Papers and Originals

L-Asparaginase in Treatment of Acute Leukaemia and Lymphosarcoma

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British Medical Journal, 1970, 1, 191-195

Summary: L-Asparaginase was used to treat 40 patients with acute leukaemia or lymphosarcoma. Fifteen with acute lymphoblastic leukaemia either untreated or in relapse after previous therapy were given "Squibb," "Bayer," or "Porton" L-asparaginase. Five of these patients had complete remission of their disease, and four had good partial remission. Eleven patients with acute myeloid leukaemia were treated for a short period with L-asparaginase alone. None of them went into remission though a pronounced fall in the numbers of circulating white cells was seen. Six patients with lymphosarcoma received L-asparaginase, two of them having good partial remissions.

The toxic side-effects of the L-asparaginase from the three sources seemed to vary, and L-asparaginase from *Erwinia carotovora* appeared to be antigenically different from the enzyme produced by *Escherichia coli*.

The way in which leukaemic cells become resistant to the action of the enzyme requires further investigation. To overcome this resistance asparaginase should be used in combination with other drugs in the treatment of acute leukaemia.

Introduction

L-Asparaginase is the first enzyme to be therapeutically effective in human malignant disease. Kidd (1953) found that the injection of guinea-pig serum caused pronounced regression of the mouse Gardner lymphosarcoma. Broome (1961, 1963) showed that guinea-pig serum was effective because of its content of asparaginase, and Old *et al* (1963) demonstrated an antileukaemic effect of L-asparaginase in mice. With the isolation of an active L-asparaginase from *Escherichia coli* by Mashburn and Wriston (1964) enough material became available for clinical trials, and a number of remissions were reported in acute lymphoblastic leukaemia (Hill *et al.*, 1967; Oettgen *et al.*, 1967).

L-Asparaginase from three sources—two from *E. coli* (supplied by E. R. Squibb and Farbenfabriken Bayer, A. G.) and one from *Erwinia carotovora* (supplied by Microbiological Research Establishment, Porton)§§—was made available and

used in the treatment of acute lymphoblastic leukaemia, acute myeloid leukaemia, and lymphoblastic lymphosarcoma.

Patients Treated and Method of Administration

Twenty-three patients with acute lymphoblastic leukaemia, 11 with acute myeloid leukaemia, and six with lymphoblastic lymphosarcoma were treated with L-asparaginase. The diagnosis was based on the appearance of films of the peripheral blood and on bone marrow examinations. In the lymphosarcoma patients confirmatory lymph node biopsy specimens were obtained where necessary.

The dosage of Squibb, Bayer, or Porton L-asparaginase was kept the same for all three preparations, except in two cases. Initially a dose of 1,000 i.u./kg. of body weight daily was given but later the dose was based on surface area because it is known that the enzyme is virtually confined to the plasma (J. Hall and C. B. Cameron, personal communication, 1969). The dose per square metre was about 35,000 i.u./day. The daily dose was divided into two halves and given intravenously every 12 hours in about 10 ml. of saline. One patient treated with the Porton enzyme received 250 i.u./kg. daily, and one treated with the Bayer enzyme received 350,000 i.u./sq. m. for the first four days. As intravenous administration is not always possible in children it may be given intramuscularly in about 4 ml. of saline.

In nearly all patients a small initial dose was given intradermally or intravenously to determine any sensitivity. One unit was followed shortly by 10 units, and then by 50 units. The full regimen was now started, being continued if possible for 28 days. The number of patients treated with each type of L-asparaginase is shown in Table I.

TABLE I

	Total	Squibb	Bayer	Porton	Bayer and Porton
Acute lymphoblastic leukaemia	23	2	16	2	3
Acute myeloid leukaemia	11	1	9	1	—
Lymphoblastic lymphosarcoma	6	—	4	1	1
Total	40	3	29	4	4

A relatively limited supply of Squibb L-asparaginase was available, so that only three patients out of 40 were treated with it, eight received Porton L-asparaginase, and most had Bayer. The patients who received Bayer and Porton L-asparaginase were those in whom toxic manifestations had arisen, and an attempt was made to continue the course with an antigenically different enzyme.

Results

The 40 patients treated, the side-effects experienced, and the results of therapy are shown in Table II.

