(Please note the date this letter was started -)

May 13 - 1943
136 East 67th St.
N.Y.

MS. DIV.
IAC. NO. 70-128

Dear Roy: —

Thanks very much for that good letter - of course, I understand why you couldn't make the party the boys gave in my honor - Naturally they didn't tell me that you or other guests outside the department had been invited - it was all to be a surprise - It would have made me very happy if you could have been with us that evening - Ernest Stillman and Ken Goodner simply told me that they thought it was about time the past & present members of the staff - all the "57 varieties" of pneumococci, - got together & had a reunion - I said I thought it a good idea but doubted whether the men could get together these stern & busy days - and perhaps it would be better to wait and not attempt it now - I was over ruled - they pointed out that it was good to

have a reunion - buck up morale - a little diversion, times like this, was just what we needed. So the plans went on & I was not consulted further. And they did come back - Dr Cole & "Do" were there - Francis Blake from Yale, Alan from Balto, Dubos from Harvard, Tommy Francis from Michigan & others; They had invited Bill Parke with whom I roomed four years at Colgate, - but he was sick in bed with Grippe - sent me a nice letter - There were about 35 men present - and it was quite impressive to see the old boys come back - and to realize how they had advanced not only in years but in rank, and position.

The boys in the Department wrote some topical verse - Bill Tillett was master of ceremonies & the whole occasion sparkled with wit, skit, and jovial good humor - happily, at no time sinking into lugubrious & doleful speeches; - bright cheerful & happy it was throughout - I really enjoyed it -

and appreciated not only the spirit which prompted it but the spirit in which it was done — an altogether happy occasion — It brought back memories of 30 very happy years spent in a stimulating environment & an association with a splendid group of men to whom I owe far more than they know or can ever realize —

Last Friday evening (May 7th) I dined with Dr Gaudpasture — We were attending the Board meeting in the Surgeon General's office in Washington — Ernest asked me to have dinner with him — We had a delightful talk together — He brought messages from you — and we discussed my future plans — about the possibility of my coming to Nashville — What a joy it is to me to know the depth & sincerity of that welcome — it means much to me these days — If this War wasn't on I tell you frankly I would liquidate my affairs here & start for Nashville this fall —

!!! (Lapse of 13 days — Letter started again May 26)

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May 26. 1943.

Almost two weeks have passed since I began this rambling letter — I shall attempt no explanations save to ask to believe that I have not been wholly idle in the meantime or unmindful of you & those I love in Nashville —

Indeed, I have been busy — just manage to keep my head above water these days — Come home each night determined to catch up my letter writing but a hundred & one other things barge in until its so late & I'm so tired & sleepy I postpone, go to bed, resolving to get up an hour earlier in the morning — of course that's fatal — as the present results show —

Now as to some work I'm doing in the Lab — and I speak of it because I know you'll be interested & also because it bears on my future plans and my wanting to liquidate my affairs here and spend the rest of my days with my family — as I mentioned at the bottom of page 3 — As you know on July 1 I relinquish Chairmanship of the Department & retire from active membership of the Institute — Both

Dr Gasser and Dr Rivers have been very kind and have insisted on my staying in - providing me an ample budget & technical assistance to carry on the problem that I've been studying - I've not published anything about it, - indeed have discussed it only with a few - because I'm not yet convinced that we have (as yet) sufficient evidence - However, I did talk to Ernest about it in Washington and I hope he has told you - for I have intended telling you first of all - I felt he should know because it bears directly on my coming eventually to Nashville -

It is the problem of the transformation of pneumococcal types - You will recall that Griffith in London, some 15 years ago described a technique whereby he could change one specific type into another specific type through the intermediate R form. For example: Type II → R → Type III. This he accomplished by injecting mice with a larger amount of heat killed Type III cells together with a small inoculum of a living R culture derived from Type II. He

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noted that not infrequently the mice so treated died & from their heart blood he recovered living, encapsulated Type III pneumococci. This he could accomplish only by the use of mice. He failed to obtain transformation when the same bacterial mixture was incubated in broth. Griffith's original observations were repeated & confirmed both in our Lab & abroad by Neufeld, & others. Then you remember Dawson & Sia reproduced the phenomenon in vitro by adding a dash of anti R serum to the broth culture. Later Alloway used filtered extracts prepared from Type III cells & in the absence of formed elements & cellular debris induced the R culture derived from Type II to become a typical encapsulated III pneumococcus. This you may remember involved several & repeated transfers in serum broth - often as many as 5-6 - before the change occurred. But it did occur & once the reaction was induced, thereafter without further addition of the inducing extract, the organisms continued to produce the Type III capsules; that is the change was hereditary ~~& that~~

and transmissible in series in plain broth thereafter. For the past 2 years, first c̄ MacLeod & now with Dr McCarty I have been trying to find out what is the chemical nature of the substance in the bacterial extract which induces this specific change. The crude extract (Type III) is full of capsular polysaccharide, C (somatic) carbohydrate, ~~nucleop~~ nucleoproteins, from nuclear acids of both the yeast & thymus type, lipids & other cell constituents. Try to find in that complex mixture, the active principle!! Try to isolate and chemically identify the particular substance that will by itself when brought into contact with the R cell derived from Type II cause it to elaborate Type III capsular polysaccharide, & to acquire all the aristocratic distinctions of the same specific type of cells as that from which the ~~the~~ extract was prepared.! Some job - full of headaches & heart breaks. ~~But~~ At last perhaps we have it. The active substance is not digested by crystalline trypsin or chymotrypsin — It does not lose activity

