UNIVERSITY OF Minnesota

SCHOOL OF PUBLIC HEALTH · LABORATORY OF PHYSIOLOGICAL HYGIENE
STADIUM GATE 27 · MINNEAPOLIS, MINNESOTA 55455

October 30, 1967

Professor F.S.P. van Buchem
Duinroosplantsoen 15
Haarlem, Netherlands

My dear van Buchem:

Finally I am back in my office in Minnesota. My return from Italy on October 15 was followed, by one day, by departure for San Francisco (American Heart Association meeting) and Miami (American Public Health Association meeting). So only now have I seen your letter dated 27 September 1967.

Of course we did not have time enough on the last day of our Minnelea conference to discuss in detail the rather complicated data from Zutphen summarized in the slides. Perhaps I should have scheduled more time for such discussions; Fidanza was very cross because he was not called on to discuss some of his detailed dietary studies.

As to your data and the various correlations, I should have to study the material carefully and at leisure to be ready to comment properly. However, I would point out that correlation analysis with many inter-related variables does not always provide ultimate "truth" but is always subject to a variety of of interpretations in regard to biological meaning. And I should emphasize, again, the large intra-individual error and variance in regard to the two major variables of the diet and the level of physical activity.

I hope soon to be able to send you draft copies of materials that came out of the Minnelea conference. Drs. Blackburn and Menotti are mailing some practical trials of classification and within a month should be able to report to us all. I still think that a target schedule of having reports on mortality reports ready to assemble for publication by next spring is reasonable. But I shall send a more detailed memorandum soon.

Kind regards to you and your wife.

Sincerely yours,

Ancel Keys, Director

AK:mh
cc: Dr. Blackburn

March 11, 1968

Professor Flaminio Fidanza
Istituto di Scienza dell'Alimentazione
Cassala Postale 333
Perugia, Italy

Dear Flaminio:

We are editing and converting to IBM cards.

We have found generally matching values between Minn. Form 2 and the enclosed typed list for 3 sec. Vit. Cap.

By exclusion, we assume all other values on form 2 are 3/4 sec. timed V. Cap. Is this true? Are we sure it is not 1 sec. timed V. Cap.?

	Minn. Form		Fidanza Tab.
	3/4 sec.	3 sec.	3 sec.
Montegiorgio	(22)	44	44
Crevalcore	25		36

Regards,

Henry Blackburn, M. D.

HB:mk
Enclosures

DR. ALESSANDRO MENOTTI
ROMA

Rome March 20 1968
Via Latina 49

To Dr Henry Blackburn
Laboratory of Physiological Hygiene
University of Minnesota
Stadium Gate 27
Minneapolis Minn.

Dear Dr Blackburn,
please excuse me for my long silence, but I have been very busy during last few weeks. I have now several points to explain you.

1. Recently I informed Dr Keys, met here in Rome, that the deaths coding is finished, except the actual coding of non cardiovascular diseases (just putting numbers) because I am still waiting from Geneva the 8th edition of the I.C.D. I have known from Dr Keys about your next travel to Japan; so I am almost sure that at your return you will find all the material which I will mail as soon as possible together with some comments. Dr Keys and I would be very happy to see some correlations between deaths and other items before the end of next summer hoping to discuss them during our stay in Dalmatia. Dr Keys feels that the preparation of a text for publication should not require so much time.
2. Together with Dr Keys and Dr Puddu we discussed also the problem of the Mnemotron tape-recorder. Dr Puddu has assured that he will do everything it is possible in order to get a permanent permission to move it easily from Italy. We hope to obtain it before August. So it should be available for the Yugoslavian study. On the other hand I would like to point out that the equipment as received back from Frankfurt can not work. At present it works satisfactory because it is coupled with some Italian devices designed for the purpose, but we are not sure to get the permission (from the industry which designed them) to export such a experimental apparatus. (control box, coupler between tape-recorder and control box, oscilloscope, cables etc). For this reason I think that a meeting, possibly in Rome, together with a technician interested in the next field work will be essential within the next 2-3 months. Hans Friedrich might be the suitable person.
3. I would like to purchase another magnifying lens for the ECG measurements like that you gave me in Corfu in 1966. Can you tell me where may I find it? Thank you.

