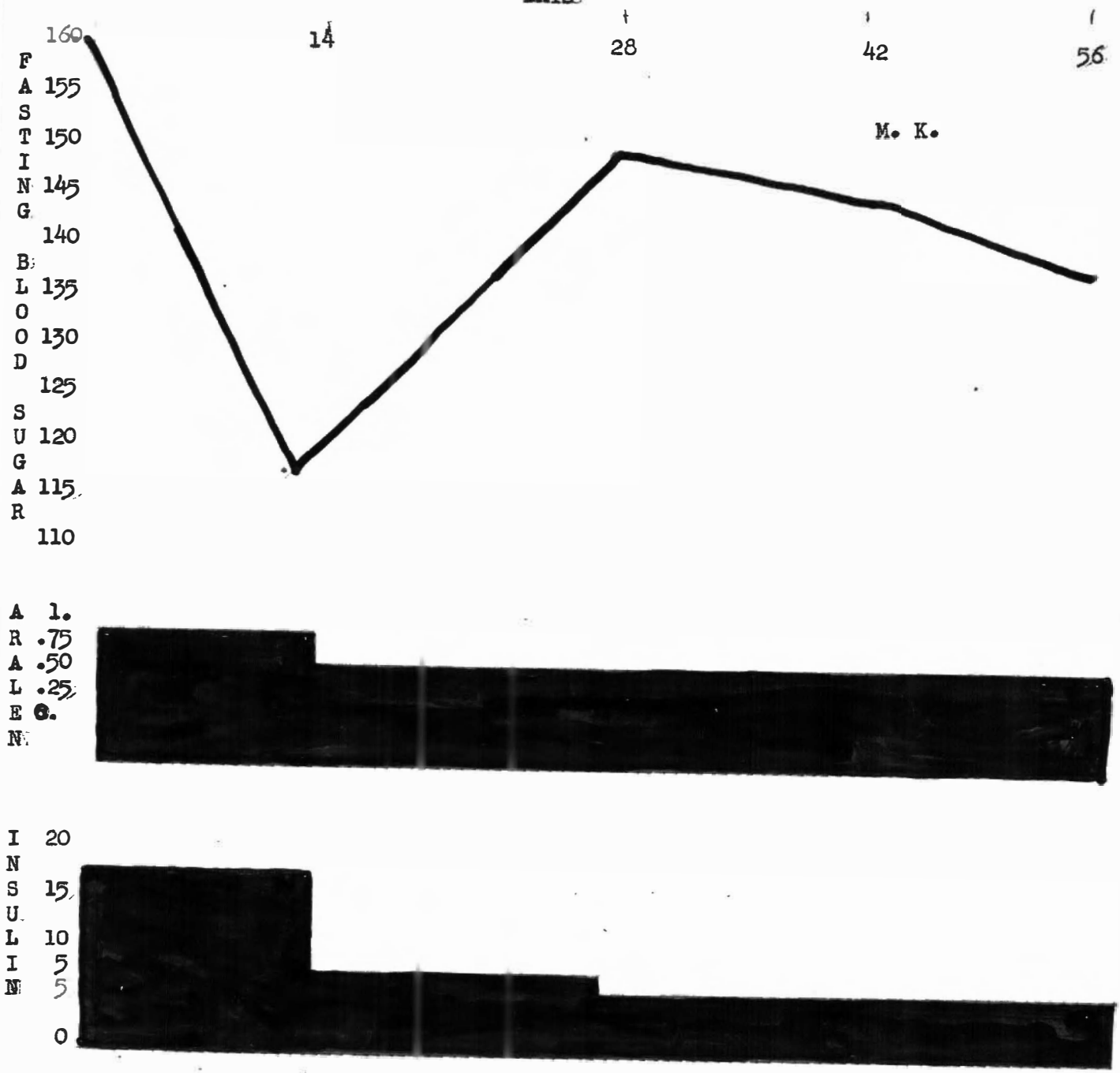
DAYS
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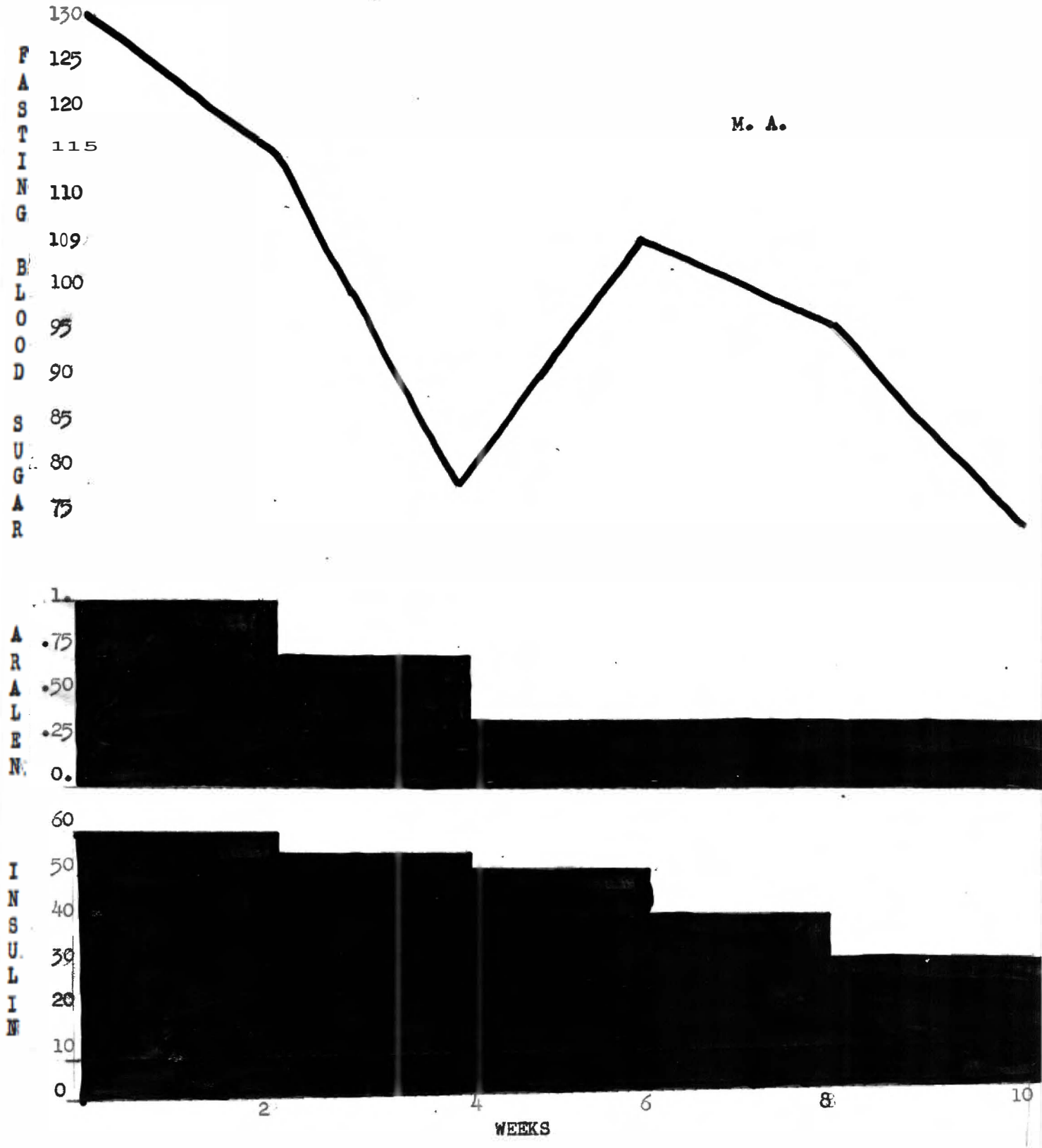
M. A.