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§§ The various asparaginase preparations are referred to as Squibb, Bayer, and Porton L-asparaginase. We are indebted to the Medical Research Council for making these supplies available.

TABLE II

Case No.	Sex and Age	Diagnosis	Previous Therapy	Asparaginase	Dose (i.u./sq. m./day × 10 ³)	Duration in Days	Toxicity	Result
1	M 8	A.L.L.	—	S.	26	9	None	P.R.
2	M 15	A.L.L.	—	S.	35	14	T.V.	F.
3	F 7	A.L.L.	+	B.	35	14	None	P.R.
4	M 5	A.L.L.	+	B.→P.	35	28	T.V.H.	C.R.
5	M 7	A.L.L.	+	B.	35	28	None	P.R.
6	M 14	A.L.L.	+	P.	1,000 i.u./kg.	28	T.V.H.	C.R.
7	F 16	A.L.L.	+	P.→B.	35	4	C.A.	P.R.
8	M 14	A.L.L.	+	B.	35	10	None	F.
9	M 12	A.L.L.	+	P.→B.	35	32	T.V.	F.
10	M 5	A.L.L.	+	B.	35	28	H.	C.R.
11	F 6	A.L.L.	+	B.	35	28	None	C.R.
12	F 3	A.L.L.	+	B.	35	28	None	C.R.
13	F 6	A.L.L.	+	B.	35	28	None	C.R.
14	F 3	A.L.L.	+	B.	35	28	None	•
15	F 6	A.L.L.	+	B.	35	28	None	•
16	F 3	A.L.L.	+	B.	35	28	None	•
17	M 5	A.L.L.	+	B.	35	28	None	•
18	F 7	A.L.L.	+	B.	35	28	None	•
19	M 50	A.L.L.	+	B.	35	7	Sh.	•
20	F 3	A.L.L.	+	B.	35	28	None	•
21	F 14	A.L.L.	+	P.	1,000 i.u./kg.	28	T.W.N.V.	F.
22	F 39	A.L.L.	+	B.	36	28	None	F.
23	F 21	A.L.L.	+	B.	35	14+	None	•
24	M 60	A.M.L.	—	B.	1,000 i.u./kg.	19	N.W.J.	F.
25	M 40	A.M.L.	—	S.	36	7	N.W.	F.
26	M 47	A.M.L.	+	B.	1,000 i.u./kg.	10	N.W.	F.
27	F 52	A.M.L.	—	B.	350 × 4 days 35 × 4 days	8	None	F.
28	M 43	A.M.L.	+	B.	35	3	V.	F.
29	M 41	A.M.L.	—	B.	35	14	None	F.
30	F 34	A.M.L.	—	B.	35	28	None	F.
31	F 47	A.M.L.	—	B.	30	14	None	†
32	F 22	A.M.L.	—	B.	35	6	None	†
33	M 56	A.M.L.	—	P.	30	18	Fi.	F.
34	M 37	A.M.L.	—	B.	250 i.u./kg.	6	None	F.
35	M 47	L.S.A.	+	B.→P.	30	23	N.W.Sh.A.G.	P.R.
36	F 39	L.S.A.	—	B.	1,000 i.u./kg.	6	N.W.	F.
37	M 20	L.S.A.	—	B.	35	1	Sh.	F.
38	M 37	L.S.A.	+	P.	25	2	G.	F.
39	M 21	L.S.A.	+	B.	35	28	None	P.R.
40	F 66	L.S.A.	+	B.	1,000 i.u./kg.	13	None	F.

* Given during remission. † Still under treatment.

A.L.L. = Acute lymphoblastic leukaemia. A.M.L. = Acute myeloid leukaemia. L.S.A. = lymphosarcoma. P. = Porton. B. = Bayer. S. = Squibb. N. = Nausea. V. = Vomiting. T. = Fever. W. = Weight loss. H. = Headache. G. = Glycosuria. Sh. = Shock. J. = Jaundice. A. = Hypoalbuminaemia. C.R. = Complete remission. P.R. = Partial remission. F. = Failure. C. = Coma. Fi. = Fibrinogenopenia.