Best whishes for the Japanese field work.

Yours sincerly

Alessandro M.

UNIVERSITY OF *Minnesota*

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STADIUM GATE 27 · MINNEAPOLIS, MINNESOTA 55455

April 29, 1968

Dr. Alessandro Menotti
Via Pandosia 22
Rome, Italy

Dear Alessandro:

I trust the enclosed statement will serve your purpose.

Thank you for the summary of death rates. These will be revised to cover only the ages 40-59 at the start of the five years and the mortality rations, O/E, will be calculated, the "expected" rates being those for U.S. white men matched for age in 5-year age groups. For this purpose, we shall use the death data you have sent to Dr. Blackburn.

The 10-year re-examinations at Tanushimaru went very well and when we finished the field work on April 14, around 95 per cent of all survivors had been re-examined. Almost all of the remaining men will be re-examined, at least for the essential items, in their homes (or in hospital where a few of them are at present). Only 5 men have refused full re-examination but the minimum of needed information will be obtained on them also. Coronary heart disease continues to be very uncommon in the Tanushimaru cohort..

When we returned from Japan (April 20) I found that U.S.P.H.S. had given final approval to the allocation of funds for my coordination of the cooperative program through 1970. Though the budget has been reduced from the amount approved previously, it will allow us to proceed with no difficulty on the basic program of follow-up and data analysis. Your own place in the program is assured at least through 1970.

I am confident that the program support will be extended through 1972 or 1973 if I can provide a good report, including morbidity and mortality rates through 1968 and the relationship of the incidence of coronary heart disease to pre-disease characteristics. That report must be finished by the end of this year, 1968, so I shall put pressure on Dr. Blackburn and the data-processing group here to get the data in shape as soon as possible.

While I would be pleased to cooperate with Dr. DeNicola, I agree that we cannot give his interests high priority. I believe coagulation and fibrinolysis data would be valuable and that DeNicola is expert in that field, but we must realize that it is uncertain how much of epidemiological value might result from his work at Makarska. It would be essential to be able to compare his findings at Makarska with data on other well-defined population samples. Accordingly,

I think that if Dr. DeNicola or an assistant is to work at Makarska, we should also plan for the same work to be done in Finland in September-October, 1969. I could allocate about $1,000 for that purpose in 1969. So I suggest you talk to Dr. DeNicola in those terms, making it clear that agreement for his participation in the work at Makarska this fall is contingent upon: 1) His acceptance of the limitation of the amount of blood that can be given to his purposes, 2) His agreement that, if his measurements at Makarska prove to be technically satisfactory, he will arrange to carry out the same procedures in Finland in 1969, at least in East Finland. This means at least some three weeks of work in September, 1969.

Personally, I feel that more of value may come from the suggested collaboration of Professor Bastenie on the thyroid. I wrote a few days ago to Professor Bastenie indicating some details that might be suitable for his participation at Makarska and will advise you when he replies. Anyway, I think it would be useful for you to spend a day at Brussels as you propose to do in the latter part of May.

Regards to you and your family.

Sincerely,

Ancel Keys, Director

AK:mh

cc: Dr. Blackburn

enclosure

June 13, 1968

Dr. Pentti Rautaharju
Department of Physiology
Dalhousie University
Halifax, Nova Scotia, CANADA

Dear Pentti:

Just a note on the ECG analysis. I am still interested in resuming the discriminatory power of the rest, exercise, and post-exercise ECG as before, to get one reasonable final set of rankings. Also if possible Frank versus a synthetic CM5 lead (azimuth angle 6.4°, elevation 50.0°, lead strength 1.28 compared to V5 at 1.00).

