

SPECIAL ARTICLES

WHEN IS CAPILLARY FRAGILITY A
SIGN OF VITAMIN-C SUBNUTRITION
IN MAN?

BY GUSTAF F. GÖTHLIN, M.D.

PROFESSOR IN PHYSIOLOGY AT UPPSALA UNIVERSITY, SWEDEN

By dietary experiment on a man and a woman whose capillary resistances to rupture were initially normal I was able to show that subsistence on a diet extremely poor in vitamin C gradually gives rise to capillary fragility (Göthlin 1931). The change proved to be reversible, for with increasing doses of fresh orange juice the strength of the cutaneous capillaries slowly returned to normal.

On these and other observations I based a method of ascertaining indirectly whether a person's supply of vitamin C is sufficient. From the very first, however, I was fully conscious that, in disease, the capillaries may become fragile from causes other than a deficiency of vitamin C, and in consequence I was also aware that the test should be used mainly for *healthy* persons. This attitude found expression in the title of my first publication (1931): "A method of establishing the vitamin-C standard and requirements of physically healthy individuals by testing the strength of their cutaneous capillaries." With regard to persons suffering from digestive affections, Öhnell (1928), using the so-called Hess's capillary test, had previously taken a large number of petechiæ as an indication of latent scurvy.

DEVELOPMENT OF THE CAPILLARY TEST

Since 1931 the use of the capillary test has developed. I must make it clear, however, that this paper does not attempt to answer criticisms directed against capillary methods other than the one I have worked out, and especially not the criticisms (Hawley, Stephenson, and Anderson 1936, Abt, Farmer, and Epstein 1936) directed against the so-called suction test (Hecht 1907, Borbély 1930, Dalldorf 1933). The basis of the over-pressure procedure is clear and unassailable, but this can by no means be said of the suction procedure.

A statistical investigation of my capillary test, carried out in 1933 by Geschwind and Rundqvist (1935), has been published under the title: "Tests carried out on 200 persons with Göthlin's method for determining the strength of the skin capillaries, and statistical treatment of the results." Their observations led to certain changes in the procedure I had described (1931 to 1933) which was intended in the first place for mass investigations. The statistical investigation comprised observations on 200 persons, whose right and left arms were examined with the 35 mm. as well as the 50 mm. test. The results led me, from the beginning of 1935, wherever possible, to make all *individual* determinations on both arms and proceed from the mean figure of the results on both arms.

Outside Sweden very little attention has been paid to my suggestion that, in cases where the strength of the capillaries is suspected of being subnormal, the stasis test ought to be made with the 35 mm. over-pressure also. Experience in recent years, however, has shown the necessity of making both the tests in individual doubtful cases, for occasionally the 35 mm. test changes the result from "normal"

to "abnormal." When the test is made with both these pressures, the determination with 35 mm. over-pressure must, of course, precede the one with 50 mm. over-pressure. Nevertheless, certain circumstances argue against making the second test immediately after the first. In a series of plethysmographic observations by Fänge (1934) on six students, it proved that the return to normal volume in the forearm after a test with 35 mm. over-pressure, as directed, might take as long as 37 minutes. It will probably be unwise to make a fresh over-pressure test while the vasomotor effects of a previous one remain. To be sure of the return to vasomotor equilibrium, I therefore decided not to make the test with 50 mm. over-pressure until at least an hour after the over-pressure test with 35 mm.

In accordance with what has been said above, an individual double-arm test resolves itself into the following systematic procedure.*

The person to be tested either sits with both arms loosely extended at the elbow-joints, supported in such a way that the folds of the elbows are on a level with the heart (third rib), or lies on his back with his arms stretched out loosely on the supporting bed. To a 5-branched star-shaped piece of metal tubing runs a tube from an air-pressure pump (for filling the system with air) fitted with a screw clamp, a tube to a Politzer's balloon contained in a compressor (for exact regulation of the pressure), two tubes to the cuffs for the two arms, and finally a tube to the manometer. A first double-arm test is made with 35 mm. over-pressure and later—not within an hour—a fresh double-arm test with 50 mm. over-pressure. Immediately before the treatment with 50 mm. over-pressure an examination is made to see whether any more petechiæ have appeared during the interval, which is not uncommon. In all readings the prescribed 5-dioptre lens must be used, otherwise a number of petechiæ will be overlooked. A lens of more than 5 dioptres must not be used, for with it more petechiæ are discovered (Billing 1935). If lenses of more or less than 5 dioptres are used my principles for judging the results cannot be applied. It is also necessary that the investigator should have full acuity of vision (10/10), and that the investigation should be made in full daylight or equivalent artificial light ("daylight" lamp).

