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August 20, 1981

*J. Stampler
"all you need to
know about
exercise"
HB*

Henry Blackburn, M.D.
Arthur S. Leon, M.D.

Dear Art and Henry:

Finally I have had a chance carefully to review your draft chapter, "Physical Inactivity and Coronary Heart Disease", for the book Preventive Cardiology being edited by Norm Kaplan and myself. I find myself in accord with the general thrust of this chapter. In that regard, I have but one comment: Given the tendency in certain quarters to emphasize exercise as a preventive for CHD, while ignoring other aspects of its multi-factor causation in modern life-styles, I believe particular pains need to be taken in this chapter to make it clear that recommendations about regular frequent moderate rhythmic exercise as part of modern life-style are in relation to an overall set of proposals for life-style improvement embracing how people eat, drink, smoke, etc.

As to the Glossary, we have a problem, I believe, since the format here in your chapter is somewhat different from the others. This is something that Norm Kaplan and I need to resolve, in terms of the style of the book. Perhaps all this excellent material is best included in an overall Glossary for the whole book, perhaps it is left here at the beginning of the chapter. I will consult Norm on this and let you know.

Now let me proceed to go through the text page-by-page, to note various matters that concern me, and need your further attention.

In the last sentence of the second paragraph, page 1, a statement is made about the health effect of aerobic exercise. This is of course the nub of our scientific problem--can one really unequivocally conclude that regular frequent aerobic exercise at a level enhancing cardiovascular and cardiopulmonary fitness confers benefit in terms of health, longevity, etc., especially in regard to cardiovascular health, given the presently available data. Without attempting any lengthy discussion of this central and troublesome question, let me hasten to give my judgment, i.e., probably yes. That is, I estimate the data to indicate that at a high level of probability habitual physical inactivity and corresponding low level cardiopulmonary fitness is an independent risk factor, at least in societies such as ours with the nutritional-metabolic prerequisites for severe premature atherosclerotic disease, and with concomitant cigarette smoking, hypertension, etc. adding insult to injury in terms of the impact of diet on serum lipids, etc. I know that there are inconsistencies in the data, as well as limitations, hence my evaluation that from an etiologic point of view one can speak of inactivity and low level fitness as a probable--rather than an unequivocally established--risk factor in the etiologic sense. Therefore, by inference, increasing activity in the proper way and thereby improving fitness can be judged as a way to improve health. Having said that, however, I do not want to see us go out on any limbs, so to speak, on this matter, and urge our seeking formulations that are in keeping with best judgment concerning

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the available knowledge. Specifically, can we find formulations that will avoid categorical and unequivocal claims in this area? I give this to you for your further consideration, in this last sentence of this second paragraph on page 1, and elsewhere as well.

As to the intriguing definition of physical fitness, top of page 3, one of the thoughts I have come to have concerning this is that it is associated with maximum capacity to adapt successfully to a wide range of circumstances--in a way that is relevant not only for man in his "primitive" condition, but also for a modern man in contemporary industrial urban society as well. Whether or not that whole idea appeals to you and merits incorporation in the definition is, I hasten to add, up to you.

Having touched on the matter of exercise, fitness and health (also mentioned in item 11.c. on page 3) let me here take up another theme that appears throughout the chapter, i.e., assessment by maximal oxygen uptake. For years, I have been uneasy about this procedure, and I remain in that status. It is at best an uncomfortable one, as I believe it can properly be said, having witnessed a good number of people go through it, and having twice been tested myself. It also takes a good deal of time and hence is costly. I remain unconvinced that it yields data of fundamental importance beyond the submaximal tests. If it be stated that the maximal is necessary to get the given individual's capacity, so as to give him/her a personal prescription for exercise at a level below that maximum, I quickly respond by ~~saying that with any approach to the gradual build up of exercise over a considerable period of time in a person sedentary for a good many years, and with concomitant setting of an eventual goal of regular frequent moderate rhythmic exercise at a submaximal level, after the careful build-up, the need for the maximal test is--I believe--rendered essentially null and void~~ (there is of course the related issue about need for testing altogether, and for whom this applies--a rather "charged" issue at the present time, given the growing "industry" in this area in the medical and cardiovascular community that we will come to later.) I would appreciate your further thoughts on this, in terms of committing this chapter and this book to an approach that makes the key test of fitness a maximal one, and essentially makes no mention of the possible utility of submaximal tests. I regard this as a rather important question, hence deal with it at some length. It first arises in the last sentence of item 11.c., on page 3, but is of course a recurrent one.

