My Childs fellowship in 3/46 was $125 per month. I think I got 150 in V-12? In medical school 9/47 ff I would have gotten 100

P/1 submitted April 1946, published June ^^ 1946 CSH also detail who was there, the other intellectual issues.

P/5 Publ. Nov 46. Written after June ~ Cites PNAS P/1 Prelim version 12/29/45 sent to Childs Fund.

Ryan said to Childs in 12/45 that I planned to work with Sam Graff on mouse milk factor when I returned to medical school 9/46 -- by way of relevance to Cancer.

The Cold Spring Harbor meetings in 1946 (and again in 1947) were also a marvelous opportunity to benefit from new or renewed introductions to outstanding figures in genetics. Many of them were also extraordinarily supportive human beings, both in thoughtfully listening to the logic of my experiments, and in offering good advice (personal and technical) about how to respond to criticisms. Discussions with figures like Andre Lwoff, Jacques Monod, Guido Pontecorvo, Maclyn McCarty, Seymour Cohen, Bernard Davis, Boris Ephrussi, Raymond Latarjet, Colin Pittendrigh, Curt Stern, C. B. van Niel, Ernst Caspari, J. F. Crow, M. Demerec, Alex Hollaender, Rollin Hotchkiss, Dan Mazia, Howard Newcombe, Elizabeth Russell, Jack Schultz, Wolf Vishniac, M. J. D. White, Evelyn Witkin -- and many others -- helped to promote lifelong correspondence and personal and scientific relationships. I remember most vividly the warmth, interest and friendship offered by Tracy Sonneborn,

H. J. Muller, and Salvador E. Luria; later also by Leo Szilard and J.B.S. Haldane, in discussing the work as it unfolded. It is hard to overestimate the importance of these meetings in sustaining the interpersonal network in science. ----------

July 1946 ff.

The July meetings at Cold Spring Harbor had been an exhilarating challenge, to have presented these findings to such a critically important audience, and to have found no significant flaw. My medical school schedule called for me to conclude my research leave at Yale and return to P&S in September. But the work was plainly in too critical a stage for that. I applied to Dewan Sevringhaus for another year's leave, and this was approved (by others' accounts, quite reluctantly. ~my letter to Sevringhaus? And Ed Tatum made a successful appeal to the Childs Fund for a renewal of my fellowship.

The following months were then a frenzy of bolstering experiments. The main agenda was a further understanding of the "sexual process" itself, in particular to explore the linkage of markers in recombination, to attempt the construction of a chromosome map of E. coli. It would be difficult to write a rounded story without isolating the (hetero)zygote; but indirect methods would have to do in delineating the life cycle, as that of a haplobiont. The only morphological leads that, fancifully, might be related to zygotes in bacteria were the "Large Bodies", or L-forms. Their best known observer was Louis Dienes at the Mass Gen Hosp. {Cf CSH ...; visited in ? Oct 46}. These eventually proved to be a red herring that, on the

one hand, confused and delayed our later work on Salmonella transduction, on the other opened new insights into the mode of action of penicillin. A myriad of other experimental details also had to be attended to, for example to distinguish E. coli recombination from DNA-mediated transfer, as in pneumococcus. Besides our inability to find genetic activity in extracts, the most telling evidence was the insensitivity of the recombination process to the addition of DNAse to the medium, an experiment that would have been impossibility without the generosity of Maclyn McCarty in providing a sample of the purified enzyme.

To continue genetic studies at this point, our most urgent need was for markers, new mutations at a varietry of sites and controlling a variety of functions. Some of these, like phage - resistance, could be selected for, though not always as cleanly (e.g. an absolute distinction between totally resistant and totally sensitive phenotypes) as one would wish; and strain K-12 had its own idiosyncrasies in responding to phages T2 and T4, which had been the canonical materials used by Delbruck and his school with E. coli B. I did get some very useful markers, however, with T1- and T5- resistance.