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ARALEN.
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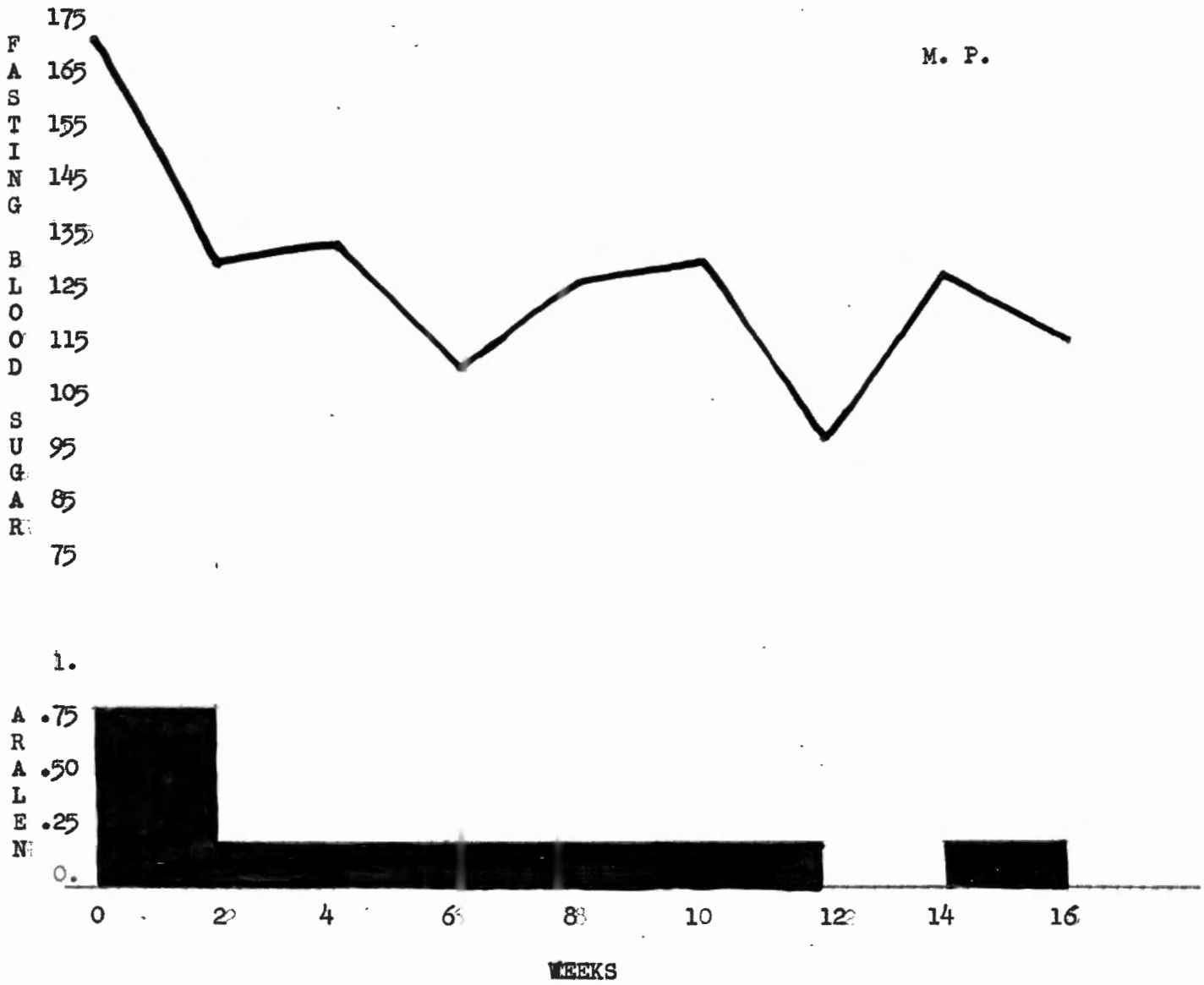
WEEKS