A numerical index of the petechiæ counted is drawn up on the following principles. More importance as an indicator of fragility must be ascribed to a petechia after the lower over-pressure of 35 mm. than to one which does not appear until after the higher over-pressure of 50 mm. Accordingly, as an approximation, every petechia which appears only with 50 mm. over-pressure is counted as 1, whereas every petechia appearing with 35 mm. over-pressure is counted double. By adding together the number of petechiæ which appear within the delimited circular areas with a 6 cm. diameter within the folds of both elbows when the 50 mm. over-pressure is applied, and twice the number of petechiæ within the same areas with 35 mm. over-pressure, a *double-sided petechial index* is obtained, which is an expression of the fragility of the cutaneous capillaries at the time of investigation. If the investigation has to be limited to one arm only—for example, if it will have to be renewed within three weeks—a *one-sided petechial index* may be drawn up on the same principles.

My earlier work indicates that the borderline between capillary fragility and a normal (or nearly normal) strength of the cutaneous capillaries lies approximately at the double-sided petechial index 12—i.e., the values that exceed 12 are to be regarded

* A complete apparatus can be obtained from Kirurgiska Instrument-Fabriks A.-B., Stockholm.

as indicating capillary fragility. In reality a sub-normal strength of the capillaries cannot be excluded with certainty with the values 9-12 (borderline cases). I now have reason not to insist on my earlier (1931) suggestion of two grades—III and IV—of insufficient capillary strength, but instead combine them into one category, a grade III of capillary strength which includes all degrees of undoubted capillary fragility. According to earlier statements, the borderline for one-sided petechial indexes lies approximately between 8 and 9—i.e., values above 8 are to be looked upon as indicating capillary fragility. Even with the borderline values 5-8 a subnormal strength of the capillaries cannot, however, be excluded.

TESTS OF THE METHOD

The accuracy of this method of estimating the sufficiency or insufficiency of the supply of vitamin C can of course be checked; but before the production of ascorbic acid in pure form, this checking took a long time. Earlier I had convinced myself that the vessel fragility I observed in school-children was due to a deficiency of vitamin C because I found that it disappeared when the children had fresh oranges for several weeks. But to recommend such a time-consuming procedure to those who might employ the method was almost useless, and I did not do so. Nowadays, when vitamin C is an article of commerce and concentrated (even heroic) doses have become possible, the checking procedure can be much improved and shortened.

The honour both of being the first to realise actual short-time control of the capillary test and of being the first to inject ascorbic acid intravenously falls to Schultzer (1933). Into a patient with scurvy, whose capillary condition was characterised by 20 petechiæ on one arm with 50 mm. over-pressure, he injected doses of ascorbic acid, each of 40 mg., intravenously. After fifteen such injections within twenty days, the capillary reaction had changed to normal—viz., 4 petechiæ—with the same over-pressure, and at the same time the scorbutic symptoms had greatly improved. In a later paper (1936), in which an account is given of a more intensive ascorbic-acid treatment of three scorbutic patients, Schultzer writes: "The clinical effect of the ascorbic acid, including the effect on the capillary resistance, appeared long before the patients were saturated."

Many people whose vitamin-C supply is to be tested will find it irksome to submit to several intravenous injections, and I therefore think it preferable as a rule to give the ascorbic acid by mouth even though the effect is slower. At my suggestion G. Andersson has made some tests of this kind at the Ulleråker Mental Hospital on patients regarded as physically healthy. A dose of 300 mg. ascorbic acid was given daily, dissolved in a small glass of water, with sugar. Usually half the dose was taken in the morning and half in the afternoon. From these investigations, which are still unpublished, Andersson obtained, *inter alia*, the following results:—

H. P. Woman aged 43. First examination on Jan. 13th, 1937, left arm, gave the result $358 + 507$ —i.e., one-sided petechial index = 23. From Jan. 15th to 19th inclusive (5 days) she received ascorbic acid 300 mg. daily, and a second examination on Jan. 20th gave the result $351 + 502$ on the right arm—i.e., petechial index = 4.

I. T. Man aged 41. First examination on Jan. 27th, 1937, left arm, gave the result $3510 + 504$ —i.e., one-sided petechial index = 24. Treated with 300 mg. ascorbic acid daily from Feb. 2nd to 5th inclusive. Second examination on Feb. 6th, left arm, gave the result $352 + 506$ —i.e., one-sided petechial index = 10.

E. G. Man aged 39. First examination on Feb. 5th, left arm, gave the result $3523 + 5019$ —i.e., one-sided petechial index = 65. From Feb. 6th to 11th inclusive (6 days) he received 300 mg. ascorbic acid daily. Second examination on Feb. 12th, right arm, gave the result $359 + 5021$, which corresponds to a one-sided petechial index of 39.