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When treated with crystalline Ribonuclease which specifically break down (Yeast nucleic acid). The Type III capsular polysaccharide can be removed by digestion with the specific Type III enzyme without losing transforming activity of a potent extract. The lipids can be extracted from such extracts by alcohol + Ether at −12° C. without impairing biological activity. The extract then be de-proteinized by Sevag Method (shaking Chloroform + amyl alcohol) until protein from and biuret negative. When extracted, treated + purified to this extent, but still containing traces of protein, lots of C carbohydrate, + nucleic acids of both the yeast + the various types are further fractionated by the dropwise addition of absolute ethyl alcohol, an interesting thing occurs. When alcohol reaches a concentration of about 9/10 volume there separates out a fibrous substance which on stirring the mixture wraps itself about the glass rod like thread on a spool + the other impurities stay behind as granules

precipitate. The fibrous material is redissolved & the process repeated several times — In short, this substance is highly reactive & on elementary analysis conforms very closely to the theoretical values of pure desoxyribose nucleic acid (thymus type). Who could have guessed it? This type of nucleic acid has not to my knowledge been recognized in pneumococcus before — though it has been found in other bacteria —

Of a number of crude enzymes preparations from rabbit bone, swine kidney, dog intestinal mucosa, & pneumococci, and fresh blood serum of human, dog & rabbit, only those containing active depolymerase capable of breaking down known ~~[illegible]~~ authentic samples of desoxyribose nucleic acid have been found to destroy the activity of our substance — indirect evidence but suggestive that the transforming principle as isolated may belong to this class of chemical

substance – We have isolated highly purified substance of which as little as 0.02 γ a micro gram is active in inducing transformation – In the Bacteria mixtures (culture medium) this represents a dilution of 1 part in a hundred million – patent stuff that – & highly specific – This does not leave much room for impurities – but the evidence is not good enough yet.

In dilution of 1:1000 the substance is highly viscous as are the aqueous preparations of deoxyribose nucleic acid derived from fish sperm – Preliminary studies with the ultra centrifuge indicate a molecular weight of approximately 500,000 – a highly polymerised substance –

We are now planning to prepare new batch & get further evidence of purity & homogeneity – by use of ultra centrifuge & electrophoresis. This will keep me here for a while longer; if things go well I hope to go up to Deer Isle, not at this – Come back

refreshed & try to pick up loose ends in the problem & write up the work. If we are right - & of course that's not yet proven, then it means that nucleic acids are not merely structurally important but functionally active substances in determining the biochemical activities and specific characteristics of cells - & that by means of a known chemical substance it is possible to induce predictable and hereditary changes in cells. This is something that has long been the dream of geneticists. The mutations they induced by X ray & ultraviolet are always unpredictable, random, & chance changes. If we prove to be right - & of course that a big if - then it means that both the chemical nature of the inducing stimulus is known & the chemical structure of the substance produced is also known - the former being thymus nucleic acid - the latter Type III polysaccharide. And both are thereafter reduplicated in the daughter cells. And after innumerable transfers and

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without further addition of the inducing agent, the same action & specific transforming substance can be recovered far in excess of the amount originally used to induce the reaction — Sounds like a virus — may be a gene. But with mechanisms I am not now concerned — one step at a time — & the first step is, what is the chemical nature of the transforming principle? — Some one else can work out the rest — Of course the problem bristles with implications. It touches the biochemistry of thymus type & nucleic acids which are known to constitute the major part of chromosomes. but have been thought to be alike regardless of origin & species — It touches genetics, enzyme chemistry, cell metabolism & carbohydrate synthesis — etc — But today it takes a lot of well documented evidence to convince anyone that the sodium salt of desoxyribose nucleic acid, protein free, could possibly be endowed with such biologically active & specific properties. & that evidence we are now trying to get. It's lots of fun to blow bubbles — but its wiser to prick them yourself before some one else tries to.

So there's the story Roy - right or wrong it's been good fun & lots of work - This supplemented by war work - and general supervision of other important problems in the Lab has kept me busy, as you can well understand.

Tack it over with Good posture but dont shout it around - until we're quite sure or at least as sure as present method permits. It's hazardous to go off half cocked - & embrassing to have to retract later.

I'm so tired & sleepy I'm afraid I have not made this very clear - But I want you to know - & sure you will see that I cannot well leave this problem until we've got convincing evidence - Then I look forward & hope we may all be together - God & the war permitting - & live out our days in peace - What a lovely picture of dear Margaret - How is she & Cath - wish we could all meet in Deer Isle - I know Minnie has kept you all posted - Things go well with us despite this cruel war but Victory must come & I'm optimistic enough to

to look forward to happier days even if they are not perfect — we can make it — & will be happy —

Forgiving this rambling epistle — with it goes my love & thoughts & the hope of better things ahead —

"With heaps & heaps of love"

Affectionately & Faithfully

O.H.

If the Board on the Surgeon General's office meets at Camp Bragg and then they may later on I shall take the opportunity of running over to Nashville for I want to talk over future plans & possibilities with you & Catherine — Do write if just a line — I want to know your address — & don't hesitate to talk to Ernest — he knows it all & we talked it over very fully —

Good night — it's long after mid-night & I know a busy day ahead — God bless you, me & all sleeping well & happy —