bances on a dose of one gram daily, she was carried without side effect on half this dosage and a gradual decrease in Insulin dosage was obtained, see Figure 8.

Our ninth patient, M.P., is a 60 year old white female who has been a diabetic for 7 years.. She had previously received BZ-55 and prior to onset of Aralen therapy had not been taking Insulin. She initially had a reaction from the Aralen and for this reason was given only 250 mg. daily.


M. P.
FASTING BLOOD SUGAR
175
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ARALEN
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16
WEEKS

Discussion

In this experiment an attempt was made to control glycemia and glycosuria of diabetic patients. Nine stable adult diabetics, five of whom had received Carbutamide, and four who had been controlled on Insulin only, were placed on a trial course of Aralen phosphate. The patients participating in the study ranged in age from 41 to eighty years. The average patient had been a diabetic for eight years.

During the study the patients were followed clinically as well as from the laboratory standpoint. A series of liver function tests were obtained on each patient; these included total serum protein, albumen-globulin ratio, Thymol turbidity, cephalin-flocculation, BSP, and alkaline phosphatase; complete blood counts and fasting blood sugar values were obtained at regular intervals. During the regularly scheduled visits the patients were evaluated for signs of drug toxicity, response to treatment, as well as for optimum control of the diabetes.

In order to maintain good control of the diabetes from the onset of the study the patients were instructed to maintain their previously established insulin schedule, and in addition to take their daily Aralen dosages, this initially ranged from .75 gram to one gram daily. As the studies progressed, it was planned to reduce daily insulin dosage and maintain the maximum tolerable dosage of Aralen.

At the first evaluation of the patients it was found that the patients on dosages of one gram daily suffered from mild epigastric distress, and two of the patients complained of visual disturbances, for this reason the dosages were reduced to .75 grams daily, and at this dosage no side effects were encountered. The patients who had previously received Carbutamide and were placed on Aralen alone were found to maintain fasting blood sugars in the normal range almost from the onset of therapy. As the study progressed it was possible to gradually lower the dosage, and after 40 days of therapy all of these patients were maintained on dosages of 250 mg. daily.