O. B. Woman aged 42. First examination on Feb. 9th, left arm, gave the result $3514 + 508$ —i.e., one-sided petechial index = 36. From Feb. 11th to 15th inclusive (5 days) she received 300 mg. ascorbic acid daily. Second examination on Feb. 16th, right arm, gave the result 350×5010 —i.e., petechial index = 10.

According to these and other observations, six days' medication with 300 mg. ascorbic acid daily suffices for the desired control, and should lead to a decrease of at least 30 per cent. in the petechial index in cases where a deficiency of ascorbic acid is the chief cause of the capillary fragility. If the petechial index does not fall after such a test it is unlikely that a deficiency of ascorbic acid has played any essential part in causing the fragility.

Where as in this test it is necessary to repeat the observation after so short a time as six days, the test must be made the first time on one arm and the second time on the other—i.e., one must determine a *one-sided* petechial index.

Commercial production of the pure vitamin (ascorbic acid) has extended the field of usefulness of the capillary test. Apart from the diseases previously (1932, 1933) mentioned by me (uncomplicated arterio-sclerosis, afebrile tuberculosis, uncomplicated afebrile gastric ulcer, uncomplicated achylia), the sufferers from certain other chronic complaints—e.g., chronic afebrile nervous diseases, chronic afebrile rheumatic diseases, provided that they are not treated with drugs that are capillary poisons—could be examined for their vitamin-C supply by the method described above. As I have no clinical hospital material at my disposal, however, I cannot express an opinion based on my own experience.

In common with Harris and Ray's (1935) method, which uses urinary excretion as a means of estimating the saturation of the body with ascorbic acid, the control method described above has two advantages. In both methods recourse to venous puncture is avoided, and if the test confirms the suspicion of a deficiency of ascorbic acid the treatment has already been begun with the investigation procedure. The capillary test has the advantage that it does not involve the laborious preservation and immediate acidifying of each urine discharge during the days that elapse before saturation is reached. The saturation procedure has the advantage that it reacts to less pronounced C-deficiency, and that, in the hands of an experienced investigator, it gives more finely graded results.

THE DEGREE OF VITAMIN-C SUBNUTRITION DETECTABLE BY THE CAPILLARY TEST

Before the chemical constitution of vitamin C was discovered, and before the pure substance became commercially available, the capillary method was the only one that afforded any indication of the supply of vitamin C in a person who was not suffering from scurvy. Certainly the information which it could give was—and still is—fairly limited. I would express the possibilities thus: if a healthy person shows subnormal strength of the capillaries, this is evidence of a subnormal supply of vitamin C; but if a person has normal strength of the capillaries, his indispensable requirements of ascorbic acid are satisfied. I have not assumed that a person with fewer petechiæ should be considered better supplied

with vitamin C than another with more petechiæ, when both the petechial indexes are below the border value. But I have assumed that if in one and the same person the number of petechiæ for the same pressure treatment diminishes to a significant extent, this diminution is evidence of increase in his supply of vitamin.

The direct determinations of ascorbic acid in the blood has now made it possible to throw light on the borderline between a vitamin-C supply that satisfies the vitamin-C requirements of the capillaries and one that does not. Parallel with determinations of the ascorbic-acid content of the blood, in accordance with Emmery and van Eekelen's (1936) method, Deggeller (1936) has made determinations by my capillary method on a number of hospital patients. Similar parallel determinations have also been made in a prolonged experiment on himself, with abstinence from ascorbic acid, by van Eekelen (1936). Provided that—as I presume—these authors' capillary tests were made according to the prescribed rules, and provided that their reduction values in the blood, found by titration, correctly represent its ascorbic-acid content, it appears that the border value of ascorbic acid in the blood which corresponds to the borderline between normal and subnormal strength of the capillaries must be below 1.4 mg. per litre of blood and be of the order of magnitude of about 1 mg. per litre. For such blood values as 4, 3, 2, and 1.5 mg. ascorbic acid per litre—all of which are characterised by Deggeller as insufficient—the capillary test would thus give no reaction. In countries where (as appears to be the case in Holland, a land of gardens) figures as low as 1 mg. ascorbic acid per litre of blood are hardly met with, there will be very little use for the capillary test. But there are other countries where the position is quite different. At least, judging from my own results and those of my co-workers, there are in Sweden thousands of individuals who, without suffering from demonstrable illnesses, develop capillary fragility during the late winter because of an insufficient supply of vitamin C. In such countries it is necessary to deal first with the severe deficiencies and to leave the slighter ones to be dealt with later, and for this reason the capillary test is of considerable value. Moreover, I cannot think it justifiable, merely from estimates of the ascorbic-acid content of the blood of the healthy population of a certain small area of the world, to decree where the borderline for man in general lies between a sufficient supply of ascorbic acid and an insufficient supply. To make such an assumption would be to proceed in much the same spirit as was shown when, from the well-known determination by C. Voit that the "average German workman" consumed 118 grammes of protein per 24 hours, the conclusion was drawn that a daily consumption below 118 g. was insufficient.