Acute Lymphoblastic Leukaemia

Fifteen of the 23 patients with acute lymphoblastic leukaemia treated with various types of L-asparaginase can be assessed regarding the immediate effect of therapy as the disease was active at the time. Eight received Bayer L-asparaginase while in remissions induced by vincristine, prednisolone, and mercaptopurine. In these patients L-asparaginase was used with methotrexate and folinic acid in a programme designed to reduce the total number of blast cells in the body to the lowest number possible without incurring undue toxic effects.

Induction of Remission

The results of treatment of 15 patients in relapse are shown in Table III.

TABLE III.—Acute Lymphoblastic Leukaemia Treated in Relapse with L-asparaginase

Type of L-asparaginase	No. in Complete Remission	No. in Partial Remission	No. of Failures	Total
Squibb	—	1	1	2
Bayer	3	2	3	8
Porton	1	—	1	2
Bayer and Porton ..	1	1	1	3
Total ..	5	4	6	15

Thirteen of them had had a considerable amount of chemotherapy. It may be seen that Squibb, Bayer, or Porton L-asparaginase can induce partial or complete remission, where complete remission has been defined as a return to health with a normal peripheral blood count and a bone marrow in which the number of leukaemic cells and blast cells is less than 5% (Holland *et al.*, 1968). The total of five complete remissions in 15 patients compares well with the proportion

seen in other series (Oettgen and Schulten, 1969; Begemann, 1969).

All the patients who responded showed a very rapid disappearance of blast cells from the circulating blood, though clearance of the bone marrow usually occurred much later. An example of this is shown in Fig. 1.

Case 13.—A girl aged 6 with acute lymphoblastic leukaemia, who initially presented with lymphoblastic lymphosarcoma and who had previously received prednisolone, vincristine, methotrexate, and cyclophosphamide, was given Bayer L-asparaginase, and within 72 hours the blast cell count in the peripheral blood had fallen from 250,000 cu. mm. to zero. The bone marrow still contained blast cells after 21 days' treatment, but at the end of the course these had disappeared and complete remission was obtained. During this period intrathecal methotrexate had to be given for meningeal leukaemia, but the blood had been cleared of leukaemic cells before methotrexate was used. The patient was subsequently treated with L-asparaginase. The second course again produced rapid clearance of blast cells from the peripheral blood and a slower return of the marrow to normal (Fig. 2). The third course acted initially in the same way, but on the 17th day of treatment blast cells appeared again in the blood and rose rapidly when treatment with L-asparaginase was stopped (Fig. 3). When, 20 days later, the leukaemic cells were tested for their sensitivity to the drug *in vitro* by means of the technique of Oettgen *et al.* (1967), they still showed sensitivity to the action of the enzyme; after 18 hours' incubation there was a reduction of 60% in the uptake of tritiated uridine by the cells grown in a medium free from asparagine or with added asparaginase, when compared with the uptake in the medium containing asparagine. A fourth course following relapse again showed a dramatic fall in the number of blast cells, but a rapid rise again as treatment continued (Fig. 4).

Maintenance of Remission

Of eight patients in remission who were treated with Bayer L-asparaginase, methotrexate, and folinic acid in an attempt to reduce the number of leukaemic cells still further, two had relapsed at the end of three months and four were still in

remission. Two patients were unable to complete the course; one has remained in remission after three months, and one has relapsed.

FIG. 1.—Case 13. Peripheral blood count following first course of L-asparaginase, showing rapid fall of blast cells.

FIG. 2.—Case 13. Peripheral blood count during second course of L-asparaginase.

FIG. 3.—Case 13. Peripheral blood count during third course of L-asparaginase, when no clinical response occurred and the blast cells reappeared. FIG. 4.—Case 13. Peripheral blood count during a fourth course of L-asparaginase.