As to the material under e., top of page 4, is it always the case that endurance training reduces body fat? I ~~know of~~ a good number of people who have improved their fitness without any weight loss, and perhaps it can be argued that in so doing they converted some fat to muscle. I hasten to add that I also know that regular frequent moderate exercise at a reasonable level can be a significant component in weight reduction of the obese, along with careful dietary recommendations. However, I am cautious about the unequivocal statement presented in line 5, top of page 4.

As to the material in the lower half of page 4, line 4 under B., I do not think it is quite accurate to say that heavy labor has been eliminated in the United States, although it has indeed become unusual. I know of workers in the steel mills who are still doing heavy work. Might this not be qualified a bit? As to the sentence beginning 3 lines further down, might we not also call attention to the automobile aspect of our passive culture.

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As to the last sentence begun on the bottom of page 4 and continuing on to page 5, there is always the matter of choice with respect to emphasizing the negative or the positive--i.e., only half (the negative approach), or by now as many as half (positive emphasis). To me the change in leisure activity has been remarkable, and perhaps the appropriate thing to emphasize here is the positive--but of course this is a small point, and I leave it to your judgment.

As to some of the adult activities listed, I would add tennis, and would perhaps eliminate bowling, since this is a recreation and not an exercise for almost all who participate in it (second complete sentence, top of page 5).

As to the material on the bottom of page 5, one of the other concerns--especially in regard to Little League competitive football--is the matter of serious injury for limbs where bone has not yet completed growth and fused. Might this matter also not be mentioned.

Might it not be good to include in the title on the top of page 6 both physical activity levels and Cardiopulmonary Fitness?

As to the correct point made in the second complete sentence on page 6, I believe many of the readers will not know what you and I mean by "contamination", and I think that decisive scientific point merits a bit of elaboration. The fact is that no single factor intervention study is feasible in our general population, nor is it feasible in any closed population, be the factor diet, exercise, smoking, since any intelligent group of health conscious people entering such a study would become more and more aware of the major aspects of life-style influencing risk, and would be more and more inclined to change traits other than the one under study in a uni-factor trial--particularly so for the active intervention group, being subjected to the most extensive information and education to motivate their change. Thus, any single factor trial is bound to become a "sloppy" multifactor trial. This recognition in the 1970's, with widespread consciousness of life-styles and life-style related risk factors, is what led me to abandon my years of effort to achieve a single factor diet-heart study. It can not be done. That must be made clear, so that the issue of getting data from such a "definitive" trial is laid to rest as a significant reason for not proceeding with mass public health efforts. The same applies in the exercise area. This is such an important point, that it should be made fully clear, and reliance not left to readers' understanding of a brief word. May I ask you then to elaborate this a bit?

As to the sentence beginning seven lines from the bottom of page 6, without taking a count, my impression is from the recent reviews I have read that it is not entirely true that most of the earlier investigations were retrospective or cross-sectional. This was not the case for example, for the early studies by Morris and his colleagues in the U.K., and their equivalence in the U.S.A. Could you double-check that statement?

In line 7, page 7, a term is used the definition of which is not entirely clear to me, case-referent. Would you either define it or get rid of it? My impression is that it is not necessary in that sentence. Further in respect to that sentence, is it true that there are several such post-mortem studies? In terms of sizeable numbers, as distinct from case reports (e.g., Clarence De Mar), I know of only a couple. Would you check that out also?