Nutritional mutants, like those used for selecting recombinants, could also be used as unselected markers -- by adding the required nutrient to the medium except in the final test, growth or no-growth, by which the marker was diagnosed. It was easy to select for nutritionally sufficient reverse mutants or recombinants (I needed a word for that phenotypic class, and coined prototrophic -- prototypic nutrition -- for that). But it was the most tedious manual labor to screen thousands upon thousands of colonies. Had I the advantage of armies of technical assistants, I might have been less motivated to think of technical expedients to ease those labors. These eventually emerged (in 1948, see penicillin method). A momentary expedient, of some limited value, was delayed enrichment: explain .... This method unfortunately is blemished by non-heritable fluctuations in colony size, perhaps remediable with carefully standardized growth contexts. Many of the mutants, not surprizingly, are so unstable as to be of no practical use. So the method did offer some modest relief. A related one was "marginal enrichment" -- plating cells into a minimal medium with enough added growth factors that any auxotrophic mutants would form colonies, but characteristically smaller than the prototrophs. This was mechanically simpler than delayed enrichment (which involved pouring a layer of nutrient agar after the preliminary incubation of the prototrophic colonies - and woe betide you if there were any colonies of contaminants on then plate). One dilemma was to guess, in advance, just how much of a supplement would be marginal for a mutant not yet isolated! I did use bacterial hydrolysates calibrated to have marginal levels of one amino acid with the thought that other growth factors might be present in requisite proportions.

Fermentation mutants, finally, were a godsend. Variation in the ability to ferment different sugars had long been used in taxonomic diagnosis -- e.g., E. coli is characterized as lactose-positive; its cousins like Salmonella and Shigella are -negative. This history supported the speculation that evolutionary differences might be repeated in the laboratory. Equally important, it had led to the development of pH indicator media, like eosin-methylene blue (EMB) lactose agar on which Lac- would form white, Lac+ intense purple colonies. The functioning of this particular medium is more craft than science, and I was particular jealous of one lot of the dye, Eosin Y, that gave uncommonly sharp color differentiation. Other sugars notably maltose and galactose and pentoses could be used in like fashion. E. coli

cultures would be exposed to radiation or mutagenic chemicals, at does that killed say 99.9% of the cells. The survivors would then be plated on EMB lactose agar, and it was not difficult to spot the Lac- mutants, which might make up, say, 0.1% of the surviving colonies (or subclones therein). This meant one could recover one to a few mutants from a single EMB agar plate, and with a high likelihood that every white colony or sector picked for isolation would be a mutant. Furthermore, as the indicator medium allowed both Lac+ and Lac- colonies to grow, with only modest advantage to the Lac+, reverse mutations were not so troublesome as they were for auxotrophs. In fact, the process of revertability could be studied as a phenomenon in its own right (see EML ...) I quickly acquired a substantial library of Lac- mutants to use for genetic markers in the mapping project. At Wisconsin, later in 1947, these were to the the centerpiece of a research program directed at studying gene expression.

---------- cf outlines 4/46; 12/5/46; 3/47 very little about Lac; The Hetrozygote; Map; autonomy of mutation. Bacterial metabolism closer to gene action than higher forms. Ever more on Neurospora; adaptation in 1633 (different?); heterokaryons: nuclear targetting? other organisms; Salmonella. ----------

At Yale, however, the main business of 1946-1947 was to consolidate the genetic map, and to write the definitive papers describing the work. The first of these was a brief note to *Nature* { }, which Tatum and I submitted on Sept. 17, 1946 and which appeared in the October 19 issue. (Not everything moves faster today). This was the first announcement in the open lecture, following upon the symposium in July, which would be published only after a year's delay. A major article on the phenomenology and physiology of recombination was prepared for the Journal of Bacteriology. Submitted in March 1947, and published in June, this bore Tatum's name as senior author. Ryan very warmly admonished me to support this arrangement: I could not have done the work without Ed's constant support and encouragement; he had supplied the essential strains of E. coli K-12; he had consciously left me a free rein to pursue E. coli genetics, while he followed the chemical investigations of Neurospora that were is forte. It was as well that I got that advice. Like most graduate students, I had a limited appreciation of the needs of a mentorial professor for his own prestige -- not just for his ego gratification and career advancement, but to justify the flow of material support to the laboratory. As Ed's professional reference group was microbiology, this was the appropriate medium to acknowledge his role.