Acute Myeloid Leukaemia

L-Asparaginase was found to have a pronounced but short-lived effect on the number of circulating leukaemic

cells in acute myeloid leukaemia. This is illustrated in Fig. 5, which shows the effect of L-asparaginase on the peripheral blood of a man aged 60 (Case 24). The blast cell count initially was 143,000/cu.mm., and the in-vitro test showed that the cells were sensitive to the enzyme. After treatment for eight days the blast cell count fell to 1,300/cu.mm., but it slowly rose to reach 54,000/cu.mm. after 19 days; at this time the cells were not sensitive to the action of the enzyme in vitro. After three courses of cytosine arabinoside the leukaemic cells disappeared from the blood. A similar effect was observed in three other patients, one of whom received 350,000 i.u./sq. m. of body surface daily in two divided doses for four days, after which she had four further daily doses of 35,000 i.u./sq. m.; in this case the leucocyte count fell from 65,000/cu.mm. before treatment to 8,700/cu.mm. on the fourth day, but during the ensuing three days it rose to 20,000/cu.mm. In five of the remaining seven cases, therefore,

FIG. 5.—Case 24. Peripheral blood count showing a transient fall in circulating blast cells.

L-asparaginase was administered alone for only five days (two patients) or six days (three patients), when cytotoxic drug therapy was added. In another case L-asparaginase was begun after the fourth of six daily injections of cytosine arabinoside. In the seventh case L-asparaginase was given alone for only three days.

The one patient who was treated with Porton L-asparaginase received 250 i.u./kg. of body weight daily for six days in two divided doses without any alteration in the blast cell count. The effect of the treatment on the total leucocyte counts of the 10 patients who received L-asparaginase alone is given in Table IV. Only one patient went into a complete

TABLE IV.—Effect of L-Asparaginase on Leucocyte Count in Acute Myeloid Leukaemia

Case No.	Source of Enzyme	Daily dose (i.u./sq. m.)	Duration of L-asparaginase as Only Treatment (days)	Leucocyte Count ($\times 10^3/\mu\text{l.}$)	
				Before L-asparaginase	On Stated day or days
24	Bayer	1,000 i.u./kg.	19	143	1.3 (day 8)
25	Squibb	36,000	7	35	6.0 (day 8)
26	Bayer	1,000 i.u./kg.	10	1.4	0.6 (day 8)
27	Bayer	350,000 $\times$ 4 days	6	65	8.7 (day 3)
		35,000 $\times$ 4			20 (day 6)
29	Bayer	35,000	6	13	1.8 (day 5)
30	Bayer	35,000	6	60	4 (day 6)
31	Bayer	35,000	5	57	10 (day 5)
32	Bayer	35,000	3	31	18 (day 3)
33	Bayer	35,000	5	132	72 (day 5)
34	Porton	9,000	6	108	98 (day 2)
					148 (day 6)

remission and one into a partial remission, but, because the L-asparaginase was only part of a treatment programme involving the administration of several drugs, it is impossible to say what part, if any, it played.

Lymphoblastic Lymphosarcoma

The similarity in the response of acute lymphoblastic leukaemia and lymphoblastic lymphosarcoma to "conventional" forms of chemotherapy prompted the use of L-asparaginase in six patients with lymphosarcoma, four of whom had numerous lymphoblasts in their peripheral blood, while one had only a few. Only two of these six patients completed the full course—one showed much improvement, while the other showed some improvement but was receiving prednisolone concurrently. Two patients deteriorated after four days and the remaining two developed unusual toxic effects.

The progress of one of the two patients who completed the course is of interest.

Case 35.—A 47-year-old man had been diagnosed as having lymphosarcoma with lymphoblasts in the peripheral blood a year previously, and had been treated with only moderate success with prednisolone, vincristine, and cyclophosphamide. In February 1969 he was readmitted with anaemia; the spleen was 19 cm. below the left costal margin. With the above chemotherapy his peripheral blast cell count was 4%. One-unit and 10-unit test doses of Bayer L-asparaginase caused no ill effect, and he was therefore given 30,000 units of Bayer L-asparaginase daily. By the 14th day he felt much better and the spleen had shrunk to 8 cm. below the costal margin. On the 17th day of the course, two minutes after injection of the morning dose, he felt faint and started to sweat, the pulse became irregular, and his diastolic pressure fell to an unrecordable level. With energetic treatment for shock he recovered. A few days later 1 unit, 50 units, and 100 units of Porton L-asparaginase were given intravenously with no ill effects and he was able to complete a seven-day course of 30,000 units with no further episodes. He was now very well, his spleen was only 5 cm. below the costal margin, and blast cells were not present in the peripheral blood. Shortly after completion of the course he developed ankle oedema and pronounced hypoalbuminaemia. His serum albumin, which had been 3.3 g./100 ml. 10 months previously, was found to be 1.6 g./100 ml. The other liver function tests showed nothing abnormal, and by the end of a further three months the serum albumin level had returned to normal.