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As to page 8, the sentence beginning in line 8, I know that Paffenbarger's studies lacked serum cholesterol at baseline. Are there others where the relationship of inactivity to risk can be discussed, with serum cholesterol controlled as well? Of course, I know that data on this are in the 10-year monograph by Keys from the Seven Countries Study. Are there any others as well? It would seem to be useful to encompass these in this review. In the next paragraph, an important point is made in the first sentence. Might there not be a reference for it? Might I note here, in regard to this review of the data, that it is hardly possible-- I think--that this chapter authored by colleagues from the Laboratory of Physiological Hygiene can fail to summarize the findings to date from the Seven Countries Study in this area. Perhaps I am turning the pages too rapidly, but I do not see them summarized here. Having just carefully read the multivariate chapter in the Keys' monograph, I am, I guess, particularly sensitive on this matter.

As to the matter of confounding, discussed in the last paragraph of page 9, is it worth making the point originally brought forward (I believe) by Meyer Freedman concerning differences between English bus men driving in London vs. the suburbs, and his hypothesis that the driver-conductor contrast reflects psychosocial stress, rather than habitual physical activity.

As to the material on the bottom of page 10 dealing with reliability, the last complete sentence there is unclear in regard to the type of replication. Specifically, does it deal with yes-no replication, or degree of activity? This is important in evaluating a level of replication of 50%, which under circumstances of efforts to quantitate, might be assessed to be not too bad.

In regard to the material on the top of page 11, it might be useful to call attention to the MPH thesis by Ruth Anderson of our Department, dealing with a 7-day exercise diary, and the demonstration that it correlates significantly with the leisure time activity questionnaire findings on the same Chicago MRFIT men. Ms. Anderson's thesis has now been approved, and she has received the MPH degree. It can be listed as available from the library of the Northwestern University Medical School.

A small point: 5 lines from the bottom, page 11, might the word persons be used instead of subjects?

The same problem exists for trials on exercise post-MI as for unifactor trials of primary prevention, i.e., the difficult and really insoluble problem of confounding by other interventions, spontaneously undertaken by the informed and concerned participants, particularly in the active intervention group.

As to the last sentence on page 11, care should be taken with respect to use of the word larger, since there is a need to be concerned with assertions that large-scale trials have yielded negative or inconclusive results. My understanding of the sample size issues here is that none of these secondary prevention trials have come close to adequate sample sizes, as is suggested by you earlier in that same paragraph. In discussing the four studies cited on the top of page 12, no mention is made of the results of the Canadian one. Could these be summarized?

At the Anacapri meeting, if I remember correctly, Blomquist indicated a favorable trend in the U.S. study. If this is so, that might be mentioned.

Am I correct in recalling that the analyses in the Kallio study indicated a contri-

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bution of chiefly of diet change to the favorable outcome in the intervention group?

As to item D., page 12, might it not be useful to reword it as follows: Possible Mechanisms for Reduction of CHD Risk by Physical Activity, since the present wording is a bit awkward.

While I agree that regular frequent moderate exercise at a reasonable level can contribute meaningfully to a program of prevention or correction of obesity, it may be relevant also to note that in at least some studies increase in activity has not been associated with loss of weight for obese middle-aged men. I believe that that was indeed the case in the cooperative study in Minneapolis, Madison, and Pennsylvania. That is, recommendation and adoption of exercise by themselves--without careful attention to dietary habits--may not be effective in dealing with the overweight problem--an important point for a volume like ours.

As to the material on the top of page 13, you may find it useful to refer to our CPEP experience (reprint attached), which indicated in the bivariate analyses of change in weight and change in pulse for men with baseline diastolic pressure in the high normal range (80-89 mmHg) that slowing of the pulse was independently related to fall in blood pressure, over and above the significant effect also of loss of weight, for these hypertension-prone men. This finding needs to be confirmed in other studies with randomly assigned controls. Nonetheless it may merit citation, since it points to a possible contribution of moderate regular frequent rhythmic exercise to prevention of hypertension in people susceptible to this disease.

