
CLINICAL PROGRESS

Research in Russia on Vitamins and Atherosclerosis

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THE EFFECTS of vitamins on atherogenesis and its clinical complications have been investigated extensively in Russia during the past 15 years. The importance of certain vitamins in the treatment of coronary heart disease and other manifestations of severe atherosclerosis seems to be generally accepted. Since some of these views are not held in the United States and other Western countries, it is of interest to present here a review of the pertinent Russian literature. The references cited are representative rather than complete, but we have attempted to include the most important studies. No attempt is made here to cover the corresponding Western literature.

Research Approaches and Methods in Russia

Several approaches have been used by Russian investigators and a general comment on their validity and limitations may be useful before reviewing specific results. The Russian work is concerned with pharmacologic dosages of vitamins, usually far in excess of normal average vitamin intakes and requirements for nutritional purposes, and not with vitamin deficiencies or variations in ordinary diets. This explains, perhaps, the absence of epidemiologic studies, such as have been done elsewhere in connection with the diet.¹⁻⁴

The evidence presented for the effects of the vitamins comes from two general sources—experiments on laboratory animals, largely confined to rabbits, and observations on the

clinical course of patients with coronary heart disease treated with vitamins.

The clinical studies on this subject in Russia are subject to serious limitations. Spontaneous variability in clinical status and in the severity and frequency of symptoms is notorious in patients with coronary heart disease. The use of these criteria, particularly subjective reports of angina pectoris, is difficult and hazardous under the best of circumstances. The double-blind experiment, with a placebo control, which we now consider to be essential in the evaluation of drug therapy where subjective criteria are involved, does not seem to have been used in any of the Russian studies.

It is not even clear that other treatment, including dietary management, was discontinued or kept absolutely constant during the trials with vitamins but it does appear that the patients knew when they were being given vitamin therapy. Since a large proportion of patients with coronary heart disease report benefit from any treatment, including placebos, it is not surprising that many clinical reports of favorable action of the vitamins are found in the literature.

Finally, in the clinical studies on vitamins, as in most medical research in Russia, inadequate attention is given to the requirements for statistical analysis, as was noted previously.^{5, 6} This is true of the reports concerned with objective criteria as well as those in which only subjective criteria were involved. Though the details required for statistical analysis are generally absent, it is obvious that almost all of the clinical samples were far too small to yield significance of the

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reported subjective improvement unless really spectacular benefit resulted from the vitamin therapy.

Electrocardiographic evidence of effects of vitamin therapy is claimed in some papers but there is no basis whatever to judge acceptability or significance of the evidence. Qualitative observations on some of the patients but no measurements of electrocardiographic items are reported. In a minority of the reports crude frequency distributions of qualitative electrocardiographic characteristics are given with no attempt at statistical evaluation.

The most acceptable evidence of vitamin effects in the Russian investigations on patients is provided by measurements of cholesterol and other lipids in the blood. While a decrease in cholesterol concentration in the blood does not necessarily mean clinical benefit, in general it will be agreed that this would be a desirable change and this criterion has been much used in Russia. Most Russian workers have used the Engelhardt-Smirnova method* for the estimation of cholesterol in studies both on animals and on patients. We have been unable to obtain detailed data on the reliability and validity of this method but it seems to give values in the range, though perhaps somewhat lower, that we would expect. These questions are not serious, however, when the same method is applied to the same patients in therapeutic trials.

Many of the Russian papers report data on plasma or serum "lecithin." It appears that this item is measured as lipid-soluble phosphorus and that "lecithin" is simply phospholipid. This measurement is widely considered to be significant, and emphasis is given frequently to the cholesterol/lecithin ratio though no statistically valid evidence is presented that the phospholipid value adds significantly to the information given by the cholesterol measurement.