Toxicity

During treatment with *E. coli* L-asparaginase (Squibb and Bayer material) nausea and vomiting, a fall in the blood levels of fibrinogen and albumin, and slight abnormalities in liver function tests were observed. Pancreatitis as described by Schein *et al.* (1969) was not encountered, and this may be because the Bayer L-asparaginase with which most of our patients were treated is obtained from the A strain of *E. coli*, whereas the Merck material used by Schein is from the B strain. When discussing the toxicity or the efficacy of L-asparaginase it is clearly important to specify the origin of the material being used, as there are significant differences in the rate of clearance and toxicity of preparations of the enzyme from different sources.

Hypersensitivity developed in several patients, and proved troublesome in a few. Two were hypersensitive to Bayer L-asparaginase: Porton L-asparaginase was therefore administered instead and was well tolerated. This confirmed the experimental work at Porton that there is no cross-sensitivity between the *E. coli* and *Erwinia* enzymes. Antibodies raised against the *E. coli* enzyme do not cross-react with those raised against *Erwinia* enzyme (A. P. MacLennan, personal communication, 1969). Clearly, to have a second enzyme preparation which is antigenically different from the first one administered may prove useful, as, for example, in one patient (Case 35) described above.

Porton L-asparaginase preparations are still being purified and it is too early to assess its toxicity. The initial material caused more fever than Bayer L-asparaginase, and in Case 38 hyperglycaemia occurred. One patient, not included in this series, went into diabetic coma and required insulin. It is possible that the unexplained coma in Case 7 was also associated with hyperglycaemia, but as this complication had not been described at that time the blood glucose was not measured. This patient recovered consciousness rapidly when treatment with the enzyme was stopped.

Discussion

Using L-asparaginase alone we have had results in the treatment of acute lymphoblastic leukaemia similar to those of Schmidt and Gallmeier (1968), Oettgen and Schulten (1969), and Begemann (1969). L-Asparaginase produces remission in about one-third of the patients with acute lymphoblastic leukaemia who have had previous treatment. The enzyme is ineffective when used alone in treating acute myeloid leukaemia, because of the development of resistance, but as it is not toxic to the bone marrow it may have a place concurrently and in sequence with daunorubicin, cytosine arabinoside, and mercaptopurine. When it is used in this way the early development of resistance may be minimized. McElwain and Hardisty (1969) reported encouraging results in acute lymphoblastic leukaemia in relapse when using L-asparaginase after a course of cytosine arabinoside.

A major problem in the use of L-asparaginase for the treatment of human malignant disease is the development of resistance to the enzyme. Furthermore, it is disappointing to find that though malignant cells, particularly in myeloblastic leukaemia and malignant melanoma, are sensitive to the action of the enzyme *in vitro*, clinical response is rare. There may be several explanations for this.

One of the most impressive effects clinically has been the rapid clearance of leukaemic cells from the blood but their very slow clearance from the marrow. This has been particularly noticeable in acute lymphoblastic leukaemia, where all the blast cells may disappear from the blood within 48 hours but the marrow may not remit for 21 to 28 days (as shown in Figs. 1-4). Another interesting observation, particularly in acute myeloid leukaemia, is that the number of blast cells in the blood may fall dramatically at first but after some days *reappear* and even increase in number.

One reason for the rapid clearance of blast cells from the blood, but the slow clearance from the marrow, could be that after injection virtually all the enzyme remains confined to the plasma and only trivial amounts enter the interstitial fluid compartment (J. Hall and C. B. Cameron, personal communication, 1969). A major factor in determining the clinical response might be whether the cells pass freely from the marrow, where the concentration of enzyme is probably low, to the blood, where it is certainly high. Another reason why the cells in the marrow may be less sensitive is that asparaginase may pass direct from normal cells to the adjacent leukaemic cells. Similar mechanisms could explain the failure of asparaginase to affect the growth of solid tumours such as malignant melanoma.