We will be able to make Japanese-Finland comparisons because I modified the test to have a break after each work increment. It is a "better" test in all respects except time required. To get everyone we will have to get the servo mill or servo resistance set-up to arrive promptly and stabilize at a desired heart rate. We can make Japanese-Velika Krsna-Finnish comparisons during and after work at a given heart rate common to most or all men.

Please tell Hans that I wasn't thinking fast about Yugoslavia. We should not try to operate in Dalmatia with the moving problems and poor quarters. We should continue collaboration with the Belgrade team and, if we do anything, record at Zdrinanin near Belgrade September 1-15 approximately.

I am personally in favor of getting every area, to continue to develop our methodology, and collect larger numbers. I don't believe the expense of ± $3000 is worth it in a period of tight finances, however, and perhaps we should concentrate on our present analyses and save and plan for Finland '69 and a big year in '70, Italy , Holland, Japan and Greece, Spring, Summer and Fall.

Please let me know your plans for coming through. It was good to get a glimpse of Herman.

Regards,

Henry Blackburn, M.D.

HB/rk

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June 19, 1968

Dr. Alessandro Menotti
Via Latina 49
Rome, Italy

Dear Alessandro:

Thank you for your response to the material sent on the question of publication of 5-year follow up findings. There are many questions to be considered in the final decision as to what should be included, how defined, etc., in the publication. The material I sent to all of the collaborators was tentative and a basis for mutual consideration. Below I shall take up the questions you raise in the order given in your letter dated June 14, 1968.

It seems reasonable to hope for inclusion of myocardial infarction in the ms. under preparation and we propose to try.

I propose several cohorts for analysis in several ways. Exclusion of diabetes, tuberculosis, rheumatic heart disease, etc. in a primary cohort seems desirable to prevent disparities in prevalence of those conditions becoming sources of confusion in analyzing total (all-causes) death rates. Actually, we may analyze 4 or more cohorts, differently defined for different purposes.

You may be sure that the disease categories "coronary" and "other heart," etc. will be carefully defined; work on those points is an early requirement, of course. We propose to list each of the defined manifestations and to provide analyses on these separately and also pooled in various ways. In regard to M.I., we do propose to distinguish between "definite" and "possible" (or "probable"). Proposed definitions and methods of classifying all of these relevant clinical conditions should be in good preliminary shape, at least, in a few weeks.

For the analysis we have not provided separately for conditions that will be too uncommon in our material to have any significance.

We propose to consider only definite angina pectoris and even that will be treated with some hesitation in comparisons.

In regard to the proposal to group centiles, in many respects the extremes are of greatest interest. Our material will be too small for analysis

by 10 deciles and probably by quintiles. The 20-30-30-20 scheme automatically provides a median cut which is useful and not available in tertile or quintile analysis.

We propose that CHD will include No. 412 (in the new revised classification) and we do propose to distinguish between definite and possible M.I. for prognosis, but would exclude possible angina pectoris from all of the analyses of total data. Local groups may, of course, wish to make internal comparisons, etc. for their own areas separately. But I, at least, am opposed to doing anything about comparing areas in regard to reported possible angina.

We shall keep you informed.

Regards.

Sincerely,

Ancel Keys, Director

AK:mh
cc: Dr. Blackburn

THOMAS STRASSER
Pasterova 14
Belgrade,Yugoslavia

June 2o, 68

Henry Blackburn, M.D.
Laboratory of Physiologiaal Hygiene
Stadium Gate 27
MINNEAPOLIS, Minn., 55455

Dear Henry:

This is a reply to your letter of June 13. We have not sent any data from Krsna II /1967/ to Mpls. Please let me know, what data do you need right now.

As a matter of fact, all of us, including prof.Djordjević, Srećko Nedeljković and myself, we all have been overloaded with work - graduate and postgraduate teaching, clinical routine, publishing etc. - and just were unable to spare the time for editing & processing the Krsna material. Unfortunately we probably will not be able to provide you with completed initial record forms before November 1968.