Anitchkov's studies on the experimental production of atherosclerosis in rabbits span

*Described in Predtechenko, V. M. Borovskaia and L. T. Margolina. *Rukovodstvo Laboratornim Metodam Issledovania*. Moskba, 1950.

half a century⁷⁻¹² and the sense of priority in this field is strong in Russia. During all this time Anitchkov has insisted, and his opinion is generally accepted in Russia, that these experimental lesions are true replicas of atherosclerosis in man. The statement is made¹⁰ that the atherosclerosis produced in rabbits is not only similar but substantially identical with that seen in man, especially when small levels of cholesterol are fed so that the development of the lesion is slow.⁷ It should be noted, however, that most of the Russian studies have used large dosages and short periods (3 to 4 months). Recently, atherosclerosis has been produced in dogs by cholesterol feeding plus thiouracil in Russia, and this too is considered to be comparable to the human lesion.^{13, 14}

The rabbit is generally preferred to chickens and dogs as the experimental animal.¹⁵ Almost all animal experiments with vitamins have involved rabbits fed large doses of cholesterol so as to produce a tremendous degree of hypercholesteremia and marked lesions in the arteries within 3 to 4 months. The experiments on animals have been rigidly controlled as a rule.

Besides measurement of cholesterol and "lecithin," a major criterion of vitamin effects on atherosclerosis in the experimental animal has been visual inspection of the aorta, sometimes after staining with Sudan red. Anitchkov¹¹ considered this to be only a crude criterion, useful to detect gross differences, and preferred measurement of the lipid extracted from the aorta. In the absence of convenient and accurate methods, however, the Russian studies with vitamins have not utilized such measurements.

It is well known from autopsy studies on man that there is only a low degree of correlation between the severity of atherosclerosis in the aorta and that in the coronary arteries. Nevertheless, in the experimental studies in Russia with the vitamins the pathologic examinations have largely been confined to the aorta. Recently, Miasnikov^{16, 17} reported atherosclerosis in the coronary arteries as well as in the aortas of 22 rabbits that had been fed cholesterol for several months. Infarction did

not occur with the cholesterol feeding alone but the addition of thrombin injections, pituitrin, or extreme exercise produced areas of necrosis in the myocardium of some rabbits. The influence of simultaneous vitamin treatment in these situations has not been reported.

Fedoseev^{13, 14} reported spontaneous electrocardiographic changes in dogs treated with thiouracil and fed massive doses of cholesterol. Atherosclerosis both in the aorta and in the coronary arteries, but not infarction, was observed in dogs treated in this way.¹⁵

As mentioned above, statistical tests of significance were not made in the Russian studies on atherosclerosis. We have supplied these for all their studies where sufficient data were reported.

Vitamin C

The relationship of this vitamin, as well as vitamin A, to the problem of atherosclerosis probably was studied first by I. A. Miasnikova,¹⁸ who used rabbits fed massive doses of cholesterol. Her original publication is not accessible to us but the essential results were reproduced by A. L. Miasnikov in 1954.¹⁹ The conclusion was that vitamin A accentuates and vitamin C inhibits the atherosclerosis produced by cholesterol feeding. In another early paper (1952) it was reported that treatment with ascorbic acid delays the serum cholesterol rise in rabbits fed cholesterol.²⁰

These findings were quickly applied to clinical trials. In 1952 Tiapina²¹ intravenously administered 500 mg. of ascorbic acid daily for several weeks to patients with coronary heart disease and reported a substantial decrease in the serum cholesterol concentration, as much as 150 mg. per 100 ml. in one patient. Later (1954) A. L. Miasnikov²² reported that ascorbic acid lowered the hypercholesteremia of cholesterol-fed rabbits. The data are inadequate to judge whether the difference was statistically significant. Loviagina's and Sinitina's data²³ show a high degree of variability in the serum cholesterol levels of rabbits treated with cholesterol for 105 days.

The treatment of patients with coronary heart disease by intravenous solution of as-

corbic acid gained popularity quickly and in 1956 Sedov^{24, 25} reported the results with 106 patients. They received 500 to 1,000 mg. daily for 20 to 30 days, and the treatment was repeated after an interval of 1 to 3 months. Before the treatment 23 per cent of the patients were stated to have had serum cholesterol values over 250 mg. per 100 ml., but after the treatment only 2.3 per cent had values that high. We find the reported cholesterol change is highly significant ($p < 0.0001$ by chi-square). The cholesterol level was unaffected in the patients who initially had low values, a finding in harmony with I. A. Miasnikova's work in 1947.¹⁸ Sedov reported clinical improvement but gave no specific data.

According to Sedov,²⁵ the serum cholesterol level falls during the first days of treatment with ascorbic acid and is kept at a depressed level with chronic medication.