Another possible reason for the development of resistance to the action of this enzyme is that in human leukaemia two populations of cells may exist from the start, as is known to be the case with the L5178Y lymphoma. Particularly in acute myeloid leukemia some cells may be sensitive to asparaginase while others are not, and if the enzyme is used alone the number of leukaemic cells falls initially but rises later owing to the growth of the resistant cell line. Finally, there is the possibility that, in the presence of asparagine deprivation, activation of the enzyme asparagine synthetase may occur, rendering the cells resistant to the action of L-asparaginase.

It is, however, difficult to explain on this basis how a patient may respond again once resistance has occurred (Figs. 1-4).

For these reasons we believe that asparaginase should be used in combination with other drugs in the treatment of acute leukaemia. Although when used alone it does not produce complete remission in acute myeloid leukaemia, it still may have a part to play when used in combination, for any treatment which can reduce the number of malignant cells without harming normal haemopoietic cells may be a useful agent when combined with other drugs. The value of L-asparaginase in the treatment of malignant disease in combination with other forms of chemotherapy or radiotherapy has still to be elucidated.

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Thermographic Localization of Incompetent Perforating Veins in the Leg

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British Medical Journal, 1970, **1**, 195-197

Summary: Incompetent perforating veins in the leg were localized separately by clinical and thermographic methods. Clinically, the methods used were a multiple tourniquet test and palpation for fascial defects. Thermographically, the diagnosis of an incompetent perforator was made by finding rapid and localized heat flow to the skin in a cooled limb with occlusion of circulation in the superficial veins distally and proximally. Exploration of all the sites marked clinically or thermographically showed that the clinical method detected 60%, missed 40%, and gave false-positive results in 40%, while thermography detected 94.5%, missed 5.5%, and contributed 13% false-positive results. All these findings show a highly significant difference ($P < 0.0005$) in favour of the thermographic technique as against the clinical method.

Introduction

The aetiology of varicose veins is in doubt, but it is well established that incompetence of the venous valves is the basic underlying defect. Incompetent perforating veins may be found in almost any area of the lower limb. Apart from saphenofemoral valvular incompetence, they are commonly present in the middle third of the inner thigh, the upper medial aspect of the leg, and both medial and lateral aspects of the lower half of the leg (Sherman, 1949; Dodd and Cockett, 1956).

Successful treatment of varicose veins, whether surgically or by sclerotherapy, depends on accurate preoperative localization of the incompetent perforating veins both in the thigh and in the leg (Sherman, 1949; Cockett and Jones, 1953; Luke, 1954; Myers, 1957; Arenander, 1960). Sherman (1949) found incompetent perforating veins in 90% of patients with varicose

veins. It is therefore not surprising that many of postoperative recurrences, or the persistence of varices, are due to difficulties in localizing incompetent perforators (Mathiesen, 1953; Lofgren, Myers, and Webb, 1956; Dodd and Cockett, 1956; Barrow, 1957; Sherman, 1964). Inaccuracy of localization of incompetent perforating veins not only renders the treatment less effective but also creates problems in adequate evaluation of postoperative recurrences.

Though many techniques are described for the localization of incompetent perforators there seems to be no single accurate method. Clinical assessment fails to detect 40 to 50% of incompetent perforating veins (Massell and Ettinger, 1948; Rosenberg and Marchese, 1963; Townsend, Jones, and Williams, 1967). Venography is more reliable than clinical methods and shows 85 to 90% of incompetent perforators accurately (Mathiesen, 1959; Townsend et al., 1967). The technique, however, is costly and time-consuming and difficulties are experienced not only in determining the incompetence of perforators due to the heaviness of the dye (Greitz, 1955; Almén and Nylander, 1962) but also in translating the information obtained from two-dimensional films into accurate landmarks for surgical incision (Dow, 1950). Infrared radiation thermometry improves the diagnostic accuracy, but the results reported by Rosenberg and Marchese (1963) do not justify its routine use in localization of incompetent perforators.

This report presents a new method which has been evolved for localization of incompetent perforating veins. It is based on a thermographic study of "heat flow" in the leg and may therefore be termed "dynamic thermography." All the sites at which incompetent perforators were suspected have been explored at operation, and the results obtained by thermography are compared with those obtained by clinical methods.

Clinical Material and Methods

Forty-five patients (33 women and 12 men) who underwent surgical treatment for varicose veins were included in this study. Their ages ranged from 20 to 73, with an average

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