Even though the Dutch statistics show that vitamin-C concentrations in the blood as low as 5-2 mg. per litre are unusual in Holland, this is in itself no proof that they are inadequate. It is the human organism itself that will show when the supply of a requisite substance is insufficient.

SUMMARY

For the reasons given above I believe that the method I described for determining the resistance to rupture of the cutaneous capillaries can still be used advantageously in cases where there are no resources for making ascorbic-acid determinations in the blood, or when the person to be examined will not permit puncture of a vein. It should be understood, however, that only in healthy persons does a single

capillary test give information about the individual's intake of vitamin C. If the test is made on a person with a chronic disease—I am excluding diseases which themselves give rise to capillary damage, and illnesses treated with drugs capable of doing so—or if it is made in a case where it is doubtful whether the person is healthy, it is necessary to have a second observation after doses of ascorbic acid, and the following procedure will be appropriate.

The capillary test is made on one arm only,† and the result calculated in the form of a petechial index as explained above. If this test shows capillary fragility 300 mg. ascorbic acid is given by mouth daily for six days. On the seventh day the capillary test is made on the other arm † and the petechial index is calculated. A fall of 30 per cent. or more in the petechial index between the first and the second examinations proves that a subnormal supply of vitamin C played a considerable part in causing the capillary fragility.

Acute illnesses which by giving rise to toxins affect the capillaries' resistance to rupture, capillary poisons—e.g., histamine, arsphenamine—and skin diseases localised in the arms, make it impossible to draw any conclusions about the supply of vitamin C from the results of my capillary test.

Judging from parallel determinations made by Deggeller and by van Eekelen, with my capillary method and with estimates of the ascorbic-acid content of the blood, my method does not reveal capillary fragility due to a subnormal supply of vitamin C until the ascorbic-acid content of the blood (Emmery and van Eekelen's method) is about 1 mg. per litre of blood or less.

In *mass investigations*, when it is desired to ascertain whether the requisite quantities of ascorbic acid are present in the regular dietary—e.g., in mental hospitals, charitable institutions, prisons, sanatoria, and regimental barracks—the capillary method is one that for practical reasons should still be considered. It is probable that a simultaneous double-arm test, with the 50 mm. over-pressure only, will here be as effective as, and take less time than, the procedure originally proposed (1931-33)—i.e., the one-arm test at 50 mm. over-pressure on one arm, and subsequent one-arm tests on the "borderline cases," with 35 mm. over-pressure on the other arm.

If it is desired to obtain information by means of mass investigations upon school-children, coming from homes with varying vitamin-C supplies, as to the variations in this respect in the different homes, the test will have to be made according to the procedure described for individual examinations with two double-arm tests (one with 35 mm. and a later one with 50 mm. over-pressure).

REFERENCES

- Abt, A. F., Farmer, C. J., and Epstein, I. M. (1936) *J. Pediat.* 8, 1.
 Billing, L. (1935) *Uppsala LäkFören. Förh.* 40, 389.
 v. Borbély, F. (1930) *Münch. med. Wschr.* 77, 886.
 Daldorf, G. (1933) *Amer. J. Dis. Child.* 46, 794.
 Deggeller, O. (1936) Thesis, Utrecht.
 van Eekelen, M. (1936) Thesis, Utrecht.
 Emmery, A., and van Eekelen, M. (1936) *Biochem. J.* 30, 26.
 Fänge, G. (1934) *Skand. Arch. Physiol.* 69, 197.
 Geschwind, H., and Rundqvist, N. (1935) *Uppsala LäkFören. Förh.* 40, 403.
 Göthlin, G. F. (1931) *Skand. Arch. Physiol.* 61, 225.
 — (1932) *Klin. Wschr.* 11, 1469.
 — (1933) *J. Lab. clin. Med.* 18, 484.
 Harris, L. J., and Ray, S. N. (1935) *Lancet*, 1, 71.
 Hawley, E. E., Stephenson, D. J., and Anderson, G. (1936) *J. Nutrit.* 11, 135.
 Hecht, A. F. (1907) *Jb. Kinderheilk.* 65, 113.
 Öhnel, H. (1928) *Acta med. scand.* 68, 176.
 Schultzer, P. (1933) *Lancet*, 2, 589.
 — (1936) *Acta med. scand.* 88, 317.

† Note that petechiæ may develop after blood-pressure determinations with a cuff on the upper arm, and that these may remain for several days.