A very rapid response to intravenous ascorbic acid, with a fall in the serum cholesterol within a few hours, was reported by Tiapina,²⁶ but this was not confirmed by Grabenko.²⁷ Both Grabenko and Tiapina agreed with the other Russian workers, however, that treatment continued for several weeks or months lowers the blood cholesterol. The results obtained by Fedorova (quoted by Miasnikov²⁸) were less uniform, with only 60 per cent of the patients showing a fall, 30 per cent no change, and 10 per cent an increase. According to Miasnikov,²⁸ a decrease in the blood cholesterol is obtained only with prolonged administration of ascorbic acid, and even then complete correction of hypercholesteremia may not be possible. Miasnikov²⁸ reported Tiapina's findings of an increase in the fecal cholesterol excretion in parallel with the decrease in the blood, but the details of chemical analysis were not given and no judgment is possible of what was actually measured in the feces.

Lobova²⁹ found that daily intravenous administration of 1,000 mg. of ascorbic acid for 10 days produced a decrease in the beta and an increase in the alpha lipoproteins in 18 among 35 patients. The responders were stated to be in an early phase of the disease, while

the 17 refractory patients were described as being in a more advanced phase.

There are some discrepancies in the reports of clinical benefits. Various studies report subjective improvement in feeling and work capacity with no specific data on controls. Lobova²⁹ reported that ascorbic acid improved the work capacity without change in the severity or frequency of angina. Fedorova (reported by Miasnikov²⁸) found fewer anginal attacks in patients on ascorbic acid therapy.

Ascorbic acid is recommended as an auxiliary in the treatment of patients with coronary artery disease by such leading Russian cardiologists as Miasnikov,^{22, 28, 30, 31} Il'inskii,³² and Ryss.³³ The daily dosage advised is 500 to 1,000 mg. orally or 300 to 500 mg. intravenously (in glucose or physiologic saline solution). With the intravenous therapy the recommendation is a series of 20 to 30 daily injections to be repeated at intervals of 2 to 3 months. A favorable feature is stated to be that in the doses used ascorbic acid does not affect blood coagulation.^{28, 34, 35}

Miasnikov,²⁸ writing in 1960, with the authority of a Member of the Academy of Medical Sciences and Director of the Institute of Experimental Therapeutics in Moscow, states, "Presently, ascorbic acid is widely used for prevention and therapy of atherosclerosis." He suggests also, without providing any data, that the great longevity of people in the mountain region of the Caucasus may be related to the high ascorbic acid content of their diet. Further, he states that the inhibiting effect of ascorbic acid on atherogenesis can be increased by combination with vitamin P, but the dosage and data are not provided.

If ascorbic acid inhibits hypercholesteremia and atherosclerosis, it might be expected that these conditions would be promoted by a deficiency of vitamin C in the diet. This was reported by Willis³⁶ to be the case in guinea pigs, and Tolmachev,³⁷ whose paper is not available to us, stated that scorbutic patients have an elevated level of cholesterol in the blood. Studies on this aspect have been little cultivated in Russia and the information is scanty. In the Western literature atheroscle-

rosis has not been reported to be a prominent feature in persons suffering from vitamin C deficiency.³⁸⁻⁴⁰

When one of us (A. K.) returned from Russia in 1956 with the information about the enthusiasm there about ascorbic acid, fully controlled experiments were initiated with patients at a Minnesota State Hospital on rigidly fixed diets with and without the addition of 1,000 mg. of ascorbic acid daily in alternating periods of 3 to 4 weeks at a time.⁴¹ Though the first trial suggested the possibility of a slight effect on the serum cholesterol concentration, more careful analysis and repetitions with various base diets failed to show any indication of a statistically significant effect, at average cholesterol levels between 160 and 200 mg. per cent, dependent on the fats in the diet. This does not necessarily contradict Sedov's results,²⁵ who found a decrease of cholesterol only at initial levels over 200 mg. per cent. This treatment has not, as far as we know, been applied in the Western World to patients with coronary heart disease.

