EFFECTS OF SALTS OF NICOTINIC ACID ON SERUM CHOLESTEROL

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In 1955, 1956, and 1958 we reported that nicotinic acid (niacin) in relatively high doses—in man 1 g. or more per 50 lb. (44 mg. per kg.) body weight per day—in many instances decreases the serum cholesterol in man and rabbits, and in rabbits inhibits experimental cholesterol atherosclerosis. This has been fully confirmed by other authors (for man by Parsons *et al.*, 1956; Achor *et al.*, 1957; O'Reilly *et al.*, 1957; Parsons and Flinn, 1957; Goldner and Vachalek, 1958; and for rabbits by Merrill and Lemley-Stone, 1957).

There is the question whether such a high dosage is toxic, especially for the liver. A number of liver-function tests and other routine examinations on patients who were being given this treatment for relatively long periods revealed nothing abnormal. In experimental animals which had received still larger doses the results were most contradictory. In 1939 Unna pointed out that the toxicity of nicotinic acid, as reported by Elvehjem *et al.* (1938) for one single dog, was likely due to the high acidity of nicotinic acid rather than to a specific action. This was borne out by the innocuity of sodium nicotinate used by Ackermann (1912), whose experiment had been repeated by Elvehjem *et al.*, but substituting nicotinic acid for the sodium salt. Unna showed that the acid has a *p*H of 3.3, whereas a solution of sodium nicotinate, corresponding to 10% of the acid, has a *p*H of 7–7.1. Unna stated further: "Sodium nicotinate is completely dissociated in solution, and thus no difference in the action of this compound from that of the acid itself is to be expected."

Even after Unna had explained the toxic action of very large doses of nicotinic acid by its high acidity and suggested the use of its sodium salt in animal experiments, a number of authors have continued to study the toxic effect of large doses of nicotinic acid and to ascribe this effect to a specific action, thus disregarding the findings of Unna. Handler and Dann (1942) reported that rats fed a diet containing 2% nicotinic acid gained weight, but developed fatty livers, as established by their increased content in fatty acids. No microscopical examination was done. On the other hand, nicotinamide did not produce fatty livers, but arrested the growth of the animals. Contrariwise, Aschkenasy and Mignot (1946) found that nicotinamide did not arrest growth, but produced necrotic foci in the liver and an increase of its fat content. These last two changes were conspicuous when the animals were given a protein-free diet, less so when the feed contained casein. Finally, Janes (1953) found no alteration of liver lipids after injection of nicotinic acid into rats. There are also many contradictory reports on blood-sugar levels and on liver glycogen after administration of nicotinic acid. Hallay (1957) and other physicians prescribe in many instances nicotinic acid for lowering the blood sugar in humans.

Animal Experiments

In animal experiments which we have performed in our laboratory on rabbits and on rats we have found that feeding of high doses of nicotinic acid caused no morphological or biochemical changes which could be ascribed to the nicotinic acid. This was especially clear in nine rabbits which had shown no pathological changes whatever, in spite of the fact that during 90 days they had received not only 45 mg. of nicotinic acid daily but also cholesterol. In four young rats, fed for 14 days a balanced diet containing 2% nicotinic acid, to duplicate the experiments of Handler and Dann (1942), the animals continued to gain weight, just as theirs did. When the rats were killed the microscopical examination showed, however, no signs of fatty liver and the chemical analysis gave no increase of total fat. It should be pointed out that in the experiments of Handler and Dann the dose of nicotinic acid per kilogram of body weight of the animal would correspond in an adult man of 70 kg. to 154 g. daily.

However, there are human cases reported in which the treatment with large doses (3 to 6 g. daily of nicotinic acid) had to be interrupted for certain periods, or discontinued altogether, because of intervening gastro-intestinal disturbances. According to Achor *et al.* (1957), in a series of 45 patients the treatment had to be abandoned in three cases on account of nausea and diarrhoea. In our opinion this may be due to the high acidity—that is, to an unspecific factor—rather than to a specific action of nicotinic acid. Therefore we decided to test large doses of buffered nicotinic acid in order to find out whether or not their effect on serum cholesterol is comparable to that of pure nicotinic acid. As a matter of fact, many clinicians who treat various diseases, but mainly such of the circulatory system, with small—that is, "vitamin"—doses of nicotinic acid do not use the acid proper, but either sodium or magnesium nicotinate, and that per os or by injections.

Present Investigation

We submitted a group of university students to a test in which they received 1 g. of buffered nicotinic acid (0.6 g. of sodium bicarbonate for each gramme of acid) three times a day for two weeks. This test is explained in Table I and

TABLE I.—*Serum Cholesterol* Before and After Administration of Buffered Nicotinic Acid (3 g. per day)*

Subject No.	Cholesterol (mg./100 ml. Serum)		
	Initial	After 7 Days	After 14 Days
1	218	160	142
2	178	143	132
3	252	225	235
4	175	152	132
5	223	214	196
6	198	182	162
7	232	195	188
8	222	166	156
9	162	176	167
10	178	141	135
11	149	130	132
12	230	335	163
Mean	201·4	184·9	161·7

* Determination by Schönheimer-Sperry's method, as modified by C. S. McArthur.

shows that relatively large doses of buffered nicotinic acid decreased serum cholesterol in young healthy adults. The decrease compares well with two previous tests on similar and partly identical groups in which unbuffered nicotinic acid had been used.