As to the ability of exercise to influence serum total cholesterol, I call your attention to the small experiment of Mastropaolo years ago in our laboratory, involving Tom Whipple and himself, with progressive increase in daily activity on the treadmill from 300-600 and then to 900 kpm in one hour, with concomitant increase in caloric intake of a fixed composition in terms of major nutrients. In that study at 900 kpm, serum cholesterol fell. I believe its results are summarized in one of our reprints and I am asking Fran Petersen to send you that.

Am I correct in noting a seeming contradiction between the last complete sentence on page 13, and the next one, most of which is on the top of page 14? I read these as apparently contradictory, and would appreciate your going over them to clarify exactly what the findings are.

With respect to line 7, page 14, I believe a better preposition is at rather than in the arterial wall, and the correct spelling of the author is Zilvermit.

With respect to the effects of exercise on glucose tolerance, and possible mechanisms, is there evidence that exercise increases the number of receptors, per the recent article in Diabetes Care on the effects of environmental factors on these receptors?

As to the last sentence beginning on the bottom of page 14 and continuing on to the top of page 15, does the 18 month mean after discontinuation of the study, i.e., the period of active training? This is unclear as that sentence is presently formulated. In terms of the English of that sentence, might it not be useful to put a semicolon after training and change the which to these?

As to the sentence beginning on the bottom of page 15 and continuing on to the top

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of page 16, a comparative is used, greater, but it is not made clear greater than what!

In regard to the effects of exercise on heart rate, might it not be useful here to cite the evidence available--albeit limited and not entirely consistent--that resting heart rate may in some populations be an independent risk factor, for coronary, cardiovascular, and/or all causes mortality. Thus, this is dealt with by Keys in the 10-year volume, and a recent paper from our group with Alan Dyer as the senior author also discusses it, based on our three long-term prospective studies.

Forgive my ignorance, but I do not fully understand the last sentence of page 16, in regard to the myocardial cell to fiber ratio. The heart being a syncitium, how exactly is this ratio measured, and how was it shown to reduce infarct size, or to be a significant variable reducing infarct size in this experiment? What kind of exercise was used in these rats? I know that each citation to relevant work here has to be brief, but I ask you to consider whether this needs a little further clarification.

As to the monkey work, discussed on page 17, I was told by Bob Wissler when he visited here along with you, Henry, that important new data on the beneficial effects of exercise in cholesterol-fat fed monkeys were presented at the Münster meeting he attended this June. Might it be useful to give him a call and get details on this? It sounded like a crucially important experimental result.

As to the sentence beginning 11 lines from the bottom of page 17, I am not sure I understand what is meant by sporadic improvement. Also, I believe the word in in the next line there is superfluous and should be deleted.

Is it correct that the one interpretation of the data described in the next to the last sentence of page 17 is indirect evidence of increased myocardial blood flow; might it also reflect greater metabolic efficiency?

As to the section in the upper half of page 18, the next to the last sentence under 4., am I correct in reading that summary of the work of De Backer, et al., as being in men free of evidence of clinical CHD, even though they had frequent ventricular premature beats? As to the material on the bottom of page 18, I believe that the judgment set forth there about psychosocial factors and CHD is rather excessively negative. In any case, it certainly is in rather stark contrast to the draft of a chapter we have from Dave Jenkins in Boston. My own judgment is that the available evidence supports the conclusion--particularly in regard to the Type A behavior pattern--that it deserves the designation of a possible or probable independent risk factor, although at this juncture not yet an established definite one, in terms of assessment of its etiologic role. I would ask that you reconsider this formulation, given a role for psychosocial factors solely in the precipitation of events in persons with already present severe atherosclerosis, if I understand your formulation on the bottom of page 18 and the top of page 19 correctly.