Vitamin A

In I. A. Miasnikova's early experiments with vitamin A it was reported that atherogenesis in rabbits fed cholesterol is promoted by the administration of vitamin A. In the early fifties restriction of vitamin A in the diet was recommended on this account,¹⁹ but later studies did not give consistent results, and in his latest (1960) review of the subject Miasnikov²⁸ states that vitamin A may be disregarded in regard to prevention or treatment of patients with atherosclerosis. Ryss³⁸ holds that there is a complex relationship between vitamin A and cholesterol metabolism. It is suggested that hypercholesteremia may be produced by vitamin A administration as a result of eliminating of cholesterol from the brain and liver.

Vitamin D₂

It appears that the effect of vitamin D₂, or calciferol, on atherogenesis is generally agreed in Russia to be unfavorable. Rabbits receiving 200 mg. of cholesterol in the daily diet for 90 days showed increases of 200 to

300 per cent in the serum cholesterol level and grade 2 to grade 3 atherosclerosis in the aortas. The addition of 100,000 units of vitamin D₂ (0.25 mg. of crystalline calciferol) to the daily diet produced an average increase of 700 per cent in the serum cholesterol and most of the rabbits exhibited grade 4 atherosclerosis in the aorta (Bavina⁴²). We have been unable to find more recent reports in the Russian literature, but restriction of vitamin D is generally recommended to patients with coronary heart disease.^{28, 32}

Thiamine

According to Miasnikov²⁸ a large series of studies in the Institute of Experimental Therapeutics in Moscow on cholesterol-fed rabbits and on patients with coronary heart disease revealed no effects of thiamine administration. In peripheral arteriosclerosis, however, Gordon⁴³ has reported some improvement after thiamine treatment for several months as indicated by an increase in the skin temperature.

Ryss,³³ after a thorough review of the literature, recommends administration of thiamine as a part of the "complex therapy of chronic heart failure," mainly because of the results of studies by Kryzhanovskaia.⁴⁴

Nicotinic Acid

Iakovleva⁴⁵ reported that the administration of nicotinic acid to cholesterol-fed rabbits increases the hypercholesteremia and degree of atherosclerosis. Since the reports of Altschul et al.⁴⁶ and Parsons and Finn,⁴⁷ in 1955 and 1957, it has been well known in the Western world that massive doses of nicotinic acid tend to depress the serum cholesterol level in man and in some but not all species of animals. At present nicotinic acid, in oral doses of 1,000 to 2,000 mg. daily, is widely used in the United States to reduce the serum cholesterol level in patients and in persons without complaints but who have marked hypercholesteremia.

In Russia, clinical benefit was reported by Nesterov⁴⁸ and by Ratner et al.⁴⁹ for patients with coronary heart disease who received from 0.5 to 5 mg. of nicotinic acid four to six times daily. Ratner et al. stated that this treatment

may prevent abnormal electrocardiographic responses to exercise.

Soibel⁵⁰ injected subcutaneously 5 to 10 ml. of an 0.86 per cent solution of nicotinic acid (43 to 172 mg. daily) in addition to an oral dose of 100 mg. This regimen was maintained for several weeks with 125 patients suffering from coronary insufficiency, 75 of whom reported significant subjective improvement, 36 moderate improvement, and only 10 reported little benefit. From serial electrocardiograms it was judged that 62 patients were considerably improved, 39 had a moderate improvement, the improvement was little in 17, and only six patients showed no change. The "improvements" were mainly in reduction in S-T depression; T-wave inversion and arrhythmias were less affected. Serum cholesterol was not reported but it was stated that the prothrombin time was increased in some patients.

In the Russian literature up to the time of writing this review (March 1961) massive dosage of nicotinic acid as used in the United States has not been studied, and it is obvious that treatment with nicotinic acid is considered to be in the experimental stage. It is not generally recommended as a part of the treatment of patients with the clinical complications of atherosclerosis.

Pyridoxine (Vitamin B₆)

The development of arterial lesions, quite different from spontaneous human atherosclerosis, was reported a dozen years ago in the United States in monkeys and dogs fed diets grossly deficient in pyridoxine (Rhinehart and Greenberg).^{51, 52} Suggestions that this may have some bearing on human atherogenesis have been discounted by almost all workers in the West. No marked effects were found on blood cholesterol in pyridoxine deficiency in dogs or various species of monkeys.⁵³ Parenteral administration of 25 mg. of pyridoxine daily to rabbits did not alter the serum cholesterol level. Recently, Sheikh-Ali⁵⁴ reported moderate decreases of serum cholesterol in the majority of 18 patients with coronary heart disease who received intravenous injections of 50 to 200 mg. of pyridoxine.