Preparations for field work in Zrenjanin are going on im adequately. Start is on Sept.2.

Best regards,

Tom

/T o m/

And as you will.

cc.:prof.Djordjević
S.Nedeljković

DR. ALESSANDRO MENOTTI
ROMA

Roma, June 4,1968
Via Latina 49

Dr Henry Blackburn
Laboratory of Physiological Hygiene
University of Minnesota
Stadium Gate 27
Minneapolis Minn.

Dear Dr Blackburn,

thank you for your letter on May 14. I appreciated very much the comments done to my codes because they solved at least some of my many doubts.

Going through your letter I can say some more things.

1) I regret for having changed an important item as specification of "other cardiac event with death-cardiac cause". I did so simply because it was not so clear to me in the context of the suggested form.
2) I perfectly agree with you to prefer 410.9 instead of 412.9 when there is a past hystory fo M.I.; I did the contrary because, according the I.C.D. 8th edition, any M.I. falls into 412 code 8 weeks after its development. But for our purposes I believe that 410.9 is better and anyhow less equivocal.
3) Accepted the comment of the three next paragraphs.

For the morbidity problem I will think about it; but when shall the morbidity (I mean incidence) data be definitely coded?

I received from the Lab. also the "proposed outline" for the report on deaths. Even though I did not studied yet it deeply I would suggest anyhow to combine, at a certain stage of the analysis, the deaths for M.I. with the sudden deaths.

Recenlty I have been to Zutphen to visit Dr Van Buchem. A part from what I will communicate to Dr Keys in my next report, I checked again the 5 years mortality in order to be sure about what I sent you recently. I can confirm that there were no gross mistakes except that notified you recently in another letter of mine. There are anyhow three points:

1) Subject N. 250 apparently died on 1962 instead of 1961, as stated on my Form 20 (the day is the same).
2) Subject named Stoffer had no serial number because he was in the roster but he was not examined at the first exam. You know what to do with him.
3) The same applies to a subject named Kuiper, born on May 7,1907 and dead in 1965 for cerebral hemorrhage. But for this no Form 20 was filled.

In order to avoid future newer troubles with Dr Van Buchem I will give specific suggestions to Dr Keys in my report.

Best regards.

Alessandro Menotti

JUL 22 1968

DR. ALESSANDRO MENOTTI

ROMA

Rome July 17,1968
Via Latina 49

Dr Ancel Keys
Laboratory of Physiological Hygiene
Stadium Gate 27
Minneapolis Minn.

Dear Dr Keys,
thank you for your letter with the definitions of cohorts and criteria for analysis of mortality and morbidity. I agree with everything except with a detail in the Classification of death. Actually letter d) and e) in the "Coronary event with death" seem to me not suitable to enter that class. I would prefer to have them included in Other cardiac event with death. In fact congestive heart failure, with unspecified cause and cardiac arrhytmia, not sudden, might be related to a coronary disease but in general there is not a clear evidence of it. Moreover these syndromes are frequently the final conclusion of the reviewer when f.i. cases of chronic pulmonary heart disease of hypertensive heart disease are not sufficently described in the record. Finally I suspect that the inclusion of these cases in that class could determine a misjudgment on the eventual relationships of types a), b), and c) to some measurable variables at the first examination. For the same reason I would prefer to keep always well separated from the others the "New coronary events" described on point 4 of the second page (Chronic heart disease of probable coronary etiology).

I hope do not be too aggressive with these newer comments.

Best regards. Sincerly yours

Alessandro Menotti

DR. ALESSANDRO MENOTTI
ROMA

Rome May 8, 1968
Via Latina 49

Dr Henry Blackburn
Laboratory of Physiological Hygiene
Stadium Gate 27
MINNEAPOLIS Minn.