As to the reference later in that paragraph to the WCGS study, could you give it its full name (you referred to it as the Western Collaborative Study)? Further, could you deal with the final papers, presenting the full 8.5-year follow-up? I do not believe that the 1975 paper is one of the final reports from that study.

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In speaking of risks, as you might guess I would be particularly sensitive to joints potentially threatened, and would suggest in your third sentence of E. on page 19 that hips be added!

As to the precautions noted in that same paragraph on page 19, all of which I agree with, I would suggest that you consider saying something about the type of surface on which jogging or running is done, and the potential problem with roads and sidewalks, vs. regular tracks, grass, etc.

As to the reference to Shephard 1978 on page 20, line 9, I am not sure what is meant in citing the observation ~~that~~ about one quarter of non-fatal heart attacks occurred during some form of physical activity. Is this meant to indicate that this activity precipitated the event, or exactly what? The datum by itself has no clear meaning.

In that same paragraph on page 20, I note nothing about the role of serum cholesterol, cigarette smoking, clinical diabetes in contributing to the heart attacks under discussion. Is there a reason for the omission of these major established risk factors?

As you well know, and as I noted briefly in passing earlier, there is much reason to be concerned with the present "business" of exercise testing. We need to be sure here that we are as sound as possible in making recommendations as to who should get a multistage exercise ECG test as part of medical screening, prior to undertaking exercise. I believe your recommendation in the last sentence of that paragraph in the upper half of page 20 is reasonable, but urge you to give it another hard look, and to perhaps clarify further what is meant by the phrase, younger people estimated to be at high coronary risk. Exactly how is that estimate to be made? Again, I call attention to the problem of the maximal vs. the submaximal test.

I of course agree very much with the thrust of your rationale on the bottom of page 20, and particular its implicit point about data from trials. However, as indicated earlier, I believe that this should be spelled out further and made as explicit as possible, in terms of the fact that no definitive unifactor trial on exercise is presently in progress, or planned, or scientifically feasible--for the reasons already indicated, hence this demand is unrealistic and inappropriate, i.e., one must go forward with recommendations using best judgment based on the available evidence, with the knowledge that data from trials of a "definitive" nature are not going to be forthcoming.

As to citations of references, top of page 21, is not the up-dated A.H.A. statement on risk factors one to be added, in that it too deals with the matter of physical activity. I believe also that the now available Volume I of the Report of the NHLBI Working Group on Arteriosclerosis might also be included. It will be in hand for everyone, off the presses, in September.

Given the very limited evidence, I would be hesitant in your point 2) on page 21 to make the unequivocal statement that increased physical activity as such helps to reduce high blood pressure. I do not believe that there are adequate data to back up that assertion. On the other hand, insofar as physical activity is helpful in weight control for the obese, along with modification of diet habits, it surely can contribute to control of blood pressure. May I suggest that you give thought to exactly how that is formulated. I am concerned that we be careful not to engage

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in any "oversell" in this or any of the other chapters.

As to item 3) on page 21, I believe it is appropriate to say that the benefits outweigh both the risks of inactivity and the risks too of exercise itself.

As to point 5) on page 21, here too I would speak of promotion of regular exercise with safety.

As to the material on page 22, there is a shift in the style of language in the last paragraph, from an active list of proposals--all set forth neatly in the items in the upper two thirds of the page--to and are encouraged formulation at the bottom. Might you not want to make the style uniform there.