There has been little interest in Russia on

this subject, judging from the literature, and it is not considered in the treatment of patients with coronary heart disease.

Vitamin B₁₂

Considerable interest in the effect of vitamin B₁₂ on atherosclerosis has developed recently in Russia. Lukomskii⁵⁵ gave 20 gamma of vitamin B₁₂ daily for 10 days to each of 18 patients with coronary heart disease and reported an average decrease of 23 mg. per 100 ml. in the serum cholesterol concentration, associated with a small decrease in the beta lipoproteins in the serum. The effect was stated to be enhanced when choline was given simultaneously. Motovilova⁵⁶ injected larger doses (50 gamma daily) for 10 days in 40 patients, and obtained an average fall of 18 mg. of cholesterol per 100 ml. of serum. We have analyzed the data statistically and find this small change is significant ($p = 0.003$).

The effect in Motovilova's patients was stated to be maintained for 2 months and to be accompanied by reduced frequency and severity of angina "in the majority" of the patients. Further it is stated that the electrocardiogram improved in some patients and became "normal" in five of them. Specific detailed data were not given on the clinical findings.

Fomina⁵⁷ provided a treatment consisting of injection of 30 to 50 gamma of vitamin B₁₂ alternating every other day with 15 to 25 mg. of testosterone. It is stated that among 43 patients with coronary heart disease, angina pectoris disappeared in 26, and 29 patients showed a decrease in the serum cholesterol level, which averaged 62 mg. per 100 ml. in these patients. Five patients had increased serum levels (average + 36 mg. per 100 ml.), and there was no change in three patients. Our calculations indicate that the distribution of these cholesterol changes, i.e., the greater frequency of a decrease, is statistically significant. No studies were made on testosterone and vitamin B₁₂ separately.

The effect of vitamin B₁₂ in rabbits fed 200 mg. of cholesterol per Kg. daily was studied by Ignatova,^{58, 59} who reported reduced hypercholesteremia and delayed atherogenesis.

When the cholesterol feeding was discontinued after 105 days, the regressive changes were followed with two groups of nine rabbits each roughly matched in regard to serum cholesterol level.⁶⁰ The serum cholesterol concentration in the control group fell from 787 to 285 mg. per 100 ml. in 112 days, while the value in the group receiving vitamin B₁₂ fell from 740 to 142 mg. per 100 ml. Individual data and statistical analysis are not reported but it seems probable that there was a significant difference between the two groups in the regression of hypercholesteremia.

Ignatova⁵⁹ made planimetric measurements of the areas of the lesions in the aortas stained with Sudan III and examined sections of the walls microscopically from which it was concluded that the severity of the atherosclerosis was considerably greater in the control rabbits than in the rabbits treated with vitamin B₁₂.*

On the basis of these results, Miasnikov²⁸ recommends the use of vitamin B₁₂ in a dosage of 0.6 mg. every second day for 2 to 4 weeks for prevention and treatment of atherosclerosis, though he indicates that clinical experience is as yet too limited for conclusive evaluation. Motovilova⁵⁶ found the prothrombin content of the blood increased in 11 out of 23 patients treated with vitamin B₁₂. Statistical analysis of her results shows an average increase of 10 per cent in the blood prothrombin, and this was statistically highly significant. It may appear, therefore, that treatment with vitamin B₁₂ would be questionable unless combined with anticoagulant treatment.

Choline

In the Russian literature on treatment of patients with atherosclerosis choline is considered together with vitamin therapy.^{28, 32, 55} In the Western World enthusiastic reports,

*In her latest study, Ignatova⁷⁰ found that daily intramuscular injection of 100 gamma vitamin B₁₂ for 2 weeks in 75 patients with coronary atherosclerosis decreased the blood cholesterol by about 20 per cent on the average. We found the distribution of decreased cholesterol in 69 of 75 patients statistically significant. Changes of blood coagulation occurred in some patients.

such as those of Morrison and Gonzales,⁶¹ about patients treated with choline have been largely discounted because of the absence of adequate controls and the finding of negative results of choline supplements on serum cholesterol in rabbits,⁶² and man.⁶³ It will be recalled also that long ago Best and Rideout⁶⁴ reported that, though choline is effective in preventing the accumulation of neutral fat in the livers of rats fed cholesterol, it has far less effect in preventing cholesterol accumulation.