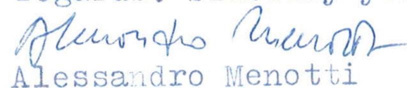
Dear Dr Blackburn,
I hope that the parcel containing the deatn codes arrived safely to Minneapolis.
Just reviewing some of the data, I discovered that in the Zuthfen group there was a mistake: so please delete n.713 which was a wrong copy of n.718.
It is possible there are other mistakes in this group because I was compelled for Zuthfen to rebuild again the mortality situation looking to a lot of piece of paper and to various editions of Form 10; some men had only one Form 10; some had two; some had none and were only listed in several other places. I tried to do my best sending you a total of 62(now 61) records. At present it is not possible to know if this is correct; but during my visit to Dr Van Buchem, before the end of this month, I shall make, together with him, a newer definitive check.

Recently I tried to apply the criteria for incidence of myocardial infarction and angina pectoris to the 5 year follow-up data of the Italian areas. Putting together definite and posible M.I. tne incidence was about 33 per thousand in Crevalcore, 20 per thousand in the Rome Rail Road, and 19 per thousand in Montegiorgio. The common feature of these data is the very high frequency of cases described in the code 01.03 that is cases with appearance of Class 1.2 Q waves not present on earlier examination, but without any nystory. And this was found even though ECG codes were the official ones for Crevalcore and Montegiorgio, and my own preliminary codes for Rome. It is very difficult to give an explanation to this finding(silent M.I.?- so frequent?).

A part from this point I would like to know if in general you use, for the evaluation of incidence, also the interim informations collected periodically on tne field togetner with mortality(I mean morbidity data).

I hope the work of analysis of deaths is going on well. Let me know if there are problems due to my faults.

Best regards. Sincerly yours.



Alessandro Menotti

May 14, 1968

Dr. Alessandro Menotti
Via Latina 49
Rome, ITALY

Dear Alessandro:

Thank you for your May 8 letter. In general I find the area deaths in very good shape, but I sent for the Minnesota Forms 10 just to have all information at hand as we finalize them.

I think when you redo your coding form for the 10 year deaths you should re-align precisely the boxes, where now decisions on the check marks are ambiguous I would also appreciate your reinserting the line on my form which you removed; under Other Cardiac Event with Death insert Cardiac Causes (specify and code) so there can be a visual comparison between English language and numerical codes.

Only a few comments on your codes:

I wonder if we should pursue your policy of changing the cause of death code for acute myocardial infarction to the code for chronic ischemic heart disease (410.9 to 412.9) on the basis of past history of heart disease. Would it not be better to leave the cause of death 410.9 as assigned by the hospital, physician or our collaborator, and record 412.9 as the first major contributory cause?

I concur with your change in assignment of an out-of-hospital death from 410.9 to 427.0 or 429.9, when the story of infarct is poor. I also concur with your change from a death certificate code of 410.9 to 795 when the death is sudden and unexpected, and out-of-hospital. However, I question the several changes you have made from 410.9 to 427.1 when the death was in-hospital. I believe we must accept that witnessed cause of death. We may eventually compare frequencies of medically witnessed deaths in the different areas.

I don't quite see how we can change an in-hospital death diagnosis of pneumonia and bronchitis to cancer as you have done for 1746 in W. Finland and I have changed it bakk to 491.

Without Forms 10 I am unable to ascertain why you changed Ushibuka 556 from paeumonia 486 to CVA 436. I also do not find this case on my Ushibuka death list, so I presume you have better information than I and have left this code.

Your point on class 01.03 as a new morbidity event is a good one. I have not tested these criteria most of which are still "armchair."

Let's make together a more detailed study of each criterion to see how sensitive and specific each ECG item is, using as independent reference the clinical history of definite, possible or no infarction. In other words, let's find the sensitivity and specificity of each ECG code suggested (01.01, 01.02, 01.03, 02.01) using as reference those cases meeting clinical code 02.02 (possible) and, separately, those meeting 01.05 (definite).

Regards,

Henry Blackburn, M.D.

HB/rk

c.c. Dr. Keys