As if there were not enough to do with E. coli, I was eager to explore other microbial systems for genetic exchange. The most promising candidate was the Salmonella group -- a/c serotypes. Learned about them August 45 from Dubos' book -- exciting premonition of evolution by recombination in bacteria. (How serotypes == species helps) Look first into their nutrition. Interesting findings (why tryp-) reversions. evol sign. P/8 submitted Febr 28 47; appeared in May.

At Cold Spring Harbor in July 1947, I met Esther Zimmer ... While in Ryan's lab, had written to her before about Neurospora pab- 1633 Excited by rumor of non-transmissible "adaptation". Married in December. Moved to Machol's (she'd been at Y) Boston AAAS in Christmas. Also visited Dienes ~ October

The Cold Spring Harbor Symposium sponsored another symposium in June, 1947 -- this time

on nucleic acids. The genetic functions of nucleic acids loomed large. Avery was unable to attend, but Harriett Taylor {~46 vs 47 -- met Ephrussi ..?) Boivin (mentioned in notes 3/47)

Tatum - prior correspondence ...

Met: Boivin, Brachet, Chargaff, Crow, Caspari, Hollaender, S Cohen Huskins, Hyden, Kelner, Lindegren, Maas, Mazia, Newcombe, Russell, Schultz, Vishniac, MJD White, Kay Wilson,

Q28 Sept 47 Biometrics mtg. Woods Hole; RA Fisher; JL comment on crossover math logic / notation

Spent July and August at the Marine Biological Laboratory at Woods Hole writing my Ph. D. dissertation, Characterize MBL Genetics article major part of it. Submitted August 1, 1947 - published in the September issue. C Stern's reaction?

(and the magnificent library of the Marine Biological Laboratory) completing the dissertation. The stacks gave a wonderful opportunity to explore the history of microbiology: how its pioneers had sought to cope with the perplexities of bacterial variability, totally isolated from the intellectual apparatus of modern genetics.

My firm plans at this point were to return to New York, and continue my interrupted medical studies. Ryan also offered me laboratory facilities, and he and Tatum looked hard and partly successfully for some financial support to make all that possible. I was disappointed not to receive a Merck fellowship, especially as George Beadle was on the selection committee. In the long run, the Childs Fund .... Meanwhile, Tatum had negotiated with Yale my retroactive registration as a graduate student, and assent from other professors that I had de facto enrolled in a number of their lecture courses and seminars. The work of 1946-47 became my dissertation, which I had already defended before an international panel of experts. A more serious personal obstacle was obligatory retroactive payment of tuition to Yale University; but the happy result was to qualify for a Ph. D. degree that would, as it turned out, widen my career options.

In mid-August, days before the resumption of medical school, I learned from Ed Tatum that the University of Wisconsin had contacted him about an opening in genetics. In a fashion revolutionary for the time, they were seeking a microbial geneticist! He had recommended my name, and as a Wisconsin graduate his word carried great weight there. I have since learned of the controversy that this proposal evoked. Understandably, the appointment of a 22-year old as an assistant professor warranted close examination. Some referees at Cal Tech were still skeptical about the E. coli research:

a painstaking review by Ray Owen (at Cal Tech, but recently from Wisconsin) did much to allay concerns in that sphere. Most troubling were allusions about character and race -- someone with far stronger suits of tact and polish than were mine would have been a more compelling nominee to be among the first Jewish professors in a midwestern college of agriculture. (There have been some happy changes in this country over forty years. We still have many burdens of fairness in meeting the cries for equity from other groups subject to

discrimination.) It has been enormously gratifying to have learned in later years of the large effort and integrity of support that were thrown in by R. A. Brink " (1897-1984) Genetics 112:1-10 (1986). and M. R. Irwin (at Wisconsin) and by E. B. Sinnott (at Yale). It is a measure of their stature that I was, in the event, offered the position; and when I did come to Madison was given no inkling of what a struggle I had entailed.