Treatment with buffered nicotinic acid for two weeks lowered the mean cholesterol level for the 12 subjects from

201.4 to 161.7 mg. per 100 ml. This difference is highly significant (k=2.44, P=0.01). The decrease after one week is statistically not significant, owing apparently to one very high reading for subject No. 12.

Six of the subjects had participated in an earlier experiment in which they received nicotinic acid. The change in cholesterol observed during the previous experiment is shown in Table II. Subject numbers for both tables are the same.

TABLE II.—*Serum Cholesterol Before and After Administration of Nicotinic Acid* (3 *g. per day*) (*from Altschul and Hoffer*, 1958)

Subject No.	Cholesterol (mg./100 ml. Serum)		
	Initial	After 7 Days	After 14 Days
1	202	179	148
2	200	160	146
3	200	182	161
4	235	207	200
5	206	155	148
6	197	157	173
Mean	206·7	173·3	162·7

The changes in cholesterol levels were practically identical in both experiments. In five of the subjects the decrease in cholesterol was within 8%.

In a previous study Hoffer and Callbeck (1957) found the following regression equation relating initial cholesterol level to expected decrease after two weeks' treatment:

$$y=0.52x-71,$$

where y=decrease in mg./100 ml.
x=initial cholesterol level in mg./100 ml.

With this equation the predicted value in this study is 167.7, the actual 161.7.

These observations show that the response to both nicotinic acid and nicotinic acid buffered with sodium salts is practically identical.

Obviously, in those cases in which sodium intake should be kept low potassium bicarbonate can be substituted in any desired proportion for the sodium bicarbonate. A very practical preparation seems to be the following: to 500 ml. of distilled water containing 32 g. of sodium bicarbonate (or 16 g. of $NaHCO_3$ and 16 g. of $KHCO_3$) is added slowly 50 g. of pure nicotinic acid, preferably in a wide container, to avoid "overbubbling." Of this solution, 1 tablespoonful of 10 ml. will contain buffered nicotinic acid corresponding to 1 g. of pure nicotinic acid. The best way to take this seems to be 1 tablespoonful diluted in one glass of water after lunch, 2 tablespoonfuls in one glass of water after the evening meal. In case larger doses are required, the amount is increased in proportion. Sipping of this solution over a prolonged period (approximately 60 minutes) may decrease the vascular dilatation, which is in some sensitive people an unpleasant side-effect. Since this vascular reaction usually disappears after three to seven days, the precaution of sipping the solution may then be discontinued. Of course, for practical reasons, especially in those cases where the patients do not take their meals at home, nicotinic acid, sodium (and potassium) bicarbonate, and some starch may be pressed into effervescent tablets and dissolved prior to taking the drug, possibly again after the main meals.

Finally, sodium nicotinate may be prescribed in the pure form, but it seems to us that in this case an unnecessarily large amount of sodium is being given.

Summary

It seems well established that nicotinic acid in relatively high doses decreases serum cholesterol in healthy and sick human beings. The toxicity of the substance is discussed, and it is pointed out that the high acidity rather than a specific action may be responsible for the occasional disturbances, such as gastro-intestinal reactions.

Tests on 12 healthy young individuals showed that a buffered solution of nicotinic acid is as efficacious in decreasing serum cholesterol as is the pure nicotinic acid.

In cases of poor tolerance of nicotinic acid a solution of nicotinic acid buffered with $NaHCO_3$ (or $NaHCO_3$ and $KHCO_3$) deserves to be tried.

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ELECTRODIAGNOSTIC STIMULATORS

A REPORT BY A SUBCOMMITTEE* OF THE MEDICAL RESEARCH COUNCIL'S NERVE INJURIES COMMITTEE

Electrical methods have long been used in the diagnosis and prognosis of lower motor neurone disorders. Erb, in 1883, described the classical faradic-galvanic test, which until recently has been the main stand-by in the electrodiagnosis of neuromuscular disorders. It is now known that this test is merely an abbreviation of the full excitability characteristics of nerve or muscle as demonstrated by the intensity-duration curve. Serious criticism has been levelled against the faradic-galvanic test (Wynn Parry, 1953; Ritchie, 1954), and the test is now regarded as obsolete. The first attempt to describe the characteristic excitability of nerve and muscle was the voltage-capacity curve (Cluzet, 1903). The curves plotted by this means, however, are not reliable, as the normal error range overlaps intermediate zones between denervated and innervated ranges. Furthermore, there are considerable technical drawbacks to the test. This technique has now been superseded by the plotting of a full intensity-duration curve using valve-controlled generators. Bauwens (1941) was the first to design an accurate electronic stimulator for this purpose.

An intensity-duration curve allows the expression of the characteristic excitability of the tissue under test in graphic form. An electrical impulse lasting 100 milliseconds or longer is applied to the muscle under test. The strength of current required to elicit minimal contraction (rheobase) is measured and expressed in milliamperes, or the potential difference required to produce this current is measured and expressed in volts. The

*The Subcommittee was appointed with the following membership: Professor J. Z. Young (chairman), Dr. P. Bauwens, Professor R. E. M. Bowden, Dr. E. A. Carmichael, Dr. F. S. Cooksey, Dr. G. D. Dawson, Sir Bryan Matthews, Professor A. E. Ritchie, Squadron-Leader C. B. Wynn Parry, and Dr. E. F. Mason (secretary).