Having, as already noted above, been reading carefully the Keys 10-year report, I am particularly sensitive to the theme that where exercise seems to be beneficial in populations, it is not at the 60% or more of VO_2 max, nor is heart rate at 70%--let alone 70-85%--of maximal. This whole matter of type, duration, intensity, remains troublesome. I do not know exactly how to treat of it here in as fully an objective way as possible, but merely pose the problem to you. I do note that on the bottom of page 25 and the top of page 26 a recommendation is made that apparently relates to data from one or two prospective studies, i.e., those of Paffenbarger, et al. Certainly we should try to make the bridges here wherever possible. In any case, I agree with the point made in the second complete paragraph on page 24, about the greater safety of lower intensity prolonged exercise. Having said that, I am a bit concerned about the recommendation of levels of 70-85% of maximal, with not only resultant sweating, but also breathlessness. I remain to be convinced about the wisdom particularly of the heart rates at 85% of maximum, as set forth in Table 3. I completely agree with the cautions in the first complete paragraph on page 25 about the first phase of an exercise program in a previously sedentary person, and would urge that this be expanded and given greater prominence. Against the background of that approach, I again ask whether really a maximal test is needed. Please note that Table 3 uses average maximal heart rates, for age. With that as a guide, is there really a need for all being tested to have their particular maximum defined, or might not submaximal testing be done, more for signs of occult cardiac problems in those sedentary for years and at relatively high risk. With a prescription to build up gradually, and supervision of what happens during that time, and cautions for that time, one can then gradually get to a target zone, suitable for the individual, without the need for the maximum test in most cases, I believe. I would appreciate your judgment on this.

Might not the formulation be that of vigorous walking in the set of exercises cited in the last lines of the second complete paragraph, upper half, page 25.

As to the next paragraph on page 25, might it not be reasonable to note--if you deem this to be correct--that the risks of musculoskeletal injury are less with the non-weight bearing types of exercise, e.g., swimming, bicycling.

In the same vein, in regard to material in the middle of page 26, my estimate would be that with non-weight bearing exercise, the possibility of injury does not increase markedly, if at all, with workouts of 7 days compared to 5 days a week. This certainly has been my personal experience with swimming. All this material in this lower half of page 26, including that in the bottom paragraph, seems to relate to exercise of the jogging type. May I ask that you reconsider exactly

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how this is formulated.

As to page 27, 7 lines from the bottom, I believe the opening word ideally is really not entirely appropriate. Multifactor programs are indeed what one should expect as the only decent programs nowadays.

As to the third paragraph on page 28, I am not convinced that the risk of cardiac arrest is correctly characterized as remote. Thus, I am aware of the Seattle supervised exercise program and the number of arrests on the floor of the gym. I have never seen a calculation of the number of persons or person years of exercise, but I find myself rather troubled about the number of arrests I have heard about. Again, I could be wrong on all this, but ask you to give this a second look. I agree with all the cautions nicely set down in the last sentence of that paragraph, and would only add the possibility or the wisdom that over the first months at least such programs should be supervised ones.

There seems to be a typo, lines 2-3, top of page 29, in that there is no verb.

I note with gratification, in the complete paragraph in the middle of page 29, reference to the use of a submaximal test!

At the same time, I note in the middle of page 30 mention of a maximal text, bringing me once again to ask you to consider whether this is really necessary.

As to the material on the top of page 31, having stopped use of a bicycle because of a back problem as I bent over to hold the handle bars, I am not completely convinced of the blanket statement that this is useful for people with low back problems! Perhaps that could be modified to state that this non-weight bearing form of exercise is widely useful, and can even be tried for people with low back problems, with a bicycle of the type that does not require a posture that aggravates back problems.

What is circuit training (line 3, page 31)?! If I am unclear on this, perhaps it is worth a bit of elaboration.

As to Table 2, might not two additional considerations be added, i.e., musculoskeletal status and safety.


As to Table 4, with your own precautions in the text about gradual slow progressive build-up, I find it rather startling to see an initial intensity of 60-70% of maximum heart rate. Would you please reconsider this? It seems to me that the admonitions can easily be lost in the text, unless they are as clear in the tables as in the text itself.

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As to Table 5, might it not be good to state that at any given point in time, if the individual is symptomatic, he/she is wise not to try to "exercise out" the symptoms.

Well, I have given you a considerable amount of detail to chew over, and look forward to seeing the final chapter that results. All the best from us here in Pioppi to all of you.

Cordially,

 /AD
Jeremiah Stamler, M.D.

JS/clt
encl.
Dictated by Dr. Stamler and signed in his absence.