The offer posed the deepest dilemma of my career. I was deeply committed to medical research. Two more years of clinical training (and to be meaningful another two or three of internship and residency) would have reinforced the medical credential, but been a grave (if not total) interruption of research at its most exciting stage. The Wisconsin position was the only one visible for unmitigated support of research in bacterial genetics. That university was furthermore a seat of biochemistry (especially in the Enzyme Institute) and had a long tradition of research in genetics and in microbiology (albeit quite separately up to that point). The Wisconsin Alumni Research Foundation, with income from professors' patents, was a further resource in aiding pioneer research. All this was, however, seated in the College of Agriculture, not Medicine. The medical school at Wisconsin at that time, furthermore, gave little emphasis to research, except for the McArdle Institute for Cancer Research. In short order, I did of course go to Wisconsin, and have never had second thoughts about the wisdom of the choice. The agricultural research context gave me a grounding in practical applications of biotechnology that I have never regretted. I enjoyed a happy collegial association with Brink and Irwin, and shortly thereafter with James F. Crow, (whom I had met at the 1947 Cold Spring Harbor symposium) and many other close friends and colleagues, that could be matched at no other time or place. In the long run, however, affiliation with a medical educational and research environment was to be a more compelling vocation. Together with Arthur Kornberg's concurrent move, this was to be the principal attraction of Stanford University, when I was invited to join the new medical school effective February 1959. That opportunity to return to medically centered activities at Stanford, and later at the Rockefeller University in 1978, have substantiated the advice I had from Tatum in 1947. ---------
---------- 1946 March 3/17 last notes Columbia. (p. 157)
Move to Tatum's lab, New Haven. Live in OBL tower (shared with Art Galston)

July Cold Spring Harbor Symposium. Tues-Fri July 2-12 (July 9/ Tuesday was picnic) Thu. July 11 most likely date own presntn.

7/3 noon-/12 pm [Wed<->Fri]notebook:abs. lab 7/2 (letter to EMZimmer. Staying at Iannone's, Queens)

See Atwood, Delbruck corresp.

At CSH, met most microbial geneticists, incl. also: B Davis, Ephrussi, Glass, Gopal, Haskins, Lwoff, McClintock, Mayr, Miller, Pirie, Ris, Skoog, Sonneborn, Stanley, Starr, Steinitz, Stern, Streisinger, Sussman, van Niel, Wollman
Pontecorvo

Already knew Columbians: Pittendrigh, Witkin, Zamenhof? Bryson, Commoner, Deitch, Graff, Krugelis, Lieb, Mirsky, Swift, !Demerec

1946

Jul							Aug							Sep						
S	M	Tu	W	Th	F	S	S	M	Tu	W	Th	F	S	S	M	Tu	W	Th	F	S
	1	2	3	4	5	6					1	2	3	1	2	3	4	5	6	7
7	8	9	10	11	12	13	4	5	6	7	8	9	10	8	9	10	11	12	13	14
14	15	16	17	18	19	20	11	12	13	14	15	16	17	15	16	17	18	19	20	21
21	22	23	24	25	26	27	18	19	20	21	22	23	24	22	23	24	25	26	27	28
28	29	30	31				25	26	27	28	29	30	31	29	30					

Luria (corresp. 7/15) starts crossing effort: phage selection doesn't work with E. coli B. This is doubtless the negative result touted at CalTech. Met Esther at CSH,July; She came to work at Yale. '"engaged"' -- ltr J.W. 9/23; married 12/13. (her bd 12/18/22) {CP Rhoads talk was a radio broadcast 12/15: Is that what I insisted on listening to?} See Dec. AAAS We lived at Machols: 33 Trumbull St. New Haven

p1 4/6/46 submitted; publ June reversion in Neurospora, PNAS "prototroph" is in that ms. p3 7/31/46 subm. small colony auxotrophic selection (cf Delayed colony) p5 .. Cancer as reversion. Scribbled in a class. Science 11/1. Not clear just when drafted. Text refers to p1.