One of these patients was removed from Aralen and instructed to follow her diet only. It was found in this patient as in those studied by Capriles[16] that for a period of four months the fasting blood sugar values remained at normal or below. At the end of four months the glycemia returned but responded immediately to Aralen administration. Two other patients of the nine were later found to be controlled on Aralen administered seven consecutive days out of 14, it was not possible in these cases to obtain a remission lasting over one week. At the present time two of these patients are controlled on 250 mg. daily five out of seven days.

One additional patient having previously received Carbutamide was also easily controlled on Aralen; with this patient it has been possible to gradually reduce his Aralen dosage to 250 mg. daily

with continuing good control. The last patient who received Carbutamide prior to Aralen studies was again requiring 25 Units of Insulin daily for control. This patient refused to continue daily recommended insulin, and varied his daily Aralen intake from .75 grams to one gram. He showed some response to Aralen, as it was possible to maintain his fasting blood sugar under 165. He was discontinued after 35 days trial however as his irregular dosage schedule made evaluation impossible.

All of the four patients who never received Carbutamide prior to Aralen therapy, showed response to Aralen by a reduction in Insulin dosage. The first patient was requiring 15 Units of Insulin daily, it was possible to reduce his dosage gradually and finally to eliminate insulin entirely; he was controlled well on 250 mg. Aralen daily at termination of the studies.

In two other patients receiving 28 and 12 Units of Insulin daily it was possible to reduce this to 8 and 6 Units daily. It was not possible however to maintain good control on Aralen alone although in the 40 day trial one of these patients had maintained good control on a reduction from 28 to 8 Units daily.

The last patient in the series was requiring 62 Units of Insulin daily for control, it was possible in her case to permit a gradual reduction of Insulin, and at the termination of studies she was well controlled on 500 mg. Aralen daily and only 20 Units of Insulin. This represented a reduction of Insulin dosage to 35% original required for control.

It can be seen from the above discussion that in these nine diabetic patients, all stable adult diabetics; it was possible to control five on Aralen alone, (patients, B.W., B.R., L.W., M.P., and H.G.). In three of these patients who were well controlled , (patients L.W., B.R., and H.G.) it was possible after 40 days of therapy to discontinue Aralen for periods ranging from one week to 16 weeks. During this time the patients remained asymptomatic, and when symptoms returned, reinstitution of Aralen brought about immediate response.

Of the remaining four patients it was possible in all cases to maintain control of hyperglycemia at lowered insulin dosages and Aralen therapy.

Although this study shows that control of hyperglycemia by Aralen administration is possible, and safe; the fact that it was possible to eliminate insulin entirely, in only three of the patients casts doubt on the feasability and practicality of Aralen as an oral substitute for Insulin Therapy for Diabetics.

Summary

In this experiment nine stable adult diabetic patients were placed on Chloroquine phosphate (Aralen) in an attempt to reduce blood sugars. The patients ages ranged from 41-80 years. The average patient had been a diabetic eight years. Insulin requirements prior to time of experiment ranged from 0-75 Units daily. Two patients had been controlled on diet alone. Five of the patients had previously received Carbutamide for their diabetes.

The patients were initially given one gram of Chloroquine daily and those on Insulin were continued on their previous insulin dosages. Due to side effects of the drug the dosages were reduced after the first two weeks to 750 or 500 mg. daily.

The patients were followed by fasting blood sugars and a gradual reduction of Insulin dosage was attempted. There were six patients who after an average of 40 days on Aralen were well controlled by Aralen alone at dosages of 250 to 500 mg. daily. The three remaining patients were all controlled at greatly reduced Insulin dosages.

Two of the patients were controlled on one gram daily every other week. One patient who was well controlled was taken off of therapy for four months before her blood sugar returned to fasting values in excess of 125 mg. This is in agreement with results obtained by Caprilles.[16]

The patients studied all underwent liver function studies, and complete blood counts prior to therapy and at termination of therapy no abnormalities were detected in repeat laboratory studies.

It was thus possible in nine diabetic patients to obtain either good control of the disease, or to obtain synificant reductions in insulin requirements on moderate dosages of Aralen, 500 mg. daily.

Conclusion

1. It has been shown possible to control Diabetes on Aralen (Chloroquine phosphate) at either greatly reduced Insulin dosages or in some cases on Aralen alone.
2. The reduction of blood sugar or insulin dosage by Aralen is accomplished only gradually over several weeks.
3. Patients once controlled by Aralen may have normal fasting blood sugars for as long as four months following cessation of therapy, at which time their blood sugars again rise they can be controlled with re-institution of therapy.
4. The mechanism by which Chloroquine lowers blood sugars was not determined.
5. It has been shown that while control of diabetic patients with Aralen is possible; this is however accomplished slowly in some patients, and for this reason has been felt to be of less value than other available oral agents.

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