Pushkar⁶⁵ reported that the addition of 400 mg. of choline to the daily diet of rabbits fed 200 mg. of cholesterol, did not affect the serum cholesterol level but did delay atherogenesis. Sinitsina^{66, 67} found a decrease in the serum cholesterol level as well as reduced atherosclerosis in the cholesterol-fed rabbit. In two groups of 21 rabbits each fed cholesterol for 4 months, the mean value was 1,033 mg. per 100 ml. in the control group but only 615 in the group that had received, subcutaneously, 300 to 400 mg. of choline per Kg. of body weight. Our computations indicate that this difference was significant at the level of $p = 0.05$. Sinitsina⁶⁷ also reported that the regression of atherosclerosis after discontinuance of cholesterol feeding is accelerated by choline treatment.

Koropova⁶⁸ found a tendency for the blood cholesterol to fall in 20 patients with coronary heart disease who received, by mouth, 5 Gm. of choline daily for a month. With continued choline dosage in 39 patients for a year, Koropova found that the cholesterol level was decreased in only nine patients, increased in two, and was unchanged in the other 28 patients. Subjective improvement was reported but this may have been the result of suggestion, according to Miasnikov.²⁸

P. M. Savenkov (reported by Lukomskii⁵⁵) gave 5 to 6 Gm. of choline by mouth daily for 3 weeks to 68 patients with coronary heart disease. Angina pectoris was reported by 35 patients to be significantly reduced, 18 patients said they were slightly improved, 11 patients noted no change, and one patient said he was worse. The serum cholesterol concentration

fell, on the average, 40 mg. per 100 ml. in 53 of the 68 patients, a decrease of 15.6 per cent from the initial level. The serum cholesterol level rose in 15 patients, and 11 of these patients had had serum cholesterol values of 200 mg. per 100 ml., or less, before the treatment. Every patient whose initial cholesterol level was over 250 showed a decrease with choline treatment. In 26 of these hypercholesteremic patients measurements were made of the beta lipoproteins in the serum. All showed elevated values before treatment and these fell with treatment in 20 of the 26 patients. Van Chii³⁵ did not find consistent changes of prothrombin and fibrinogen in 38 patients treated with choline (5 Gm. per day) for 10 days.

There is a suggestion in the Russian literature that atherosclerosis is associated with a deficiency of choline or an abnormality in its metabolism. Anisimov⁶⁹ studied the blood choline content in 21 patients with coronary heart disease and in 33 control subjects. A subnormal level of choline in the blood was found in 11 of the 21 patients and this rose on a daily diet providing 73 Gm. of protein, 53 Gm. of fat, 334 Gm. of carbohydrate, and 1.5 Gm. of choline. It will be noted that this is a low-fat diet (22 per cent of total calories from fats) but we do not know how far it is below the fat content of the usual Russian diet or what other differences were involved.

Lukomskii⁵⁵ recommends choline administration for the prevention and treatment of atherosclerosis but stresses the necessity for repeated courses of treatment over a long time. The extent to which this treatment is actually used in Russia at present is not clear from the literature.

General Comment

Some of the characteristics of Russian medical research will have been indicated by this review. There is much eagerness to find effective methods of treatment, and a hopeful attitude is evident about medication such as with vitamins. Ascorbic acid is accepted as a standard part of the treatment of patients with coronary heart disease, though it is impossible to judge how many patients actually receive

this therapy. According to Miasnikov²⁸ it is widespread. It appears likely, too, that treatment with vitamin B₁₂ will receive acceptance. It is curious, however, that massive dosage with nicotinic acid, currently so popular in the United States, has as yet been given little attention in Russia.

The possible mechanisms involved in the reported effects of the vitamins are discussed at length by Russian authors but a presentation of these considerations, some quite speculative, would require far more space than is appropriate to a review devoted to the basic clinical and experimental reports. Obviously, the reports reviewed here require careful consideration. Repetition of some of the studies, with more attention to controls and statistical analysis would be essential for critical evaluation. The great contributions of the pioneering work in Russia on atherosclerosis are obvious to all, and we may be sure that valuable research will continue in that country.

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