p4 CSH, delivered ?? 7/11 Thurs. recall long evening debate so not Friday.(back in lab) Were V1-r data added to ms. later for publn?

p7 Nature, subm. 9/17/46; publ. 10/19/46

~Oct. Visit Dienes lab, Boston Dec.7 Conn Valley Br.,Soc Amer Bacteriol., Yale (see abstr. Q11B) report on crossing to bacteriologists unpublished married 12/13. Dec. AAAS Xmas mtgs., Boston c/ EML (honeymoon); Genetics Soc met Haldane and Spurway (wasps in her purse)

1947 Jan '47[year??] Zelle letter on single-cell isolates; cf notebook
Feb lectures at Columbia (Sager corresp.) P&S.
Mar Luria corresp: cartoon as reassurance

Summer: write dissertation at MBL: Woods Hole. UWis job offer dilemma! Continue for M.D. at P&S? No Merck fellowship (dubious whether Beadle supported) visit Madison (first plane trip); accept and move there. BUT, Childs fund did approve limited fellowship in June Cf. Peyton Rous' doubts -- Childs Archives Cf. P/9b p6 J Bact subm 3/10 publ. 6/47 p9 Genetics recd 8/1/47:definitive re E coli K-12 recombination. p8 Salmonella nutrition, preparatory to recombination tests. '47 CSH symposium June 11-20 comments on Boivin paper -- we thought we might have transformed his strains of E coli But used Chloroacetate resistant mutants as markers (cf Penfold, hydrogenlyase-def)

Harriett Taylor's paper on pn. transformation an irritant

Met: Boivin, Brachet, Chargaff, Crow, Caspari, Hollaender, S Cohen Huskins, Hyden, Kelner, Lindegren, Maas, Mazia, Newcombe, Russell, Schultz, Vishniac, MJD White, Kay Wilson, Q28 Sept 47 Biometrics mtg. Woods Hole; RA Fisher; JL comment on crossover math logic / notation Sept. short course on methods at CSH (Witkin corresp) Sept. 16. NWA DC-4 move to Madison; stayed with Atwoods NYC (Art Galston corresp.) Truax Field barracks as place to live to start '46, 47 SAB: Detroit, Phila. resp. Could I have attended (met more bacteriologists?) Dec. GSA in Chicago ----------

5. Wisconsin - exptl. work in microbial genetics 1947-58
recruitment: material in P/269 P/9a

Arrived Sept. 16, 1947 on a NWA DC-4 at Truax Field, which also sited the barracks where (along with myriad students) we would live until ... ~ rent other quarters. Initial salary: 3600. Lab budget: $10,000 for lab equipment and remodelling; 5000 addnl. from UW. 2600 from WARF for '48; 3 x 2500 from Rockefeller Fn. (See first NIH application, on Genetics of Salmonella for July 1948. Includes NIH fellowship - to N D Zinder?) C-2157. Fairly complete files from 1952 ff. Ask Raub

"Program - Wisconsin 9/47:

Highlights: Transformation; Salmonella; Carbohydrases; E coli zygote

and Collaborative programs in plant pathology; Botany; Biochem; Bact.

Initial research program proposals -- RF, WARF Not surprised at unpredictable course, could not foresee what would and wouldn't.

UW, LaFollette tradition; Ag School KP Link; LJ Cole tradition

K-12 mechanisms (Hayes, Wollman) transduction
Salmonella, ; Fla lysogeny (lambda) plasmids (F)
replica plating Mechanism of penicillin ...
Streptomyces chemical mutagens

GSA Committee on [Lysenkoism] [] posture. Cf Sapp 87.